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RESEARCH**

APPLICATION NUMBER:

205109Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW-ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 205109	Biopharmaceutics Reviewer: Elsbeth Chikhale, PhD	
Submission Date:	February 1, 2013		
Division:	Division of Cardio Renal Products	Biopharmaceutics Team Leader: Angelica Dorantes, PhD	
Applicant:	Vifor Fresenius Medical Care Renal Pharma	Acting Supervisor: Richard Lostritto, PhD	
Trade Name:	Velphoro™	Date Assigned:	February 7, 2013
Generic Name:	Sucroferric oxyhydroxide	Date of Review:	November 7, 2013
Indication:	to control hyperphosphataemia in patients with end-stage renal disease (ESRD)	Type of Submission: 505(b)(1) Original New Drug Application	
Dosage form/ strengths	Chewable tablets/ 500 mg elemental iron equivalent/tablet		
Route of Administration	Oral		

SUMMARY:

Submission:

The proposed drug product is a chewable tablet containing 2.5 g PA21 drug substance (equivalent to 500 mg iron). The drug substance, PA21, is a mixture of polynuclear iron(III)-oxyhydroxide (pn-FeOOH), sucrose and starches. The drug product is a chewable tablet indicated for the control of hyperphosphataemia in patients with end-stage renal disease (ESRD).

Review:

ONDQA-Biopharmaceutics reviewed the original NDA 205109 submitted 2/1/2013, and a Biopharmaceutics review authored by Dr. Elsbeth Chikhale was placed in DARRTS on 9/29/2013. The review concluded the following:

“Based on the discriminating capability of the dissolution method and the overall dissolution data from the clinical and registration batches, the proposed acceptance criterion of $Q = (b) (4)$ at 45 minutes is not acceptable and a dissolution acceptance criterion of $Q = (b) (4)$ at 30 minutes is recommended for this product.”

This dissolution acceptance criterion recommendation was conveyed to the Applicant in a teleconference held on 9/25/2013. However, the Applicant was concerned that the proposed drug product would fail this criterion during stability and therefore they will not get the desired shelf life of $(b) (4)$ for their product. During this teleconference, FDA agreed that the Applicant could have a wider dissolution acceptance criterion for their product if the results from in vitro

phosphate adsorption/binding studies comparing an old failed batch (b) (4) of drug product with a slower dissolution rate vs. a new acceptable fresh batch of drug product with a faster dissolution rate, demonstrated that the phosphate adsorption and binding between these product are equivalent. The Applicant provided the in vitro phosphate adsorption/binding data in an amendment dated 10/18/2013. The Applicant demonstrated that the phosphate adsorption of a fresh drug product batch is comparable to the phosphate adsorption of a 32 month old batch:

Batch No.	Release Analysis		Results After 32 Months	
	Phosphate Adsorption (mg P/mg Fe)	Iron Release % (m/m)	Phosphate Adsorption (mg P/mg Fe)	Iron Release % (m/m)
014011B11	0.278	1.6	0.289	2.7
014011C11	0.287	1.8	0.298	2.7

These results indicate that the decreased dissolution rate observed with aging of the drug product batches when they are stored for more than 2 years, does not affect the phosphate binding capacity of the drug product. Therefore, setting a wider than originally recommended dissolution acceptance criterion has been adequately justified with supportive data and is acceptable.

In the amendment dated 10/18/2013, the Applicant proposed a dissolution acceptance criterion of $Q = (b) (4)$ at 30 minutes. Since it is important to keep Q at (b) (4) or (b) (4) in order to assure full dissolution, on 10/22/2013, the Applicant was informed via e-mail that FDA recommended the implementation of a dissolution acceptance criterion of $Q = (b) (4)$ at 45 minutes or $Q = (b) (4)$ at 60 minutes. On 10/30/2013, the Applicant submitted their response accepting the implementation of a dissolution acceptance criterion of $Q = (b) (4)$ at 45 minutes for their drug product.

RECOMMENDATION:

The following dissolution method and acceptance criterion are acceptable for batch release and stability testing:

Drugs Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance Criterion
Velphoro	Chewable Tablets	USP 2 (Paddle)	50	900 mL 0.1 N HCl at 37°C	(b) (4) (Q) after 45 minutes

From a Biopharmaceutics perspective, NDA 205109 for Velphore (sucroferric oxyhydroxide) Chewable Tablets is recommended for **APPROVAL**.

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cc: RLostritto

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/s/

ELSBETH G CHIKHALE
11/07/2013

ANGELICA DORANTES
11/07/2013

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	PA21
NDA:	205-109
PRODUCT (Brand Name):	Velphoro®
DOSAGE FORM:	Chewable Tablets
DOSAGE STRENGTHS:	500 mg iron
INDICATION:	Control of serum phosphorus levels in patients with end-stage renal disease (ESRD)
NDA TYPE:	Standard
SUBMISSION DATE:	1/31/2013
SPONSOR:	Vifor (International) Inc.
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1.0 EXECUTIVE SUMMARY

This is an original NDA 205109 submitted by Vifor (International) Inc., on February 1, 2013 seeking for approval of Velphoro (PA21) as a phosphate binder for the control of serum phosphorus levels in patients with end-stage renal disease (ESRD).

PA21 is an iron-based phosphate binder. It consists of a mixture of polynuclear iron (III)-oxyhydroxide, stabilized by sucrose and starches with approximately (b)(4) of iron content. The proposed product is a chewable tablet containing 500 mg iron. The proposed starting dose is 3 tablets (1,500 mg) per day, administered as 1 tablet (500 mg) 3 times daily with meals. Titration can be started 1 week after initiation of treatment and doses can be titrated in decrements or increments of 500 mg (1 tablet) per day until an acceptable serum phosphorus level (≤ 5.5 mg/dL) is reached. The maximum daily dose is 3000 mg (6 tablets) per day.

In this submission, there are 9 human study reports submitted to support the dosing and the proposed claim for PA21, including 7 clinical pharmacology studies (5 *in vivo* DDI, 1 ADME and 1 PK studies) and 2 Phase 2 and 3 pivotal trials. In addition, there are 22 *in vitro* studies conducted for evaluation of potential drug-drug interactions.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical pharmacology information submitted in the NDA 205-109. The submission is acceptable from a clinical pharmacology perspective provided an agreement is reached on the Agency's proposed labeling recommendations (outlined in Section 3.0).

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

- Following oral administration, the uptake of ^{59}Fe -PA21 was found to be $< 0.1\%$ in patients with chronic kidney disease (CKD) and 0.43% in healthy subjects supporting minimal absorption of iron from PA21.
- Commonly used drugs in the target population were screened in an attempt to characterize the interaction potential *in vitro*. Among drugs studied, furosemide, losartan, atorvastatin, doxycycline, alendronate, levothyroxine, and paricalcitol were found to show extensive binding with PA21 when incubated in an aqueous solution that mimics the conditions of the gastro-intestinal (GI) tract. The binding of levothyroxine, paricalcitol and atorvastatin to PA21 were less pronounced with the presence of phosphate.
- Systemic exposure of losartan, furosemide, omeprazole, digoxin and warfarin were not altered when administered either concomitantly with PA21 or 2 hour after PA21 compared to the testing drug alone.
- Lipid-lowering effects of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors were not altered by PA21 over 52 weeks.

- A trend of dose-dependent serum phosphorous lowering effect was observed although the relationship is relatively shallow over the range of 1000 mg iron/day to 2500 mg iron/day.
- Near maximum serum phosphate lowering effects of PA21 was seen in 2 weeks on all doses that showed an effect.

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?*

Dosage Form/Strengths: 500 mg iron chewable tablets

Indication: The proposed indication for Velphoro[®] (PA21, Sucroferic oxyhydroxide) is for the control of serum phosphorus levels in patients with end-stage renal disease (ESRD).

Pharmacologic Class: Phosphate binder

Chemical Name: Mixture of polynuclear iron (III)-oxyhydroxide, sucrose and starches

Molecular formula: pn-FeOOH

Chemical structure:



Figure 1 Schematic Diagram of the Structure of PA21

Physical Characteristics: The particle size distribution was measured in the range of (b) (4) with a D₅₀ of approximately (b) (4). The polynuclear iron (III)-oxyhydroxide core and the starches are practically insoluble in water.

Formulation: PA21 chewable tablets containing 500 mg iron. The to-be marketed formulation was used in the pivotal clinical trial.

2.1.2 What are the proposed mechanism of action and therapeutic indications?

PA21 is a chewable tablet proposed to be taken with meals and to bind phosphate in the food content thereby reducing the intake of phosphate. Following oral administration, in the aqueous environment of the GI tract, phosphate binding takes place by ligand exchange between hydroxyl groups and/or water in PA21 and the phosphate in the diet. The bound phosphate is eliminated with feces. *In vitro* studies have demonstrated the phosphate binding capacity of PA21 over the entire physiologically relevant pH range of the GI tract (1.2-7.5).

The proposed indication for PA21 is to control serum phosphate levels in the target population.

2.1.3 What are the proposed dosages and route of administration?

The sponsor proposed dose is 500 mg chewable tablet three times daily with meal. Doses can be titrated in the increment of 500 mg per day as soon as one week after initiation of the treatment. The maximum daily dose is 3000 mg.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

There are 9 human study reports submitted to support the dosing and the proposed claim for PA21: 7 clinical pharmacology studies, a Phase 2 study and a Phase 3 trial.

The PA21 clinical pharmacology program included the following assessments:

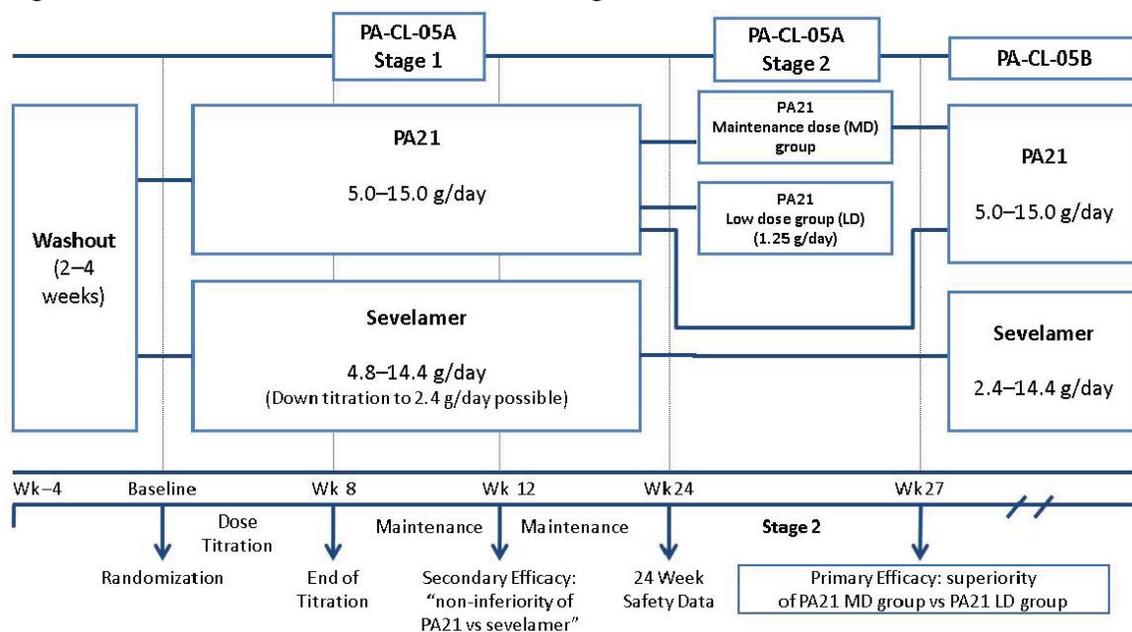
- An ADME study to evaluate the potential and extent of iron absorption following PA21 administration.
- A SAD and MAD study to evaluate the safety, tolerability of PA21.
- An *in vitro* DDI screening of 22 drugs that are likely be concomitantly administered in CKD to evaluate drug interaction potential.
- Five *in vivo* DDI studies to investigate drug interaction potential.
- Assessment of the potential impact of PA21 co-administration on the lipid lowering effect of statins in the Phase 3 trial.

The Phase II study (PA-CL-03A) was a 6-week open-label, randomized, active-controlled, dose-ranging (1.25 to 12.5 g PA21/day i.e., 250 mg iron/day – 2500 mg iron/day) study in ESRD patients on hemodialysis (HD).

The Phase III study (PA-CL-05A) was a 27 week confirmatory study to evaluate the efficacy of the serum phosphate lowering effect of PA21 with an extension phase of PA-CL-05A for long term safety evaluation. This was a 2-stage study (see Figure 1). Stage

1 enrolled 1,059 ESRD patients on HD or peritoneal dialysis (PD). Subjects received PA21 (N=707) at a starting dose of 1,000 mg iron/day (equals to 5 g PA21/day), or sevelamer (N=348) at a starting dose of 4.8 g/day. Dosing of both drugs was titrated to effect, based on the target serum phosphorus range of 2.5 to 5.5 mg/dL, over 8 weeks, and then continued for a further 16 weeks (Stage 1, 24 weeks treatment). On completion of Stage 1, 99 PA21-treated HD subjects with controlled serum phosphorus levels were re-randomized to either PA21 maintenance dose (MD) (i.e., dose taken at the end of Stage 1) or PA21 non-effective low dose (LD) (250 mg iron/day = 1.25 g PA21/day) for a further 3 weeks. After the last dose of study medication, all subjects, except those treated in the PA21 LD arm of Stage 2, were able to continue their treatment with either PA21 or sevelamer in an ongoing extension study, PA-CL-05B.

Figure 1: Schematic of the Phase III trial design



Primary efficacy endpoint in this study is change from Week 24 in serum phosphorus levels at Week 27 – a superiority comparison between the PA21 MD group and the PA21 LD control group.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

The aim of treatment with dietary phosphate binders is to achieve control of serum phosphorous levels in ESRD patients. Consequently, the primary efficacy measure used in the evaluation of effectiveness is changes in serum phosphate. The serum phosphate levels were measured in local as well as a central laboratory by standard procedures.

In the Phase II study, the primary endpoint was change from baseline in serum phosphate levels at the end of the treatment. The key secondary endpoint was pairwise comparison

of the change from baseline in serum phosphate levels for each of the higher doses of PA21 to the lowest PA21 dose (1.25 g PA21/day=250 mg iron/day).

In the Phase III study, the primary efficacy measure was change from baseline in serum phosphate levels from week 24 (baseline) to week 27 (end of withdrawal). The comparison was between PA21 MD group and LD group for superiority.

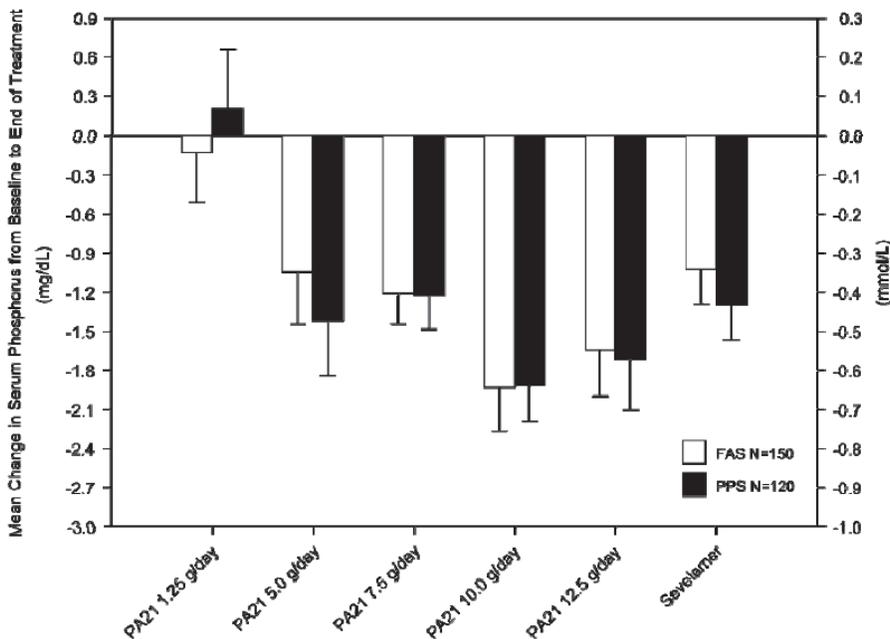
In these studies, one of the key secondary endpoint is percent of subjects with controlled serum phosphorous according to KDOQI (Kidney Disease Outcomes Quality Initiative) target range.

2.2.3 What are the characteristics of exposure-response (E-R) or dose-response (D-R) relationships for efficacy and safety?

The E-R relationship was not conducted in this submission as the drug is intended to work in the GI tract and there is minimal absorption of the product. However, a Phase II dose-ranging study (PA-CL-03A) was conducted to provide dose-response information to support the dose selection. In the Phase II study 5 doses over the range of 1.25 – 12.5 g PA21/day (250 mg-2500 mg iron/day) were studied.

Significant serum phosphate lowering effect was observed at all dose levels except the lowest dose of 250 mg iron/day (1.25 g PA21/day). Doses of 1,000 mg iron/day (5.0 g PA21/day) and 1,500 mg iron/day (7.5 g PA21/day) appeared to show equivalent effect when compared with active control, Sevelamer. The applicant states that there were very few dose-dependent or dose-limiting AEs observed up to 2500 mg iron/day (12.5 g PA21/day).

Figure 2: Change from Baseline in Serum Phosphorus Levels (mmol/L and mg/dL) at End of Treatment



Based on these findings, applicant concluded that:

1. The lowest dose (250 mg iron/day=1.25 g PA21/day) is a non-effective dose.
2. A reasonable starting dose is 1000 mg iron/day (5 g PA21/day).
3. The maximum daily dose would be 3000 mg iron/day (15 g PA21/day) for the pivotal Phase III study.

The dose selection seems reasonable. It must be noted that over the range of 5.0 g PA21/day (1000 mg iron/day) to 12.5 g PA21/day (2500 mg iron/day), the dose-response relationship is shallow, with numerically higher effects for the higher doses till 10 g PA21/day. The 12.5 g PA21/day did not seem to be numerically better than 10 g/day in efficacy on a population level in this phase 2 study, but the phase 3 study had several individuals who benefitted from up-titration of dose from 10 to 12.5 and further to 15 g PA21/day in controlling serum phosphate levels (refer to Appendix II). There were no dose-response trends seen in treatment emergent adverse events of interest (diarrhea, GI hyperplasia) or rates of discontinuations in patients who got up-titrated due to lack of efficacy to any of the two higher doses (12.5 and 15 g PA21/day) as compared to patients who stayed on lower doses. Thus, from efficacy and safety perspective the dose selection and proposed dose range in the label seems reasonable.

2.2.4 What are the PK characteristics of PA21?

There is only minimal absorption of iron from PA21. Hence, no conventional clinical pharmacology studies were conducted in this submission.

2.2.4.1 What are the characteristics of drug absorption?

PA21 is not expected to be absorbed. However, possibility of the iron released from PA21 and absorbed into the systemic cannot be completely ruled out. A radio-labeled Fe study (Q24120) was conducted to confirm the extent of iron absorption from PA21 in 16 CKD subjects (8 pre-dialysis and 8 HD), and 8 healthy volunteers with low iron stores (ferritin <100 mcg/L). ⁵⁹Fe uptake was observed to be ~0.43% and < 0.1% in healthy subjects and CKD patients, respectively, confirming that PA21 has minimal iron absorption.

Table 1: Circulating radioactivity in blood in 3 groups of participants (volunteers, pre-dialysis patients and hemodialysis patients)

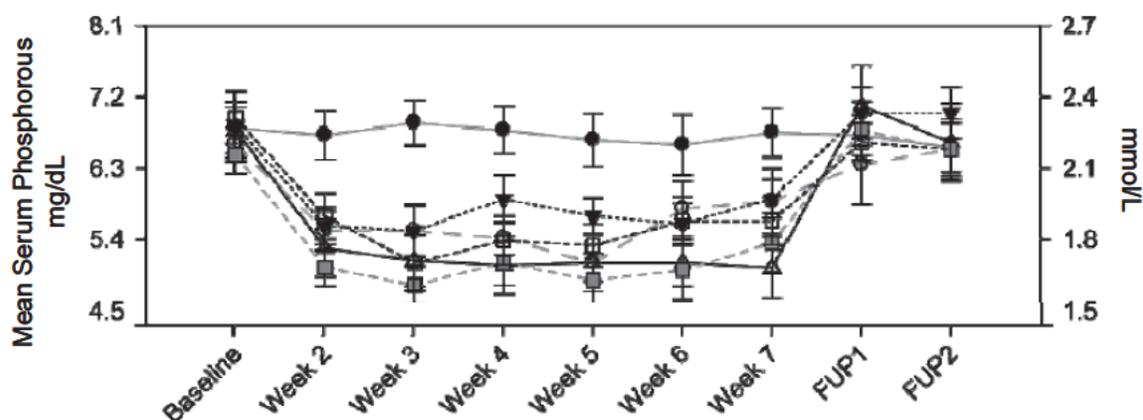
	Iron uptake	
	Median	Range
Healthy	0.43%	0.16 -1.25%
HD	0.02%	0 – 0.04%

pre-dialysis	0.06%	0.008 - 0.44%
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2.2.5 What are the PD characteristics of the drug?

As mentioned previously, pharmacodynamic activity of PA21 was mainly assessed by the serum phosphate level changes from baseline. The decreased of serum phosphate levels were consistently observed in multiple clinical studies. Based on the time course of the serum phosphate lowering effects observed in the phase II study, it can be clearly seen that near maximum effects following a fixed dosing are achieved by 2 weeks.

Figure 3: Mean Serum Phosphorus Levels Over Time



This supports the titration to a higher dose every two weeks in the phase 3 study.

2.2.5.1 How does PD of the drug in healthy adults compare to that in patients

The pharmacodynamics of PA21 was also investigated in study Q-24120 where healthy subjects and CKD patients were studied. This study indicated that the serum phosphate lowering effect was greater in CKD patients as compared to healthy subjects. This finding is expected as the renal excretion is impaired in ESRD.

Table 2: Mean serum phosphate change from baseline in 3 groups of participants (volunteers, pre-dialysis patients and hemodialysis patients)

	Serum phosphate
	Mean change from BL (mg/dL)
Healthy	- 0.25

HD	- 1.86
Pre-dialysis	- 1.05

2.3 INTRINSIC FACTORS

Intrinsic factors are not expected to impact the availability of PA21 at the site of action and hence were not evaluated.

2.4 EXTRINSIC FACTORS

There is only minimal absorption of iron from PA21. No conventional clinical pharmacology studies were conducted in this submission. The focus in this NDA was on the potential of PA21 to bind concomitant drugs in the GI tract and reduce the bioavailability of the concomitant drugs.

2.4.1 *Is PA21 a substrate, inhibitor or inducer of CYP enzymes and/or transporters?*

The potential of PA21 to be a substrate, inhibitor or inducer of CYP enzymes and/or transporters is expected to be minimal and were not evaluated in this NDA.

2.4.2 *Is there an in vitro basis to suspect drug-drug interaction?*

Yes. *In vitro* studies were conducted using aqueous solutions which mimic the physico-chemical conditions of the GI tract to evaluate the worst scenario of PA21 to bind commonly concomitant drugs. The solutions were incubated at pH 3.0, 5.5 and 8.0 at 37°C for 6 hours. The amount of the concomitant drug remaining at the end of the incubation was measured to evaluate the extent of binding to PA21. Some drugs were also examined in the solution contained phosphate to reflect the more clinically relevant condition.

Extensive binding were observed for furosemide, losartan, atorvastatin, doxycycline, alendronate, levothyroxine and paricalcitol. The binding were less pronounced for levothyroxine, paricalcitol and atorvastatin in the presence of phosphate.

No interactions were observed for ciprofloxacin, digoxin, enalapril, hydrochlorothiazide, metformin, metoprolol, nifedipine, quinidine and warfarin and thus no dose adjustment is warranted.

2.4.3 *What extrinsic factors (such as herbal products, diet, smoking and alcohol) influence exposure and or response and what is the impact of any differences in exposure on pharmacodynamics?*

The effects of extrinsic factors like herbal products and smoking is not expected to be clinically relevant and have not been conducted.

2.4.4 *Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are co-administered? If yes, is there a need for dosage adjustment?*

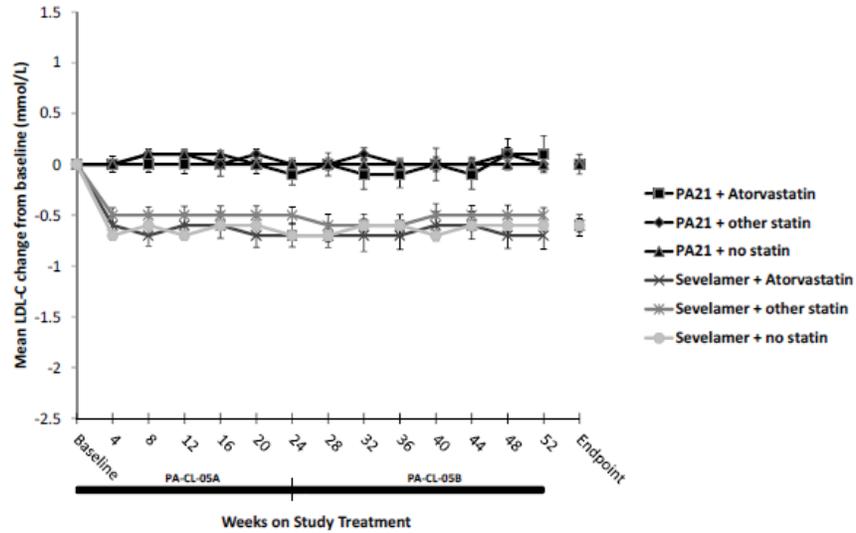
In vivo DDI were conducted with 5 drugs. Losartan and furosemide showed strong binding with PA21 *in vitro* requiring *in vivo* evaluation. The *in vitro* findings with omeprazole could not be interpreted; hence, an *in vivo* study was conducted. Although *in vitro* binding study did not indicate interaction potential, *in vivo* drug interaction studies with digoxin and warfarin were performed as these drugs have narrow therapeutic index. Systemic exposure of losartan, furosemide, omeprazole, digoxin and warfarin were not altered when concomitantly administered with PA21 or 2 hour after PA21 when compared with the testing drug alone.

As atorvastatin was found to be bound to PA21 in the *in vitro* study, additional evaluation was warranted. Since statins were used in the phase III study and lipid parameters were routinely collected, applicant proposed to evaluate the lipid lowering effect of statins for characterizing the drug interaction potential of PA21 with statins. The analysis was performed in two sets, atorvastatin set and simvastatin set. Within each set, treatment of PA21 was compared with treatment of sevelamer. The primary lipid parameter was LDL-C. Data were excluded for any changes to the dose of statins or any addition or deletion of a statin to avoid any changes in the lipid parameters by the changes in the statin doses.

Atorvastatin set

LDL-C levels were not altered before and after PA21 treatment and maintained stable over 52 weeks regardless of whether there was concomitant administration of a statin or not. In sevelamer treatment group, LDL-C levels decreased after first dose of sevelamer and maintained stable over 52 weeks regardless of whether there was concomitant administration of a statin or not. This observation is a known effect of sevelamer and is described in the sevelamer package insert.

Figure 4: Mean (\pm SEM) Serum LDL-C Change from Baseline at Each Time Point (Atorvastatin set)

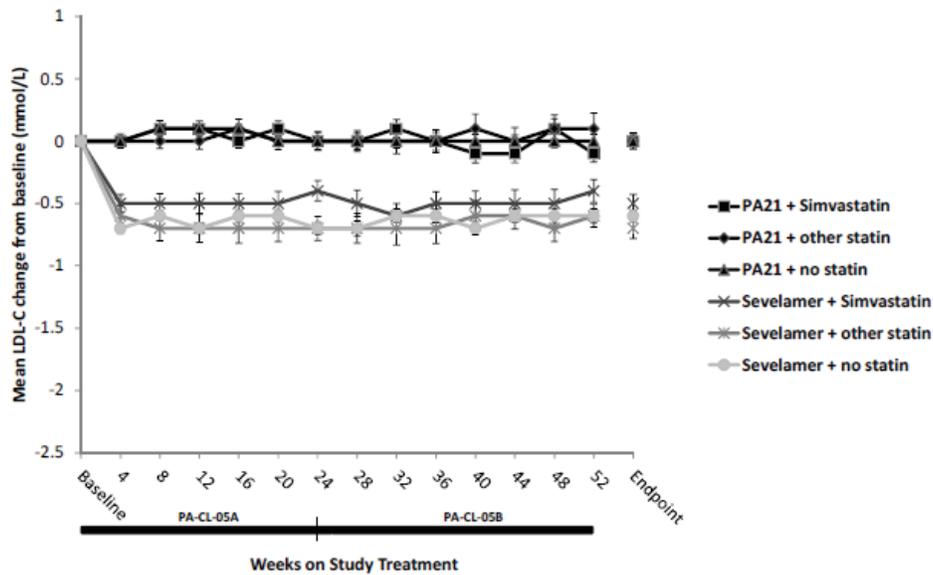


Notes: Baseline was defined as the latest evaluable value prior to the first study drug intake in PA-CL-05A. Endpoint was defined as the PA-CL-05B Week 28 value (i.e., Week 52 in combined PA-CL-05A/PA-CL-05B) or the latest non-missing evaluable value when 05B Week 28 is missing/not evaluable.
 LDL-C = Low density lipoprotein cholesterol; SEM = Standard error of the mean.
 Source: Section 5, Table 1.4.1.1.

Simvastatin set

Similar findings were observed in the simvastatin set.

Figure 5: Mean (\pm SEM) Serum LDL-C Change from Baseline at Each Time Point (Simvastatin set)



Notes: Baseline was defined as the latest evaluable value prior to the first study drug intake in PA-CL-05A. Endpoint was defined as the PA-CL-05B Week 28 value (i.e., Week 52 in combined PA-CL-05A/PA-CL-05B) or the latest non-missing evaluable value when 05B Week 28 is missing/not evaluable.
 LDL-C = Low density lipoprotein cholesterol; SEM = Standard error of the mean.
 Source: Section 5, Table 2.4.1.1.

Based on the above findings, no dose adjustment is required when PA21 is concomitantly administered with losartan, furosemide, omeprazole, digoxin, warfarin, simvastatin and atorvastatin.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The final to-be marketed formulation was used in the pivotal clinical trial. In addition, the product is only minimally absorbed. Hence, bioequivalence studies were not conducted.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

The assay validations for losartan, its active metabolite (EXP 3174), furosemide, omeprazole, digoxin and warfarin in the *in vivo* DDI studies are acceptable. Concentrations in plasma were determined using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Adequate concentrations of Quality Controls (QCs) were used in these assay validations.

3.0 DRAFT LABELING RECOMMENDATION

Only the sections containing OCP recommended changes are provided below. The reviewer's labeling recommendations are shown by track changes to the sponsor proposed label. Labeling discussions are on going at the time these recommendations are provided:

HIGHLIGHTS

----- DRUG INTERACTIONS -----

(b) (4)

- Take alendronate and doxycycline at least 1 hour before Velphoro. (7)
- Velphoro can be administered concomitantly with ciprofloxacin, digoxin, enalapril, furosemide, HMG-CoA reductase inhibitors, hydrochlorothiazide, losartan, metformin, metoprolol, nifedipine, omeprazole, quinidine and warfarin. (7)

(b) (4)

Reviewer's notes:

- *Both levothyroxine and paricalcitol showed a clear signal for binding in an in vitro study and lack in vivo information. Levothyroxin package insert (PI) states to separate at least 4 hrs with iron products because of the formation of ferric-thyroxine complex. However, 4 hour separation is not practical with phosphate binders. For paricalcitol, the sponsor proposed to evaluate potential PD interaction from the pivotal Phase III trial but was unable to do so due to majority of the patients who concomitantly used of vitamin D analogs were dosed through IV route. Since both drugs have parenteral form available, the interaction can be avoided. Please see above the OCP's recommendation.*
- *Similarly, alendronate and doxycycline showed a clear signal for binding in in vitro study but lack in vivo information. Since the PIs of these two indicate that they are taken in fasted state if possible. Hence to be consistent with their PIs, the recommendation for these two drugs is to take them at least 1 hour before PA21.*

7 DRUG INTERACTIONS

<u>Drugs that can be administered concomitantly with Velphoro</u>	
<u>Ciprofloxacin</u> <u>Digoxin</u> <u>Enalapril</u> <u>Furosemide</u> <u>HMG-CoA reductase inhibitors</u> <u>Hydrochlorothiazide</u> <u>Losartan</u> <u>Metformin</u> <u>Metoprolol</u> <u>Nifedipine</u> <u>Omeprazole</u> <u>Quinidine</u> <u>Warfarin</u>	
<u>Drugs that are to be separated from Velphoro and meals</u>	
	<u>Dosing Recommendations</u>
<u>Alendronate</u> <u>Doxycycline</u>	<u>Taking these drugs at least 1 hour before Velphoro.</u>

(b) (4)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

The active moiety of Velphoro, polynuclear iron(III)-oxyhydroxide (pn-FeOOH), is practically insoluble and therefore not absorbed and not metabolized. Its degradation product, mononuclear iron species, can however be released from the surface of pn-FeOOH and be absorbed.

Due to the insolubility and degradation characteristics of Velphoro, no classical pharmacokinetic studies can be carried out.

The sucrose and starch components of Velphoro can be digested to glucose and fructose, and maltose and glucose, respectively. These compounds can be absorbed in the blood. One tablet is equivalent to 1.4 g of carbohydrates.

(b) (4)

(b) (4) The iron uptake from radiolabelled Velphoro drug substance, 2,000 mg in 1 day, was investigated in 16 chronic kidney disease patients (8 pre-dialysis and 8 hemodialysis patients) and 8 healthy volunteers with low iron stores (serum ferritin <100 mcg/L). In healthy subjects, the median uptake of radiolabelled iron in the blood was 0.43% on Day 21. In chronic kidney disease patients, the median uptake was minimal, 0.04% on Day 21. (b) (4)

(b) (4)

Drug Interaction Studies

In vitro

In vitro interactions were conducted in aqueous solutions which mimic the physico-chemical conditions of the gastro-intestinal tract with or without the presence of phosphate (400 mg). The study was conducted at pH 3.0, 5.5 and 8.0 with incubation at 37°C for 6 hours.

Interaction with Velphoro is seen with the following drugs: alendronate, doxycycline, levothyroxine, and paricalcitol.

Following drugs did not show interaction with Velphoro: ciprofloxacin, enalapril, hydrochlorothiazide, metformin, metoprolol, nifedipine, and quinidine.

In vivo

Five in vivo drug interaction studies (N=40/study) were conducted with losartan, furosemide, digoxin, omeprazole and warfarin in healthy subjects receiving 1,000 mg Velphoro 3 times a day with meals. Velphoro did not alter the systemic exposure as measured by the area under the curve (AUC) of the tested drugs when co-administered with Velphoro or given 2 hours after.

Data from the clinical studies (Study-05A and Study-05B) show that Velphoro does not affect the lipid lowering effects of HMG-CoA reductase inhibitors.

4.0 APPENDIX

4.1 APPENDIX I

INDIVIDUAL STUDY REVIEWS

4.1.1 IN VITRO STUDIES PERTINENT TO PK USING HUMAN BIOMATERIALS

Study STU-PA21DDI-B101527-001- (In vitro DDI-Doxycycline)

Study Report # STU-PA21DDI-B101527-001

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Title: Investigation of possible interaction of Doxycycline in aqueous alpha-amylase solution with PA21 by UPLC-MS/MS detection

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). One tablet of Doxysol (200 mg doxycycline/ tablet) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 0h, 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then analyzed by UPLC-MS/MS. The pH value of all solutions was controlled during the complete study.

Quantification of doxycycline was performed by UPLC with mass tandem spectrometry detection.

The observed effects are considered as maximum interactions between PA21 and doxycycline. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- Doxycycline showed ~ 50 % adsorption to PA21 at pH 3.0 and complete adsorption to PA21 at pH 5.5 and 8.0. Data below are percent difference of drug concentrations between test solution (PA21 placebo and PA21) and placebo solution (H₂O+ alpha-amylase).

Table 4: Summary of Doxycycline adsorption at pH 3.0

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 3.0	-0.103	-1.46	-0.771
Adsorption to PA21 a pH 3.0	-46.2	-45.5	-46.8
Adsorption to active compound of PA21 at pH 3.0	-46.1	-44.7	-46.4

Table 8: Summary of Doxycycline adsorption at pH 5.5

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 5.5	-0.890	-0.145	6.05
Adsorption to PA21 at pH 5.5	-97.1	-98.9	-100
Adsorption to active compound of PA21 at pH 5.5	-97.1	-98.9	-100

Table 12: Summary of Doxycycline adsorption at pH 8.0

	<i>Sampling time</i>		
	<i>T+2h</i>	<i>T+4h</i>	<i>T+6h</i>
Adsorption to placebo at pH 8.0	55.6	28.9	17.5
Adsorption to PA21 at pH 8.0	-97.7	-100	-100
Adsorption to active compound of PA21 at pH 8.0	-98.5	-100	-100

- The performance of the assay method during study sample analysis is acceptable. The inter-run relative standard deviations were ranging from 1.5 to 4.1% and accuracies were ranging from 0.2 to 10.0%.

Conclusions:

- Complete adsorption of doxycycline to PA21 was observed at pH 5.5 and 8.0.
- At pH 3.0, ~ 50% adsorption of doxycycline to PA21 was observed.

Study STU-PA21DDI-B101528-001 (In vitro DDI-Cinacalcet)

Study Report # STU-PA21DDI-B101528-001

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Title: Investigation of possible interaction of Cinacalcet in aqueous alpha-amylase solution with PA21 by UPLC-MS/MS detection

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). Two tablets of Mimpara (90 mg cinacalcet/ tablet) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, processed and then injected into the UPLC system with tandem mass detection. The pH value of all solutions was controlled during the complete study.

Quantification of cinacalcet involved a separation by UPLC with tandem mass spectrometry detection.

The observed effects are considered as maximum interactions between PA21 and cinacalcet. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- Cinacalcet showed no adsorption to PA21 at pH 3.0 and ~11-12% to PA21 and placebo at pH 5.5. At pH 8.0 the analyte is not stable and the concentrations were very low due to low solubility. The results observed at pH 8.0 are considered inconclusive. Data below are percent difference of drug concentrations between test solution (PA21 placebo and PA21) and placebo

solution (H₂O+ alpha-amylase).

Table 4: Summary of Cinacalcet adsorption at pH 3.0

	<i>Sampling time</i>		
	T_{+2h}	T_{+4h}	T_{+6h}
Adsorption to placebo at pH 3.0	-0.266	-0.078	-0.788
Adsorption to PA21 at pH 3.0	-0.510	-0.695	-0.521
Adsorption to active compound of PA21 at pH 3.0	-0.245	-0.617	0.269

Table 8: Summary of Cinacalcet adsorption at pH 5.5

	<i>Sampling time</i>		
	T_{+2h}	T_{+4h}	T_{+6h}
Adsorption to placebo at pH 5.5	-17.7	-17.7	-19.5
Adsorption to PA21 at pH 5.5	-12.7	-11.3	-12.8
Adsorption to active compound of PA21 at pH 5.5	6.17	7.74	8.39

Table 12: Summary of Cinacalcet adsorption at pH 8.0

	<i>Sampling time</i>		
	T_{+2h}	T_{+4h}	T_{+6h}
Adsorption to placebo at pH 8.0	45.7	65.8	8.06
Adsorption to PA21 at pH 8.0	-64.7	-43.6	-38.0
Adsorption to active compound of PA21 at pH 8.0	-75.7	-66.0	-42.7

- The performance of the assay method during study sample analysis is acceptable. The inter-run relative standard deviations were ranging from 2.8 to 9.9% and accuracies were ranging from -0.1 to 3.8%.

Conclusions:

- There was no adsorption of cinacalcet to PA21/placebo at pH 3.0 and 5.5.
- The results observed at pH 8.0 are not inconclusive due to instability and low solubility.

Study STU-PA21DDI-B101529-001- (In vitro DDI-Levothyroxine)

Study Report # STU-PA21DDI-B101529-001

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Title: Investigation of possible interaction of Levothyroxine in aqueous alpha-amylase solution with PA21 by UPLC-MS/MS detection

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0. Three tablets of Eltroxin-LF (100 µg doxycycline/ tablet) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 0h, 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then analyzed by UPLC-MS/MS. The pH value of all solutions was controlled during the complete study.

Quantification of levothyroxine was performed by UPLC with mass tandem spectrometry detection.

The observed effects are considered as maximum interactions between PA21 and levothyroxine. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- Levothyroxine was found to be completely adsorbed by PA21 at pH 5.5. Significant adsorption was also observed at pH 3.0 (~85%) and pH 8.0 (~ 65%). Data below are percent difference of drug concentrations between test solution (PA21 placebo and PA21) and placebo solution (H₂O+ alpha-amylase).

Table 4: Summary of Levothyroxine adsorption at pH 3.0

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 3.0	13.5	15.4	15.0
Adsorption to PA21 at pH 3.0	-83.1	-85.3	-84.9
Adsorption to active compound of PA21 at pH 3.0	-85.1	-87.3	-86.9

Table 8: Summary of Levothyroxine adsorption at pH 5.5

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 5.5	-4.41	1.41	-1.46
Adsorption to PA21 at pH 5.5	-94.0	-95.8	-96.3
Adsorption to active compound of PA21 at pH 5.5	-93.8	-95.9	-96.2

Table 12: Summary of Levothyroxine adsorption at pH 8.0

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 8.0	-26.2	-16.9	-8.75
Adsorption to PA21 at pH 8.0	-66.0	-66.9	-66.9
Adsorption to active compound of PA21 at pH 8.0	-53.9	-60.1	-63.8

- The performance of the assay method during study sample analysis is acceptable. The inter-run relative standard deviations were ranging from 6.2 to 7.7% and accuracies were ranging from 2.3 to 2.7%.

Conclusions:

- Complete adsorption of levothyroxine to PA21 was observed at pH 5.5.
- At pH 3.0 and 8.0, ~ 85% and 65% adsorption of levothyroxine to PA21 were observed, respectively.

**Study STU-PA21DDI-B200713-001
(In vitro DDI-Levothyroxine+Phosphate)**

Study Report # STU-PA21DDI-B200713-001

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Title: Investigation of possible interaction of Levothyroxine with PA21 in phosphate buffer with alpha-amylase by UPLC-MS/MS detection

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or phosphate buffer+alpha amylase only. Phosphate concentration of 400 mg/L simulates an average dietary phosphate of 400 mg phosphorus per meal (i.e. 1200 mg daily) in patients with chronic kidney disease. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). Three tablets of Eltroxin-LF (100 µg doxycycline/ tablet) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken processed and measured by UPLC-MS/MS system. The pH value of all solutions was controlled during the complete study.

Quantification of levothyroxine involved separation by UPLC and detection by tandem MS.

Results

- In the presence of phosphate, levothyroxine has been found to be ~12% adsorbed by PA21 at pH 3.0; ~30% adsorption at pH 5.5 and no adsorption at pH 8.0. Data below are percent difference of drug concentrations between test solution (PA21 placebo and PA21) and placebo solution (phosphate buffer + alpha-amylase).

Table 5: Summary of Levothyroxine adsorption at pH 3.0

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 3.0	24.7	5.97	10.2
Adsorption to PA21 at pH 3.0	-3.49	-12.3	-12.4
Adsorption to active compound of PA21 at pH 3.0	-22.6	-17.2	-20.5

Table 9: Summary of Levothyroxine adsorption at pH 5.5

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 5.5	3.77	-1.05	5.11
Adsorption to PA21 at pH 5.5	-32.0	-32.2	-30.3
Adsorption to active compound of PA21 at pH 5.5	-34.5	-31.5	-33.7

Table 13: Summary of Levothyroxine adsorption at pH 8.0

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 8.0	-43.1	-34.8	-25.8
Adsorption to PA21 at pH 8.0	-3.37	-8.63	-4.34
Adsorption to active compound of PA21 at pH 8.0	69.8	40.1	28.9

- The performance of the assay method during study sample analysis is acceptable.

Conclusion:

- At the presence of phosphate, levothyroxine has been found to be (~12% adsorbed by PA21 at pH 3.0; ~30% adsorption at pH 5.5 and no adsorption at pH 8.0.

Study STU-PA21DDI-B101615-001 (In vitro DDI-Glipizide)

Study Report # STU-PA21DDI-B101615-001

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Title: Investigation of possible interaction of Glipizide in aqueous alpha-amylase solution with PA21 by UPLC-MS/MS detection

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). Three tablets of Glipizide (5 mg glipizide/ tablet) was added to each solution and incubated at 37°C for 6 hours. At

the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged, processed and then injected into the UPLC system with tandem mass detection. The pH value of all solutions was controlled during the complete study.

Quantification of glipizide involved a separation by UPLC with tandem mass spectrometry detection.

The observed effects are considered as maximum interactions between PA21 and glipizide. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- At pH 3.0 and 5.5, glipizide is not stable and the concentrations were very low due to low solubility. The results observed at pH 3.0 and 5.5 are considered inconclusive.
- Glipizide dissolved ~completely at pH 8.0 as the observed concentrations were close to expected. Glipizide showed no adsorption to PA21 at pH 8.0. Data below are percent difference of drug concentrations between test solution (PA21 placebo and PA21) and placebo solution (H₂O+ alpha-amylase).

Table 4: Summary of Glipizide adsorption at pH 3.0

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 3.0	-1.73	2.34	23.7
Adsorption to PA21 at pH 3.0	-9.43	-12.8	26.1
Adsorption to active compound of PA21 at pH 3.0	-7.83	-14.9	1.90

Table 8: Summary of Glipizide adsorption at pH 5.5

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 5.5	-4.06	-60.4	10.5
Adsorption to PA21 at pH 5.5	21.1	-50.2	45.3
Adsorption to active compound of PA21 at pH 5.5	26.3	25.6	31.5

Table 12: Summary of Glipizide adsorption at pH 8.0

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 8.0	-1.69	-3.15	2.44
Adsorption to PA21 at pH 8.0	0.171	6.26	8.58
Adsorption to active compound of PA21 at pH 8.0	1.90	9.71	5.99

- The performance of the assay method during study sample analysis is acceptable. The inter-run relative standard deviations were ranging from 0.8 to 2.0% and accuracies were ranging from

1.4 to 5.3%.

Conclusions:

- The results observed at pH 3.0 and 5.5 are not inconclusive due to instability and low solubility.
- There was no adsorption of glipizide to PA21/placebo at pH 8.0.

Study STU-PA21DDI-B101616-001 (In vitro DDI-Quinidine)

Study Report # STU-PA21DDI-B101616-001

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Title: Investigation of possible interaction of Quinidine in aqueous alpha-amylase solutions with PA21 by UPLC-MS/MS detection

Study Design: PA21/placebo was spread with a mortar before they were added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). Three tablets of Kiniduron (prolonged-release 200 mg quinidine sulphate tablet corresponding to 165.5 mg quinidine base per tablet) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken processed and measured by UPLC-MS/MS system. The pH value of all solutions was controlled during the complete study.

Quantification of quinidine involved separation by UPLC and detection by tandem MS.

The observed effects are considered as maximum interactions between PA21 and quinidine. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- No adsorption of quinidine by PA21 or PA21 placebo at all pH was observed. Data below are percent difference of drug concentrations between test solution (PA21 placebo and PA21) and placebo solution (H₂O+ alpha-amylase).

Table 4: Summary of Quinidine adsorption at pH 3.0

	<i>Sampling time</i>		
	<i>T+2h</i>	<i>T+4h</i>	<i>T+6h</i>
Adsorption to placebo at pH 3.0	1.94	1.68	-1.27
Adsorption to PA21 at pH 3.0	5.01	1.86	0.769
Adsorption to active compound of PA21 at pH 3.0	3.01	0.181	2.06

Table 8: Summary of Quinidine adsorption at pH 5.5

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 5.5	-4.94	-0.185	0.357
Adsorption to PA21 at pH 5.5	0.558	0.681	0.792
Adsorption to active compound of PA21 at pH 5.5	5.79	0.868	0.434

Table 12: Summary of Quinidine adsorption at pH 8.0

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 8.0	-2.25	-0.499	0.381
Adsorption to PA21 at pH 8.0	-3.99	-3.44	-2.95
Adsorption to active compound of PA21 at pH 8.0	-1.79	-2.95	-3.32

- The performance of the assay method during study sample analysis is acceptable.

Conclusion:

- Quinidine showed no adsorption on placebo or PA21 at any pH level tested.

Study STU-PA21DDI-B101617-001- (In vitro DDI-Alendronate)

Study Report # STU-PA21DDI-B101617-001

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Title: Investigation of possible interactions of Alendronate in aqueous alpha-amylase solution with PA21 by UPLC-FLR detection

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0. One tablet of Fosamax (70 mg alendronate/ tablet) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 0h, 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then analyzed by UPLC. The pH value of all solutions was controlled during the complete study.

Quantification of alendronate was performed by UPLC with fluorescence detection.

The observed effects are considered as maximum interactions between PA21 and alendronate. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- Alendronate showed a complete adsorption to PA21 at pH 3.0, 5.5 and 8.0. Data below are percent difference of drug concentrations between test solution (PA21 placebo and PA21) and placebo solution (H₂O+ alpha-amylase).

Table 4: Summary of Alendronate adsorption at pH 3.0

	<i>Sampling time</i>		
	T_{+2h}	T_{+4h}	T_{+6h}
Adsorption to placebo at pH 3.0	-8.99	-9.38	-11.3
Adsorption to PA21 at pH 3.0	-97.8	-98.8	-99.0
Adsorption to active compound of PA21 at pH 3.0	-97.6	-98.7	-98.9

Table 8: Summary of Alendronate adsorption at pH 5.5

	<i>Sampling time</i>		
	T_{+2h}	T_{+4h}	T_{+6h}
Adsorption to placebo at pH 5.5	-7.31	-5.16	-8.73
Adsorption to PA21 at pH 5.5	-100	-100	-100
Adsorption to active compound of PA21 at pH 5.5	-100	-100	-100

Table 12: Summary of Alendronate adsorption at pH 8.0

	<i>Sampling time</i>		
	T_{+2h}	T_{+4h}	T_{+6h}
Adsorption to placebo at pH 8.0	-6.02	-0.524	11.7
Adsorption to PA21 at pH 8.0	-99.1	-100	-100
Adsorption to active compound of PA21 at pH 8.0	-99.1	-100	-100

- The performance of the assay method during study sample analysis is acceptable. The inter-run relative standard deviations were ranging from 2.9 to 4.0% and accuracies were ranging from 0.6 to 4.6%.

Conclusions:

- Complete adsorption of alendronate to PA21 was observed at pH 3.0, 5.5 and 8.0.

Study (b) (4) **(In vitro DDI-Paricalcitol)**

Study Report # (b) (4)

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Title: Determination of possible interaction of paricalcitol in aqueous solutions with PA21 by LC-

MS/MS under GLP conditions

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). 20 mL of paricalcitol solution were added to each solution and mixed well to achieve a concentration of 32 ng/mL and incubated at 37°C for 6 hours. At the set time points of 0h, 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then analyzed by LC-MS/MS. The pH value of all solutions was controlled during the complete study.

Quantification of paricalcitol was performed by LC-MS/MS.

The observed effects are considered as maximum interactions between PA21 and paricalcitol. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- Paricalcitol showed a complete adsorption to PA21 at pH 3.0 and pH 5.5 (>93%) while ~30-75% adsorption were also observed with placebo.
- Paricalcitol was mostly adsorbed to PA21 at pH 8.0 (69-80%) while ~42-68% adsorption was also observed with placebo.

Table 13: Summary results of the concentrations of Paricalcitol in unknown aqueous solution samples

Theoretical pH value	Time point (h)	Mean aqueous solution [ng/mL] "1"	Mean aqueous solution containing placebo [ng/mL] "2"	Difference "2"/"1" (%)	Mean aqueous solution containing PA21 [ng/mL] "3"	Difference "3"/"1" (%)	Difference "3"/"2" (%)
pH 3.0	0	13.25	7.399	-44.2	0.743	-94.4	-90.0
	2	13.24	3.437	-74.0	blq	-97.6*	-90.7*
	4	9.321	3.636	-61.0	blq	-96.6*	-91.2*
	6	11.07	2.811	-74.6	blq	-97.1*	-88.6*
pH 5.5	0	2.779	6.619	138.2	2.000	-28.0	-69.8
	2	15.56	8.168	-47.5	blq	-97.9*	-96.1*
	4	15.45	10.42	-32.6	1.019	-93.4	-90.2
	6	16.42	8.126	-50.5	0.743	-95.5	-90.9
pH 8.0	0	11.03	8.108	-26.5	2.249	-79.6	-72.3
	2	9.759	5.577	-42.9	2.113	-78.3	-62.1
	4	19.17	6.079	-68.3	6.045	-68.5	-0.6
	6	20.83	6.684	-67.9	5.118	-75.4	-23.4

*: values were calculated assuming a concentration of 0.32 ng/mL (LLOQ) for "3", meaning that the true difference "3"/"1" and "3"/"2" are at least as pronounced as calculated.

Reviewer's note:

- *None of the concentrations were close to the expected level of 32 ng/mL during incubation at all pHs. The concentrations are ~35%-60% lower than expected in the aqueous solution. As paricalcitol was added as solution, target concentrations should be achieved. The sponsor stated this could be explained by the very low concentrations and possible adsorption to the glass bottle.*
- *To confirm the stability of paricalcitol in the solution, validation report, (b) (4) was reviewed. Based on the report, paricalcitol is stable in H₂O +alpha-amylase (0.1mg/mL) in the autosampler (4°C) for 8 days. At 37°C, concentrations for paricalcitol showed a decrease of 13.1%, 7.9% and 6.8% at pH 3, 5.5 and 8, respectively. However, this degree of degradation is still much lower than the observed 35-60%.*

The performance of the assay method during study sample analysis is acceptable.

Conclusions:

- Complete adsorption of paricalcitol to PA21 was observed at pH 3.0 and pH 5.5 (>93%) while the placebo also contributed to the adsorption.
- Good amount of adsorption of paricalcitol to PA21 was observed at pH 8.0 (69-80%) while the placebo also contributed to the adsorption.

**Study STU-PA21DDI-B200830-001
(In vitro DDI-Paricalcitol+Phosphate)****Study Report #** STU-PA21DDI-B200830-001

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Title: Investigation of possible interaction of Paricalcitol with PA21 in phosphate buffer with alpha-amylase by UPLC-MS/MS detection

Objectives: To assess the possible interaction between PA21 and Paricalcitol in the presence of phosphate by measuring the remaining concentration of the drug in phosphate solution obtained after incubation with PA21.

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or phosphate buffer+alpha amylase only. Phosphate concentration of 400 mg/L simulates an average dietary phosphate of 400 mg phosphorus per meal (i.e. 1200 mg daily) in patients with chronic kidney disease. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). 500 µL of parocalcitol solution (32 µg/mL) were added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken processed and measured by UPLC-MS/MS system. The pH value of all solutions was controlled during the complete study.

Quantification of paricalcitol involved separation by UPLC and detection by tandem MS.

Results

- In the presence of phosphate, paricalcitol was significantly adsorbed to PA21 at pH 3.0 (70-80%) and pH 5.5 (60-70%). At pH 8.0, a marked increase (75-160%) in solubility of paricalcitol was observed in the presence of PA21. Significant adsorption to placebo was also observed at pH 3.0 (55-70%), pH 5.5 (40-60%) and pH 8.0 (65-75%). Data below are percent difference of drug concentrations between test solution (PA21 placebo and PA21) and placebo solution (phosphate buffer+ alpha-amylase).

Table 4: Summary of Paricalcitol adsorption at pH 3.0

	<i>Sampling time</i>		
	<i>T+2h</i>	<i>T+4h</i>	<i>T+6h</i>
Adsorption to placebo at pH 3.0	-55.0	-62.3	-68.9
Adsorption to PA21 a pH 3.0	-71.8	-77.5	-70.7
Adsorption to active compound of PA21 at pH 3.0	-37.3	-40.5	-5.74

Table 8: Summary of Paricalcitol adsorption at pH 5.5

	<i>Sampling time</i>		
	<i>T+2h</i>	<i>T+4h</i>	<i>T+6h</i>
Adsorption to placebo at pH 5.5	-57.4	-48.1	-39.9
Adsorption to PA21 at pH 5.5	-62.0	-68.8	-64.7
Adsorption to active compound of PA21 at pH 5.5	-10.7	-39.9	-41.3

Table 12: Summary of Paricalcitol adsorption at pH 8.0

	<i>Sampling time</i>		
	<i>T+2h</i>	<i>T+4h</i>	<i>T+6h</i>
Adsorption to placebo at pH 8.0	-75.5	-64.6	-72.3
Adsorption to PA21 at pH 8.0	158	113	76.7
Adsorption to active compound of PA21 at pH 8.0	952	501	538

Reviewer's note:

- *The observed data showed that placebo itself binds paricalcitol at all pHs suggesting the ingredient(s) in the PA21 formulation play a significant role in binding paricalcitol.*
- *The reason for increased solubility of paricalcitol at pH 8.0 when PA21 is presence is not clear.*
- *While in the study, there are indications of instability of paricalcitol at pH 3.0 and 5.5, the stability data in the validation report indicated that paricalcitol is stable in phosphate buffer + α -amylase [0.1 mg/mL] at pH 3.0, 5.5 and 8.0 at room temperature for at least 6 hours. The only difference is the incubation temperature of 37°C in this study.*
- *The performance of the assay method during study sample analysis is acceptable. The inter-run relative standard deviations were ranging from 2.6 to 8.1% and accuracies were ranging from -3.3 to 0.8%.*

Conclusion:

- *At the presence of phosphate, paricalcitol was significantly adsorbed to PA21 at pH 3.0 (70-80%) and pH 5.5 (60-70%). At pH 8.0, a marked increase (75-160%) in solubility of Paricalcitol was observed in the presence of PA21. Significant adsorption to placebo was also observed at pH 3.0 (55-70%), pH 5.5 (40-60%) and pH 8.0 (65-75%).*

Reviewer's comment:

- *High binding of paricalcitol by PA21 or PA21 placebo was seen in the absence as well as in the presence of phosphate in the in vitro studies. While there are some in vitro observations that cannot be explained and no clinical data is available to evaluate the potential drug interaction because majority of the patients in the Phase III study received paricalcitol as an I.V. administration, it is recommended to use alternate route or choose alternate phosphate binder when co-administered with vitamin D analogs is necessary.*

Study (b) (4) **(In vitro DDI-Atorvastatin)**

Study Report # (b) (4)

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(b) (4)-pre-clinical-study-report.pdf

Title: Determination of possible interaction of atorvastatin in aqueous solutions with PA21 by HPLC UV detection under GLP conditions

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). One tablet of Sotris mg (80 mg atorvastatin) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then an aliquot (50 µl) of each solution was injected into the HPLC system. The pH value of all solutions was controlled during the complete study.

Quantification of atorvastatin was performed by HPLC with UV detection.

The observed effects are considered as maximum interactions between PA21 and atorvastatin. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- Atorvastatin showed a complete adsorption to PA21 at pH 3.0 and pH 5.5 (>95%).
- No adsorption of atorvastatin to PA21 at pH 8.0 was observed.
- At pH 8.0 atorvastatin showed a slightly increased solubility in the presence of PA21 (20-25%) and, to some extent, placebo (about 10%) when compared to the aqueous solution without PA21 and placebo.

Table 10: Summary results of the concentrations of Atorvastatin in unknown aqueous solution samples

Theoretical pH value	Time point [h]	Mean aqueous solution [µg/mL] "1"	Mean aqueous solution containing placebo [µg/mL] "2"	Difference "2"/"1" [%]	Mean aqueous solution containing PA21 [µg/mL] "3"	Difference "3"/"1" [%]	Difference "3"/"2" [%]
pH 3.0	0	23.5	6.15	-73.8	1.23	-94.8	-80.0
	2	28.9	26.9	-6.9	blq	-98.3*	-98.1*
	4	26.5	19.0	-28.3	blq	-98.1*	-97.4*
	6	26.3	23.7	-9.9	blq	-98.1*	-97.9*
pH 5.5	0	48.6	47.9	-1.4	12.3	-74.7	-74.3
	2	50.6	49.5	-2.2	1.87	-96.3	-96.2
	4	50.4	49.1	-2.6	1.09	-97.8	-97.8
	6	49.7	47.8	-3.8	0.798	-98.4	-98.3
pH 8.0	0	64.0	1.57	-97.5	54.6	-14.7	3377.7
	2	64.9	73.1	12.6	79.9	23.1	9.3
	4	66.4	73.4	10.5	81.5	22.7	11.0
	6	67.3	72.9	8.3	81.5	21.1	11.8

*: values were calculated assuming a concentration of 0.500 µg/mL (LLOQ) for "3", meaning that the true difference "3"/"1" and "3"/"2" are at least as pronounced as calculated

- The performance of the assay method during study sample analysis is acceptable.

Reviewer's note: No explanation was provided for the increased solubility in the presence of PA21 at pH 8.0.

Conclusions:

- Complete adsorption of atorvastatin to PA21 was observed at pH 3.0 and pH 5.5.
- There was no adsorption of atorvastatin to PA21 at pH 8.0.
- At pH 8.0 atorvastatin showed a slightly increased solubility in the presence of PA21 (20-25%) and, to some extent, placebo (about 10%) when compared to the aqueous solution without PA21 and placebo.

**Study STU-PA21DDI-B201319-001
(In vitro DDI-Atorvastatin+Phosphate)**

Study Report # STU-PA21DDI-B201319-001

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Title: Investigation of possible interaction of Atorvastatin with PA21 in phosphate buffer with alpha-amylase by UPLC-MS/MS detection

Objectives: To assess the possible interaction between PA21 and Atorvastatin in the presence of phosphate by measuring the remaining concentration of the drug in phosphate solution obtained after incubation with PA21.

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or phosphate

buffer+alpha amylase only. Phosphate concentration of 400 mg/L simulates an average dietary phosphate of 400 mg phosphorus per meal (i.e. 1200 mg daily) in patients with chronic kidney disease. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). One tablet of Sortis (80 mg atorvastatin) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken processed and measured by UPLC-MS/MS system. The pH value of all solutions was controlled during the complete study.

Quantification of atorvastatin involved separation by UPLC and detection by tandem MS.

Results

- Atorvastatin concentrations at pH 3.0 did not exceed 25% of the expected concentration and were variable during the incubation. 28% and 21% adsorption were observed after 2 hour and 4 hour incubation, respectively, but no adsorption was observed after 6 hour incubation.
- No adsorption of atorvastatin by PA21 or PA21 placebo at pH 5.5 and pH 8.0 was observed. Data below are percent difference of atorvastatin concentrations between test solution (PA21 placebo or PA21) and placebo solution (Phosphate buffer+ alpha-amylase).

Table 4: Summary of Atorvastatin adsorption at pH 3.0

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 3.0	-11.5	19.8	7.60
Adsorption to PA21 at pH 3.0	-36.5	-5.72	2.11
Adsorption to active compound of PA21 at pH 3.0	-28.2	-21.3	-5.10

Table 8: Summary of Atorvastatin adsorption at pH 5.5

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 5.5	31.6	-1.30	15.7
Adsorption to PA21 at pH 5.5	33.7	5.10	13.6
Adsorption to active compound of PA21 at pH 5.5	1.67	6.49	-1.75

Table 12: Summary of Atorvastatin adsorption at pH 8.0

	<i>Sampling time</i>		
	T+2h	T+4h	T+6h
Adsorption to placebo at pH 8.0	5.14	-10.9	-3.06
Adsorption to PA21 at pH 8.0	-0.366	-4.46	-3.77
Adsorption to active compound of PA21 at pH 8.0	-5.23	7.18	-0.736

- The performance of the assay method during study sample analysis is acceptable. For each pH the inter-run relative standard deviations were ranging from 3.1 to 6.3% and accuracies were ranging from -1.6 to 3.9%.

Conclusion:

- At pH 3.0, atorvastatin showed 20-30% adsorption early during the incubation (2-4 hours) in the presence of phosphate, however with wide variability.
- Atorvastatin showed no adsorption to placebo or PA21 at pH 5.5 and pH 8.0 when phosphate is present.

Study [REDACTED] (In vitro DDI-Hydrochlorothiazide)**Study Report # [REDACTED]**

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[REDACTED]-pre-clinical-study-report.pdf

Title: Determination of possible interaction of Hydrochlorothiazide in aqueous solutions with PA21 by HPLC UV detection under GLP conditions

Study Design: PA21/placebo was spread with a mortar before they were added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). Four tablets of Esidrex (hydrochlorothiazine 100 mg) were added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then an aliquot (10 µl) of each solution was injected into the HPLC system. The pH value of all solutions was controlled during the complete study.

Quantification of hydrochlorothiazine was performed by HPLC with UV detection.

The observed effects are considered as maximum interactions between PA21 and hydrochlorothiazine. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- No adsorption of hydrochlorothiazine to PA21 or PA21 placebo at all pH was observed.

Table 10: Summary results of the concentrations of Hydrochlorothiazide in unknown aqueous solution samples

Theoretical pH value	Time point [h]	Mean aqueous solution [µg/mL] "1"	Mean aqueous solution containing placebo [µg/mL] "2"	Difference "2"/"1" [%]	Mean aqueous solution containing PA21 [µg/mL] "3"	Difference "3"/"1" [%]	Difference "3"/"2" [%]
pH 3.0	0	blq	1.67	n.a.	1.05	n.a.	-37
	2	95.8	91.0	-5.0	89.7	-6.4	-1.4
	4	96.9	96.0	-0.9	94.8	-2.2	-1.3
	6	97.4	96.8	-0.6	96.6	-0.8	-0.2
pH 5.5	0	30.7	30.7	0.0	65.3	112.7	112.7
	2	98.6	97.1	-1.5	96.7	-1.9	-0.4
	4	97.3	97.2	-0.1	96.3	-1.0	-0.9
	6	97.3	96.1	-1.2	95.5	-1.8	-0.6
pH 8.0	0	46.8	15.7	-66.5	7.04	-85.0	-55
	2	95.9	95.7	-0.2	96.6	0.7	0.9
	4	93.3	93.8	0.5	94.5	1.3	0.7
	6	93.1	92.7	-0.4	93.5	0.4	0.9

n.a.: not applicable

- The performance of the assay method during study sample analysis is acceptable.

Conclusions:

- Hydrochlorothiazide showed no adsorption on placebo or PA21 at any pH level.

Study (b) (4) (In vitro DDI-Metformin)

Study Report # (b) (4)

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 (b) (4)-pre-clinical-study-report.pdf

Title: Determination of possible interaction of Metformin in aqueous solutions with PA21 by HPLC UV detection under GLP conditions

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). One tablet of Metfin 1000 (1000 mg Metformin hydrochloride corresponding to 780 mg Metformin) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then an aliquot (10 µl) of each solution was injected into the HPLC system. The pH value of all solutions was controlled during the complete study.

Quantification of metformin was performed by HPLC with UV detection.

The observed effects are considered as maximum interactions between PA21 and metformin. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- No adsorption of metformin by PA21 or PA21 placebo at all pH was observed.

Table 13: Summary results of the concentrations of Metformin in unknown aqueous solution samples

Theoretical pH value	Time point [h]	Mean aqueous solution "1" [µg/mL]	Mean aqueous solution containing placebo "2" [µg/mL]	Difference "2"/"1" [%]	Mean aqueous solution containing PA21 "3" [µg/mL]	Difference "3"/"1" [%]	Difference "3"/"2" [%]
pH 3.0	0	blq	27.5	n.a.	blq	n.a.	n.a.
	2	794	781	-1.6	784	-1.3	0.4
	4	788	779	-1.1	784	-0.5	0.6
	6	786	775	-1.4	776	-1.3	0.1
pH 5.5	0	49.4	135	173.3	320	547.8	137.0
	2	760	789	3.8	769	1.2	-2.5
	4	763	791	3.7	771	1.0	-2.5
	6	761	785	3.2	770	1.2	-1.9
pH 8.0	0	18.7	245	1210.2	blq	n.a.	n.a.
	2	765	765	0.0	754	-1.4	-1.4
	4	761	755	-0.8	746	-2.0	-1.2
	6	760	759	-0.1	743	-2.2	-2.1

n.a.: not applicable

- The performance of the assay method during study sample analysis is acceptable.

Conclusions:

- Metformin showed no adsorption on placebo or PA21 at any pH level.

Study (b) (4) (In vitro DDI-Candesartan Cilexetil)

Study Report # (b) (4)

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 (b) (4)-pre-clinical-study-report.pdf

Title: Determination of possible interactions of candesartan cilexetil in aqueous solutions with PA21 by HPLC UV detection under GLP conditions

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). One tablet of Atacand (32 mg candesartan cilexetil) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then an aliquot (50 µl) of each solution was injected into the HPLC system. The pH value of all solutions was controlled during the complete study.

Quantification of candesartan cilexetil was performed by HPLC with UV detection.

The observed effects are considered as maximum interactions between PA21 and candesartan cilexetil. The study was done in absence of phosphate or nutritional components being competitive

for adsorption on PA21.

Results

- All samples were below LOQ (due to poor dissolution of the tablets). Adsorption of candesartan cilexetil to PA21 or placebo could not be assessed.

Table 10: Summary results of the concentrations of candesartan cilexetil in unknown aqueous solution samples

Theoretical pH value	Time point [h]	Mean aqueous solution [µg/mL] "1"	Mean aqueous solution containing placebo [µg/mL] "2"	Difference "2"/"1" [%] "A"	Mean aqueous solution containing PA21 [µg/mL] "3"	Difference "3"/"1" [%] "B"	Difference "B"/"A" [%]
pH 3.0	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	blq	blq	n.a.	blq	n.a.	n.a.
	6	blq	blq	n.a.	blq	n.a.	n.a.
pH 5.5	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	blq	blq	n.a.	blq	n.a.	n.a.
	6	blq	blq	n.a.	blq	n.a.	n.a.
pH 8.0	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	blq	blq	n.a.	blq	n.a.	n.a.
	6	blq	blq	n.a.	blq	n.a.	n.a.

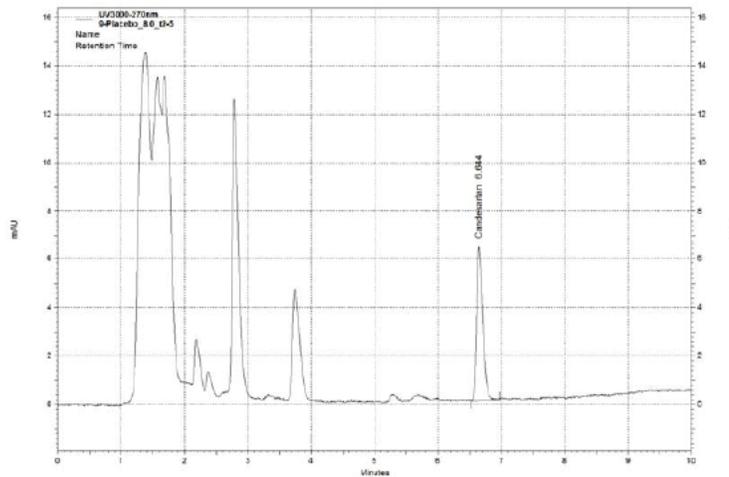
n.a.: not applicable

- The performance of the assay method during study sample analysis is acceptable and is summarized below.

Candesartan cilexetil Concentration of quality control samples [µg/mL]	Number of valid quality control samples	Inter-assay precision (CV%)	Inter-assay accuracy (%)
QC _{low} 14.0	12	1.4	103.6
QC _{medium} 30.0	12	1.7	100.0
QC _{high} 45.0	12	1.1	100.9

Reviewer's Note: Although based on the sponsor all the concentrations are below LOQ, it seems that there is actual peak with very clear baseline(chromatography below for an unknown sample) suggesting detection of candesartan cilexetil concentrations could be feasible with proper adjustment of the analytical method and calibration range if deemed necessary.

Figure 7: Sample of unknown aqueous solution sample containing placebo at pH 8.0, t2-5, with back calculated concentration for candesartan cilexetil: blq, analyzed on August 24, 2011



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Conclusions:

- No conclusion could be made as to whether or not candesartan cilexetil is adsorbed to PA21 due to low aqueous solubility of candesartan cilexetil across the physiological pH range.

Study (b) (4) (In vitro DDI-Pioglitazone)

Study Report # (b) (4)

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(b) (4)-pre-clinical-study-report.pdf

Title: Determination of possible interaction of pioglitazone in aqueous solutions with PA21 by HPLC UV detection under GLP conditions

Study Design: PA21/placebo was spread with a mortar before they were added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). One tablet of Actos 45 mg (45 mg pioglitazone) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then an aliquot (50 µl) of each solution was injected into the HPLC system. The pH value of all solutions was controlled during the complete study.

Quantification of pioglitazone was performed by HPLC with UV detection.

The observed effects are considered as maximum interactions between PA21 and pioglitazone. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- At pH 3.0 and 5.5, concentrations of Pioglitazone were slightly reduced (20 – 35%) in the presence of PA21 and placebo suggesting some adsorption of Pioglitazone to PA21. This

effect was marginal at pH 3.0 (about 10%). This finding suggests that Pioglitazone is not adsorbed to the active compound of PA21 but rather to other components of the tablet

- At pH 8.0 Pioglitazone showed a slightly to moderately increased solubility in the presence of PA21 (15 - 40%) when compared to the aqueous solution without PA21 and placebo.

Table 9: Summary results of the concentrations of Pioglitazone in unknown aqueous solution samples

Theoretical pH value	Time point [h]	Mean aqueous solution [µg/mL] "1"	Mean aqueous solution containing placebo [µg/mL] "2"	Difference "2"/"1" [%]	Mean aqueous solution containing PA21 [µg/mL] "3"	Difference "3"/"1" [%]	Difference "3"/"2" [%]
pH 3.0	0	0.326	0.322	-1.2	blq	n.a.	n.a.
	2	40.5	35.5	-12.3	35.7	-11.9	0.6
	4	41.1	35.4	-13.9	37.9	-7.8	7.1
	6	41.2	35.5	-13.8	37.3	-9.5	5.1
pH 5.5	0	0.361	2.77	667.3	1.39	285.0	-49.8
	2	22.0	17.0	-22.7	15.2	-30.9	-10.6
	4	21.5	17.8	-17.2	14.1	-34.4	-20.8
	6	28.7	19.9	-30.7	22.0	-23.3	10.6
pH 8.0	0	9.53	8.63	-9.4	0.373	-96.1	-95.7
	2	24.0	24.6	2.5	32.2	34.2	30.9
	4	23.7	23.8	0.4	33.0	39.2	38.7
	6	24.8	20.4	-17.7	29.2	17.7	43.1

n.a.: not applicable

- The performance of the assay method during study sample analysis is acceptable.

Reviewer's note: No explanation was provided for the increased solubility in the presence of PA21 at pH 8.0.

Conclusions:

- Marginal to slight adsorption (10-30%) of Pioglitazone to PA21 and placebo was seen at pH 3.0 and pH 5.5 suggesting that Pioglitazone is not adsorbed to the active compound of PA21 but rather to other components of the tablet.
- There was no adsorption of pioglitazone to PA21 at pH 8.0.
- Pioglitazone showed a slight to moderate increased solubility in the presence of PA21.

Study (b) (4) (In vitro DDI-Ciprofloxacin)

Study Report # (b) (4)

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(b) (4)-pre-clinical-study-report.pdf

Title: Determination of possible interactions of ciprofloxacin in aqueous solutions with PA21 by HPLC UV detection under GLP conditions

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase

only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). One tablet of Ciproxin 750 (750 mg ciprofloxacin) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then an aliquot (5 µl) of each solution was injected into the HPLC system. The pH value of all solutions was controlled during the complete study.

Quantification of ciprofloxacin was performed by HPLC with UV detection.

The observed effects are considered as maximum interactions between PA21 and ciprofloxacin. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- Ciprofloxacin showed no adsorption to PA21 at pH 3.0 and 8.0. At pH 5.5 the analyte showed slight adsorption to PA21 as suggested by a decreased concentration of around 24-27%.

Table 10: Summary results of the concentrations of ciprofloxacin in unknown aqueous solution samples

Theoretical pH value	Time point [h]	Mean aqueous solution [µg/mL] "1"	Mean aqueous solution containing placebo [µg/mL] "2"	Difference "2"/"1" [%]	Mean aqueous solution containing PA21 [µg/mL] "3"	Difference "3"/"1" [%]	Difference "3"/"2" [%]
pH 3.0	0	35.6	90.8	155.1	25.4	-28.7	-72.0
	2	662	688	3.9	619	-6.5	-10.0
	4	655	688	5.0	621	-5.2	-9.7
	6	650	689	6.0	611	-6.0	-11.3
pH 5.5	0	674	668	-0.9	548	-18.7	-18.0
	2	669	667	-0.3	503	-24.8	-24.6
	4	670	667	-0.4	497	-25.8	-25.5
	6	667	660	-1.0	490	-26.5	-25.8
pH 8.0	0	213	363	70.4	296	39.0	-18.5
	2	191	207	8.4	183	-4.2	-11.6
	4	174	176	1.1	165	-5.2	-6.3
	6	183	184	0.5	164	-10.4	-10.9

- The performance of the assay method during study sample analysis is acceptable.

Conclusions:

- There was no adsorption of ciprofloxacin to PA21 at pH 3.0 and 8.0.
- Slight adsorption on PA21 was observed at the pH level of 5.5 where the analyte concentration decreased by around 25%.

Study (b) (4) (In vitro DDI-Enalapril)

Study Report # (b) (4)

\\cdsesub1\evsprod\nda205109\0000\m4\42-stud-rep\421-pharmacol\4214-pd-drug-interact (b) (4)
 (b) (4)-pre-clinical-study-report.pdf

Title: Determination of possible interaction of enalapril in aqueous solutions with PA21 by HPLC UV detection under GLP conditions

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). One tablet of Reniten (20 mg enalapril maleate, corresponding to 15.28 mg enalapril) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then an aliquot (25 µl) of each solution was injected into the HPLC system. The pH value of all solutions was controlled during the complete study.

Quantification of enalapril and enalaprilat was performed by HPLC with UV detection.

The observed effects are considered as maximum interactions between PA21 and enalapril and/or enalaprilat. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- No adsorption of enalapril by PA21 or PA21 placebo at all pH was observed. No enalaprilat was formed during the incubation.

Table 12: Summary results of the concentrations of enalapril in unknown aqueous solution samples

Theoretical pH value	Time point [h]	Mean aqueous solution "1" [µg/mL]	Mean aqueous solution containing placebo "2" [µg/mL]	Difference "2"/"1" [%]	Mean aqueous solution containing PA21 "3" [µg/mL]	Difference "3"/"1" [%]	Difference "3"/"2" [%]
pH 3.0	0	11.8	10.9	-7.6	10.4	-11.9	-4.6
	2	15.7	15.8	0.6	15.2	-3.2	-3.8
	4	15.9	15.5	-2.5	14.6	-8.2	-5.8
	6	15.6	15.4	-1.3	14.1	-9.6	-8.4
pH 5.5	0	5.87	7.34	25.0	6.49	10.6	-11.6
	2	15.5	16.6	7.1	15.0	-3.2	-9.6
	4	15.5	16.6	7.1	14.4	-7.1	-13.3
	6	15.4	16.5	7.1	13.9	-9.7	-15.8
pH 8.0	0	8.12	7.29	-10.2	6.31	-22.3	-13.4
	2	16.8	16.7	-0.6	16.3	-3.0	-2.4
	4	16.6	16.5	-0.6	16.2	-2.4	-1.8
	6	16.5	16.4	-0.6	16.2	-1.8	-1.2

Table 16: Summary results of the concentrations of enalaprilat in unknown aqueous solution samples

Theoretical pH value	Time point [h]	Mean aqueous solution [µg/mL] "1"	Mean aqueous solution containing placebo [µg/mL] "2"	Difference "2"/"1" [%]	Mean aqueous solution containing PA21 [µg/mL] "3"	Difference "3"/"1" [%]	Difference "3"/"2" [%]
pH 3.0	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	blq	blq	n.a.	blq	n.a.	n.a.
	6	blq	blq	n.a.	blq	n.a.	n.a.
pH 5.5	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	blq	blq	n.a.	blq	n.a.	n.a.
	6	blq	blq	n.a.	blq	n.a.	n.a.
pH 8.0	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	blq	blq	n.a.	blq	n.a.	n.a.
	6	blq	blq	n.a.	blq	n.a.	n.a.

n.a.: not applicable

- The performance of the assay method for enalapril and enalaprilat during study sample analysis is acceptable.

Conclusions:

- Enalapril showed no adsorption on placebo or PA21 at any pH level.

Study (b) (4) (In vitro DDI-Metoprolol)

Study Report # (b) (4)

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 (b) (4)-pre-clinical-study-report.pdf

Title: Determination of possible interaction of metoprolol in aqueous solutions with PA21 by HPLC UV detection under GLP conditions

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). One tablet of Lopresor 100 (100 mg metoprolol tartrate, corresponding to 78.1 mg metoprolol) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then an aliquot (25 µl) of each solution was injected into the HPLC system. The pH value of all solutions was controlled during the complete study.

Quantification of metoprolol was performed by HPLC with UV detection.

The observed effects are considered as maximum interactions between PA21 and metoprolol. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- No adsorption of metoprolol by PA21 or PA21 placebo at pH 3.0 and 5.5 was observed. At pH 8.0 concentrations of metoprolol were decreased by 14–15%.

Table 10: Summary results of the concentrations of metoprolol in unknown aqueous solution samples

Theoretical pH value	Time point [h]	Mean aqueous solution [µg/mL] "1"	Mean aqueous solution containing placebo [µg/mL] "2"	Difference "2"/"1" [%]	Mean aqueous solution containing PA21 [µg/mL] "3"	Difference "3"/"1" [%]	Difference "3"/"2" [%]
pH 3.0	0	1.42	4.07	186.6	5.99	321.8	47.2
	2	97.9	97.0	-0.9	94.3	-3.7	-2.8
	4	97.7	98.3	0.6	98.4	0.7	0.1
	6	97.3	98.0	0.7	99.1	1.8	1.1
pH 5.5	0	1.98	5.93	199.5	6.02	204.0	1.5
	2	98.4	98.4	0.0	98.0	-0.4	-0.4
	4	96.6	97.1	0.5	96.1	-0.5	-1.0
	6	97.8	96.5	-1.3	97.1	-0.7	0.6
pH 8.0	0	14.9	8.35	-44.0	3.86	-74.1	-53.8
	2	109	107	-1.8	94.1	-13.7	-12.1
	4	107	106	-0.9	92.6	-13.5	-12.6
	6	108	105	-2.8	90.9	-15.8	-13.4

- The performance of the assay method during study sample analysis is acceptable.

Reviewer's Note: The concentrations in the unknown samples were higher than expected. While the expected concentration should be ~78 µL/mL based on the strength (78mg/1000mL), the measured concentrations appeared to be > 95 µL/mL to 108 µL/mL. No explanations were provided although an additional run was conducted to confirm the results (results not provided). No organic solvents were used in the solutions or in preparing the stock solution which could cause concentration shift if evaporated. The calibration curves and QCs appear to be acceptable. This unexplained finding did not affect the conclusion of the study.

Conclusions:

- Metoprolol showed no adsorption to PA21 at pH 3.0 and 5.5. Marginal adsorption on PA21 was observed at pH 8.0 where the analyte concentration decreased by around 15%.

Study (b) (4) (In vitro DDI-Nifedipine)

Study Report # (b) (4)

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 (b) (4)-pre-clinical-study-report.pdf

Title: Determination of possible interactions of nifedipine in aqueous solutions with PA21 by HPLC UV detection under GLP conditions

Study Design: PA21/placebo was spread with a mortar before they were added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase

only. The pH values were then set to the designated levels (pH 3.0, 5.5 and 8.0). One tablet of Adalat CR (60 mg nifedipine) was added to each solution and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged and then an aliquot (10 µl) of each solution was injected into the HPLC system. The pH value of all solutions was controlled during the complete study.

Quantification of nifedipine was performed by HPLC with UV detection.

The observed effects are considered as maximum interactions between PA21 and nifedipine. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- Nifedipine showed no adsorption to PA21 at pH 3.0 and 5.5.
- At pH 8.0 the analyte showed slight adsorption to PA21 and placebo as suggested by a decreased concentration of around 20-30%. The data suggest that nifedipine is not adsorbed to the active compound of PA21 but rather to other components of the tablet.

Table 10: Summary results of the concentrations of nifedipine in unknown aqueous solution samples

Theoretical pH value	Time point [h]	Mean aqueous solution [µg/mL] "1"	Mean aqueous solution containing placebo [µg/mL] "2"	Difference "2"/"1" [%]	Mean aqueous solution containing PA21 [µg/mL] "3"	Difference "3"/"1" [%]	Difference "3"/"2" [%]
pH 3.0	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	2.41	2.07*	-14.1	2.21	-8.3	6.8
	6	4.28	3.60	-15.9	3.83	-10.5	6.4
pH 5.5	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	3.23	3.23	0.0	3.09	-4.3	-4.3
	6	4.83	4.40	-8.9	4.11	-14.9	-6.6
pH 8.0	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	2.84	1.99	-29.9	1.95	-31.3	-2.0
	6	5.27	4.17	-20.9	4.24	-19.5	1.7

n.a.: not applicable

*: Mean out of 3 results and not out of 6 results.

- The performance of the assay method during study sample analysis is acceptable.

Conclusions:

- There was no adsorption of nifedipine to PA21 at pH 3.0 and 5.5.
- Slight adsorption to both PA21 and placebo was observed at the pH 8.0 where the analyte concentration decreased by around 20-30% suggesting that nifedipine is not adsorbed to the active compound of PA21 but rather to other components of the tablet.

Study (b) (4) (In vitro DDI-Bile Acids)

Study Report # (b) (4)

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(b) (4)-pre-clinical-study-report.pdf

Title: Determination of possible interactions of the bile acids Cholylglycine, Chenodeoxycholylglycine and Deoxycholyltaurine in aqueous solutions with PA21 by HPLC UV detection under GLP conditions

Study Design: PA21/placebo was spread with a mortar before they were be added to the different solutions to generate three types of solutions containing PA21, PA21 placebo or alpha amylase only. The pH values were then set to the designated levels (pH 5.5 and 8.0). 1.68 g of Sodium glycocholate hydrate, 1.57 g of Sodium glycochenodeoxycholate and 0.58 g of Sodium taurodeoxycholate hydrate were added to each solution in order to achieve a concentration of 6.43 mM for Cholylglycine and Chenodeoxycholylglycine and 2.14 mM for Deoxycholyltaurine (i.e. 15 mM for total bile acids) and incubated at 37°C for 6 hours. At the set time points of 2h, 4h and 6h, an aliquot of each sample was taken, centrifuged, diluted and then an aliquot (10 µl) of each solution was injected into the HPLC system. The pH value of all solutions was controlled during the complete study.

Quantification of Cholylglycine, Chenodeoxycholylglycine and Deoxycholyltaurine was performed by HPLC with UV detection.

The observed effects are considered as maximum interactions between PA21 and Cholylglycine, Chenodeoxycholylglycine and Deoxycholyltaurine. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- At pH 5.5 and 8.0 Cholylglycine and Deoxycholyltaurine showed no adsorption to PA21 or placebo.
- At pH 5.5 and 8.0 Chenodeoxycholylglycine showed no adsorption to placebo but some marginal adsorption to PA21 as suggested by a $\leq 15\%$ decrease in concentration.

Table 14: Summary results of the concentrations of Cholylglycine in generated test samples

Theoretical pH value	Time point (hours)	Mean aqueous solution [µg/mL] "1"	Mean aqueous solution containing placebo [µg/mL] "2"	Mean aqueous solution containing PA21 [µg/mL] "3"	Difference "2"/"1" (%)	Difference "3"/"1" (%)	Difference "3"/"2" (%)
pH 5.5	0	3114	3089	2971	-0.8	-4.6	-3.8
	2	3107	3129	2971	0.7	-4.4	-5.0
	4	3130	3145	2971	0.5	-5.1	-5.5
	6	3165	3171	2997	0.2	-5.3	-5.5
pH 8.0	0	3124	3097	3051	-0.9	-2.3	-1.5
	2	3116	3100	3026	-0.5	-2.9	-2.4
	4	3111	3104	3014	-0.2	-3.1	-2.9
	6	3120	3111	3024	-0.3	-3.1	-2.8

Table 18: Summary results of the concentrations of Chenodeoxycholyglycine in generated test samples

Theoretical pH value	Time point (hours)	Mean aqueous solution "1" [$\mu\text{g/mL}$]	Mean aqueous solution containing placebo "2" [$\mu\text{g/mL}$]	Mean aqueous solution containing PA21 "3" [$\mu\text{g/mL}$]	Difference "2"/"1" (%)	Difference "3"/"1" (%)	Difference "3"/"2" (%)
pH 5.5	0	2986	2946	2645	-1.3	-11.4	-10.2
	2	2967	2954	2565	-0.4	-13.5	-13.2
	4	3006	2983	2561	-0.8	-14.8	-14.1
	6	3048	3012	2581	-1.2	-15.3	-14.3
pH 8.0	0	2957	2919	2708	-1.3	-8.4	-7.2
	2	2938	2908	2607	-1.0	-11.3	-10.4
	4	2924	2899	2567	-0.9	-12.2	-11.5
	6	2931	2893	2563	-1.3	-12.6	-11.4

Table 22: Summary results of the concentrations of Deoxycholytaurine in generated test samples

Theoretical pH value	Time point (hours)	Mean aqueous solution "1" [$\mu\text{g/mL}$]	Mean aqueous solution containing placebo "2" [$\mu\text{g/mL}$]	Mean aqueous solution containing PA21 "3" [$\mu\text{g/mL}$]	Difference "2"/"1" (%)	Difference "3"/"1" (%)	Difference "3"/"2" (%)
pH 5.5	0	1044	1039	1003	-0.5	-3.9	-3.5
	2	1048	1054	1013	0.6	-3.3	-3.9
	4	1065	1069	1018	0.4	-4.4	-4.8
	6	1085	1087	1037	0.2	-4.4	-4.6
pH 8.0	0	1044	1041	1027	-0.3	-1.6	-1.3
	2	1043	1048	1022	0.5	-2.0	-2.5
	4	1037	1043	1014	0.6	-2.2	-2.8
	6	1040	1043	1018	0.3	-2.1	-2.4

- The performance of the assay method during study sample analyses is acceptable.

Conclusions:

- There was no adsorption of Cholyglycine and Deoxycholytaurine to PA21 at pH 5.5 and 8.0.
- Slight adsorption on PA21 was observed for Chenodeoxycholyglycine at the pH 5.5 (11-15%) and 8.0 (8-13%).

Study (b) (4) **(In vitro DDI)**

Study Report # (b) (4)

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 (b) (4)-pre-clinical-study-report.pdf

Title: Determination of possible interactions of ciprofloxacin, digoxin, enalapril, furosemide, losartan, metoprolol, nifedipine, omeprazole and warfarin with PA21 by HPLC detection under GLP conditions

Objectives: To assess the possible interaction between PA21 and ciprofloxacin, digoxin, enalapril and its metabolite enalaprilate, furosemide, losartan, metoprolol, nifedipine, omeprazole and warfarin by measuring the remaining concentrations of these drugs in aqueous samples.

Study Design: Tablets of the different compounds were incubated for the time points 2h, 4h and 6h in aqueous solutions containing PA21, PA21 placebo or only alpha amylase at pH 3.0, 5.5 and 8.0. The pH value of all solutions was controlled during the complete study. PA21/placebo was spread with a mortar before they were added to the different solutions. The samples were temperatured at 37°C ± 1°C. At the set time points an aliquot of each sample was taken, centrifuged and then an aliquot of each solution (5-200 µl, depending on the analyte concentration) was injected into the HPLC system.

Quantification of the analytes ciprofloxacin, digoxin, enalapril, enalaprilate, furosemide, losartan, metoprolol, nifedipine, omeprazole and warfarin was performed by HPLC with UV detection.

The observed effects are considered as maximum interactions between PA21 and the drugs investigated. The study was done in absence of phosphate or nutritional components being competitive for adsorption on PA21.

Results

- The performance of the assay method during study sample analyses is acceptable for all the studied drugs.
- Digoxin showed < 23% adsorption on PA21 at pH 3 and 5.5 after 4 to 6h but not at placebo. At pH 8, digoxin showed no adsorption on PA21.

Table 64: Summary results of the concentrations of digoxin in unknown aqueous solution samples from study VIT01 (part one).

theoretical pH value	Time point [h]	Mean aqueous solution [ng/ml] (A)	Mean aqueous solution containing PA21 Placebo [ng/ml] (B)	Difference (B)/(A) in %	Mean aqueous solution + PA21[ng/ml] (D)	Difference (D)/(A) in %	Difference (D)/(B) in %
pH 3	0	78.7	61.3	-22.1	68.7	-12.7	12.1
	2	224	258	15.2	221	-1.3	-14.3
	4	250	289	15.6	222	-11.2	-23.2
	6	245	263	7.3	214	-12.7	-18.6
pH 5.5	0	95.6	67.4	-29.5	82.5	-13.7	22.4
	2	259	296	14.3	255	-1.5	-13.9
	4	249	291	16.9	248	-0.4	-14.8
	6	260	294	13.1	246	-5.4	-16.3
pH 8	0	85.4	64.7	-24.2	39.8	-53.4	-38.5
	2	273	293	7.3	273	0.0	-6.8
	4	276	290	5.1	265	-4.0	-8.6
	6	252	288	14.3	262	4.0	-9.0

- Enalapril showed < 14% adsorption on PA21 at pH 3 and 5.5. Enalaprilate could not be analyzed during the whole study.

Table 72: Summary results of the concentrations of enalapril in unknown aqueous solution samples from study VIT01 (part one).

theoretical pH value	Time point [h]	Mean aqueous solution [µg/ml] (A)	Mean aqueous solution containing PA21 Placebo [µg/ml] (B)	Difference (B)/(A) in %	Mean aqueous solution + PA21[µg/ml] (D)	Difference (D)/(A) in %	Difference (D)/(B) in %
pH 3	0	1.36	0.775	-43.0	0.632	-53.5	-17.9
	2	16.5	15.2	-7.9	14.8	-10.3	-2.6
	4	16.6	15.1	-9.0	14.4	-13.3	-4.6
	6	16.5	15.2	-7.9	14.2	-13.9	-6.6
pH 5.5	0	0.988	blq	na	0.723	-26.8	na
	2	16.3	14.8	-9.2	14.5	-11.0	-2.0
	4	16.4	14.7	-10.4	14.2	-13.4	-3.4
	6	16.2	14.6	-9.9	14.0	-13.6	-4.1
pH 8	0	1.84	1.80	-2.2	1.44	-21.7	-20.0
	2	15.8	15.5	-1.9	15.4	-2.5	-0.6
	4	15.7	15.3	-2.5	15.2	-3.2	-0.7
	6	15.8	15.1	-4.4	15.0	-5.1	-0.7

- Furosemide showed a strong adsorption effect on PA21 at pH 3 (up to 60%, Table 85) but not on PA21 placebo. At the pH value of 5.5 furosemide showed a slight adsorption effect on PA21 ($\leq 23\%$), and at pH 8 PA21 caused an enhanced solubility of furosemide (up to 69%).

Table 85: Summary results of the concentrations of furosemide in unknown aqueous solution samples from study VIT01 (part two).

theoretical pH value	Time point [h]	Mean aqueous solution [µg/ml] (A)	Mean aqueous solution containing PA21 Placebo [µg/ml] (B)	Difference (B)/(A) in %	Mean aqueous solution + PA21[µg/ml] (D)	Difference (D)/(A) in %	Difference (D)/(B) in %
pH 3	0	0.574	0.539	-6.1	blq	n.a.	n.a.
	2	11.8	12.1	2.5	4.73	-59.9	-60.9
	4	12.7	12.8	0.8	6.44	-49.3	-49.7
	6	13.4	13.2	-1.5	8.42	-37.2	-36.2
pH 5.5	0	2.40	1.43	-40.4	2.19	-8.8	53.1
	2	114	141	23.7	88.5	-22.4	-37.2
	4	161	186	15.5	124	-23.0	-33.3
	6	166	222	33.7	159	-4.2	-28.4
pH 8	0	2.37	3.12	31.6	4.32	82.3	38.5
	2	176	217	23.3	263	49.4	21.2
	4	253	277	9.5	320	26.5	15.5
	6	280	317	13.2	349	24.6	10.1

- Losartan showed a strong adsorption effect on PA21 at pH 3 (up to 61%, Table 92) but not on PA21 placebo.

Table 92: Summary results of the concentrations of losartan in unknown aqueous solution samples from study VIT01 (part one).

theoretical pH value	Time point [h]	Mean aqueous solution [µg/ml] (A)	Mean aqueous solution containing PA21 Placebo [µg/ml] (B)	Difference (B)/(A) in %	Mean aqueous solution + PA21[µg/ml] (D)	Difference (D)/(A) in %	Difference (D)/(B) in %
pH 3	0	38.0	36.5	-3.9	66.7	75.5	82.7
	2	42.3	42.5	0.5	20.4	-51.8	-52.0
	4	42.9	42.3	-1.4	17.8	-58.5	-57.9
	6	44.5	44.6	0.2	17.2	-61.3	-61.4
pH 5.5	0	93.1	94.3	1.3	99.7	7.1	5.7
	2	93.4	88.1	-5.7	85.3	-8.7	-3.2
	4	92.3	87.7	-5.0	81.0	-12.2	-7.6
	6	94.3	90.2	-4.3	85.2	-9.7	-5.5
pH 8	0	91.2	108	18.4	104	14.0	-3.7
	2	93.5	111	18.7	105	12.3	-5.4
	4	92.5	113	22.2	105	13.5	-7.1
	6	93.6	111	18.6	104	11.1	-6.3

- Metoprolol showed < 12% adsorption after 6 h at pH 8.

Table 97: Summary results of the concentrations of metoprolol in unknown aqueous solution samples from study VIT01.

theoretical pH value	Time point [h]	Mean aqueous solution [µg/ml] (A)	Mean aqueous solution containing PA21 Placebo [µg/ml] (B)	Difference (B)/(A) in %	Mean aqueous solution + PA21[µg/ml] (D)	Difference (D)/(A) in %	Difference (D)/(B) in %
pH 3	0	77.8	79.9	2.7	76.8	-1.3	-3.9
	2	73.7	81.6	10.7	80.5	9.2	-1.3
	4	74.2	81.2	9.4	80.6	8.6	-0.7
	6	76.1	80.7	6.0	78.3	2.9	-3.0
pH 5.5	0	70.7	75.2	6.4	67.9	-4.0	-9.7
	2	72.9	73.7	1.1	78.1	7.1	6.0
	4	72.7	75.9	4.4	75.6	4.0	-0.4
	6	74.0	70.9	-4.2	75.8	2.4	6.9
pH 8	0	71.9	75.5	5.0	69.5	-3.3	-7.9
	2	73.7	74.5	1.1	72.5	-1.6	-2.7
	4	71.6	74.5	4.1	67.1	-6.3	-9.9
	6	73.9	74.9	1.4	65.3	-11.6	-12.8

- Nifedipine showed no effects at all pH values but it was only slightly soluble under the set conditions.

Table 101: Summary results of the concentrations of nifedipine in unknown aqueous solution samples from study VIT01.

theoretical pH value	Time point [h]	Mean aqueous solution [µg/ml] (A)	Mean aqueous solution containing PA21 Placebo [µg/ml] (B)	Difference (B)/(A) in %	Mean aqueous solution + PA21 [µg/ml] (D)	Difference (D)/(A) in %	Difference (D)/(B) in %
pH 3	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	4.19	4.24	1.2	3.83	-8.6	-9.7
	6	5.91	5.96	0.8	5.49	-7.1	-7.9
pH 5.5	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	2.89	3.09	6.9	2.76	-4.5	-10.7
	6	4.69	5.14	9.6	4.61	-1.7	-10.3
pH 8	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	5.00	4.94	-1.2	5.40	8.0	9.3
	6	7.39	7.38	-0.1	7.47	1.1	1.2

- With omeprazole, effects of degradation (omeprazole is not stable at pH 3) and enhanced solubility (predominantly after 2h at pH 5.5 and 8) as well as a possible slight adsorption (pH 5.5) were observed.

Table 108: Summary results of the concentrations of omeprazole in unknown aqueous solution samples from study VIT01 (part one).

theoretical pH value	Time point [h]	Mean aqueous solution [µg/ml] (A)	Mean aqueous solution containing PA21 Placebo [µg/ml] (B)	Difference (B)/(A) in %	Mean aqueous solution + PA21 [µg/ml] (D)	Difference (D)/(A) in %	Difference (D)/(B) in %
pH 3	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	blq	blq	n.a.	blq	n.a.	n.a.
	4	blq	blq	n.a.	blq	n.a.	n.a.
	6	blq	blq	n.a.	blq	n.a.	n.a.
pH 5.5	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	0.638	3.20	401.6	2.87	349.8	-10.3
	4	15.1	16.3	7.9	20.0	32.5	22.7
	6	11.5	9.39	-18.3	10.2	-11.3	8.6
pH 8	0	blq	blq	n.a.	blq	n.a.	n.a.
	2	7.91	6.12	-22.6	23.5	197.1	284.0
	4	34.8	33.6	-3.4	36.7	5.5	9.2
	6	34.2	33.8	-1.2	36.0	5.3	6.5

- With warfarin, no interactions were observed.

Table 113: Summary results of the concentrations of warfarin in unknown aqueous solution samples from study VIT01.

theoretical pH value	Time point [h]	Mean aqueous solution [µg/ml] (A)	Mean aqueous solution containing PA21 Placebo [µg/ml] (B)	Difference (B)/(A) in %	Mean aqueous solution + PA21[µg/ml] (D)	Difference (D)/(A) in %	Difference (D)/(B) in %
pH 3	0	1.11	1.46	31.5	1.75	57.7	19.9
	2	3.46	3.37	-2.6	3.24	-6.4	-3.9
	4	3.53	3.39	-4.0	3.24	-8.2	-4.4
	6	3.53	3.40	-3.7	3.23	-8.5	-5.0
pH 5.5	0	0.26	0.28	7.7	0.26	0.0	-7.1
	2	4.44	4.36	-1.8	4.20	-5.4	-3.7
	4	4.44	4.34	-2.3	4.16	-6.3	-4.1
	6	4.41	4.31	-2.3	4.11	-6.8	-4.6
pH 8	0	0.27	0.33	22.2	0.25	-7.4	-24.2
	2	4.53	4.54	0.2	4.54	0.2	0.0
	4	4.45	4.53	1.8	4.55	2.2	0.4
	6	4.54	4.52	-0.4	4.50	-0.9	-0.4

Reviewer's note:

- The upper ranges of drug concentration measured are close to the expected concentrations calculated from the strength for all drugs except nifedipine where the expected concentration is 60 µg/mL, the maximum measured concentration is only 7.48 µg/mL (page 44). The sponsor stated nifedipine was only slightly soluble under the set conditions.
- Dedicated in vitro studies were also conducted for ciprofloxacin, enalapril, metoprolol and nifedipine. Similar findings were observed as reported in this study.

Conclusions:

- Among the tested drugs, furosemide and losartan showed strong adsorption at pH 3.
- Ciprofloxacin showed ~25 % adsorption at pH 5.5.
- Omeprazole showed degradation at pH 3, enhanced solubility at pH 5.5 and 8.
- Digoxin, enalapril, metoprolol nifedipine and warfarin showed no or slight adsorption.

Study REP000075SR-EN03v3 (In vitro DDI)

Study Report # REP000075SR-EN03v3

\\cdsesub1\evsprod\nda205109\0000\m4\42-stud-rep\421-pharmacol\4214-pd-drug-interact\rep000075sr-en03v3\rep000075sr-en03v3-pre-clinical-study-report.pdf

Title: Interaction studies on PA21 API with vitamins, amino acids, fluoride, sulfate and oxalate

Objectives: To assess the possible interaction between PA21 and vitamins, amino acids, fluoride, sulfate and oxalate by measuring the remaining concentrations (recovery) of these analyte after incubation.

Study Design: Experiment was conducted by different methods, A-F (A: without phosphate; B: with phosphate; C: gastro-intestinal passage, with phosphate; D: inverse addition, with phosphate; E: gastro-intestinal passage, simultaneous addition, with phosphate; F: gastro-intestinal passage, with phosphate, with/without oxalate). Concentrations for different analytes were designed based on the recommended daily intake divided by 1 liter gastric fluid (final volume in the experiment to be 10 mL). Low daily uptake of phosphate, 800 mg (8 mg/10mL) and 5 g of PA21 (50 mg/10 mL) were used. In general, working solution containing PA21 was adjusted to pH 3.0, 5.5 and 8.0. Analytes were then added, pH corrected and incubated for 2 hours at 37°C. At 2 hours after incubation, the pH was checked and a sample was taken, filtered and quantified using corresponding method. For method C, the pH was first adjusted to 3.0 and incubated for 2 hours and pH adjusted to 5.5 and incubated for another 2 hours and then same for pH 8.0.

A high performance liquid chromatograph (HPLC) with diode array and/or mass spectrometry (MS) detection was used for the quantitation of five B-complex vitamins (folate, niacin, pantothenic acid, biotin, pyridoxine) and two amino acids (tryptophan, methionine). Fluoride, sulfate, oxalate and phosphate were determined by ion chromatography with conductivity detection.

Results

- In the most conservative condition (aqueous solution) by method A, methionine, tryptophan and sulfate showed high recoveries (low binding) at pH 3.0, 5.5 and 8.0.
- Niacin, pantothenic acid and biotin also showed high recoveries at pH 8.0 but pH dependent decrease at pH 3.0 and 5.5.
- Folate, pyridoxine, fluoride and oxalate showed low recoveries at all three pHs.

Method A

vitamin, amino acid or fluoride	pH-value	recovery [%]	rsd [%]	concentration [µg/10 ml]
methionine	3.0	96.5	0.7	7000
	5.5	95.1	0.8	7000
	8.0	95.3	0.4	7000
tryptophan	3.0	92.4	2.9	2100
	5.5	99.1	1.3	2100
	8.0	95.6	1.0	2100
sulfate	3.0	91.0	3.6	44000
	5.5	94.1	5.1	44000
	8.0	100.4	0.3	44000

niacin (B3)	3.0	45.2	1.0	160
	5.5	76.4	4.3	160
	8.0	97.9	0.7	160
pantothenic acid (B5)	3.0	16.1	15.4	50
	5.5	49.5	11.0	50
	8.0	91.9	4.6	50
biotin (B7, H)	3.0	17.1	13.2	0.3
	5.5	65.6	3.0	0.3
	8.0	93.7	2.1	0.3
folate (B9, B11)	3.0	< 14.0 (LOD) ⁷	-	4
	5.5	< 7.2 (LOD) ⁷	-	4
	8.0	12.7	15.0	4
pyridoxine (B6)	3.0	71.2	4.2	13
	5.5	12.4	10.2	13
	8.0	13.3	3.9	13
fluoride	3.0	5.0	12.9	40
	5.5	26.8	21.2	40
	8.0	83.7	1.9	40
oxalate	3.0	< 3.0 (LOD) ⁷	-	1000
	5.5	< 1.0 (LOD) ⁷	-	1000
	8.0	69.6	2.3	1000

- In the presence of phosphate in method B, no pH dependency of recovery rates was found for niacin, pantothenic acid and biotin at pH 3.0 and 5.5.
- Folate and fluoride showed increased recoveries.
- Oxalate showed an increase of observed recovery rates with increasing pH while pyridoxine showed decrease of the recovery rate of with increasing pH with the competitive approach.

Method B

vitamin, amino acid or fluoride	pH-value	recovery [%]	rsd [%]	concentration [µg/10 ml]
niacin (B3)	3.0	94.1	0.4	160
	5.5	96.9	0.8	160
pantothenic acid (B5)	3.0	97.0	2.8	50
	5.5	97.8	2.4	50
biotin (B7, H)	3.0	107.1	2.9	0.3
	5.5	107.5	4.9	0.3
folate (B9,B11)	3.0	71.9	9.1	4
	5.5	104.4	1.0	4
	8.0	100.7	1.1	4

fluoride	3.0	23.0	11.5	40
	5.5	92.0	3.2	40
oxalate	3.0	45.9	2.9	1000
	5.5	77.8	2.7	1000
	8.0	102.1	0.4	1000
pyridoxine (B6)	3.0	95.9	2.4	13
	5.5	76.6	2.5	13
	8.0	75.5	4.7	13

- Folate and fluoride showed > 92% recoveries.
- For pyridoxine, an increase in recovery from 76.6 % and 75.5 % (method B, pH 5.5, 8.0) to 95.8 % (method C) was observed.
- For oxalate a recovery rate from 79.4 % was found.

Method C

vitamin, amino acid or fluoride	recovery [%]	rsd [%]	concentration [µg/10 ml]
folate (B9,B11)	96.4	1.9	4
pyridoxine (B6)	95.8	1.1	13
fluoride	92.1	1.2	40
oxalate	79.4	1.5	1000

- Oxalate does not disturb the binding capacity of phosphate in PA21.

Method F

incubation (method F)	phosphorous [mg P/50 mg PA21-	rsd, assay [%]	mass balance (Σ ICP-OES, IC) [% recovery, % rsd]
with oxalate	2.19	7.8	97.8 (2.4)
without oxalate	2.08	7.9	95.7 (4.1)

Conclusions:

- No biologically relevant adsorption or degradation of B-complex vitamins (folate, niacin, pantothenic acid, biotin, pyridoxine), fluoride and amino acids (tryptophan, methionine) by PA21 takes place under physiologically relevant conditions.
- No influence of macronutrients (sulfate, oxalate) on the binding capacity of phosphate in PA21-2 was detectable.

4.1.2 PHARMACOKINETICS

ADME-Normal VS Renal Impairment

Report # Q-24120	Study Period 06/07/05-10/27/05
Title	The uptake of iron from a new oral phosphate binder, PA-21. An open label safety study with ⁵⁹ Fe labeled PA-21 in patients with chronic kidney disease (CKD) and healthy volunteers.
EDR Link	\\cdsesub1\EVSPROD\NDA205109\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\q-24120\q-24120-report-body-1.pdf

Rationale: A possible uptake of iron from PA-21 could lead to an iron overload during long term treatment in the target population. This study was conducted to evaluate uptake of iron from orally administered PA-21 in CKD patients (target group) and healthy volunteers (control group).

Study Design

Multiple-Dose	Non-Randomized	Open-Label	Parallel	Single-Center		
No. of Groups	3	<input checked="" type="checkbox"/> Normal	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input checked="" type="checkbox"/> Pre-dialysis (stage 3 and 4)	<input checked="" type="checkbox"/> HD (maintenance)
No. of Subject /Completed	24/24	8			8	8
Males/Females	18/14	1/7			6/2	6/2
Age, Mean(SD)		30.5(9.7)			61.5(7.9)	57.0(12.9)
Body Weight, kg, Mean(range)		71.6 (18.2)			84.1 (11.6)	74.4 (13.1)
Dose	10 g	10 g			10 g	10 g
<p>Treatments: The CKD patients received unlabeled PA-21 from treatment day 1 to 6 and PA-21 labeled with ⁵⁹Fe on the seventh treatment day. The healthy controls received ⁵⁹Fe labeled PA-21 on treatment day 1 and the unlabeled PA-21 from treatment day 2 to 7. The uptake of iron was followed for 28 days by regular determination of ⁵⁹Fe in the blood.</p> <p>Dose and dosing regimen: 10 g per day (1 x 2.5 g at breakfast, 2 x 2.5 g at lunch and 1 x 2.5 g at dinner) for 7 days</p> <p>Sampling Times: ⁵⁹Fe, blood and plasma: Days 2, 8, 15, 22 and 29 days post ⁵⁹Fe dose.</p> <ul style="list-style-type: none"> Pre-dialysis patients (CKD stage 3 and 4) with GFR <60 mL/min (as calculated according to the Cockcroft–Gault formula), Hb >100 g/L Hemodialysis in the maintenance phase with Hb >100 g/L, Tsat 20-50% and/or S-ferritin 200-800 µg/L Healthy volunteers with S-ferritin <100 µg/L and with no underlying disease (e.g. young females, vegetarians) 						

Test product, dose and mode of administration, batch number:

Unlabeled PA-21(batch number 42900), powder (b)(4) per day, oral administration as suspension

⁵⁹Fe-labeled PA-21 (batch number PA21_050530 (used for healthy volunteers), PA21_050824 (used for renal patients)), powder (b)(4) per day, oral administration as suspension

Analysis of ⁵⁹Fe

⁵⁹Fe activity in plasma and blood was measured by a gamma counter. For each point of the radioactivity measurements, a standard deviation (SD) was calculated depending on measuring statistics and other influencing factors.

Blood volume was determined from the height and weight of each study participant. The blood radioactivity concentration measured was then multiplied with the blood volume to obtain the total amount of circulating ⁵⁹Fe. This value was divided by the amount of administered ⁵⁹Fe to obtain the percentage of ⁵⁹Fe that had been absorbed.

- Classification of renal function is consistent with the FDA Guidance Recommendations:

Yes No Not Applicable

This is not a standard PK study in renal impairment. Categories for chronic kidney disease (CKD) were applied and the stages of CKD were shown in the table below:

Table 1 Stages of Chronic Kidney Disease

Stage	GFR (mL/min/1.73m ²)	Related Terms
1	≥90	Albuminuria, proteinuria, haematuria
2	60-89	Albuminuria, proteinuria, haematuria
3	30-59	Early chronic renal insufficiency
4	15-29	Late early chronic renal insufficiency, pre-ESRD
5	<15 (or dialysis)	Renal failure, ESRD

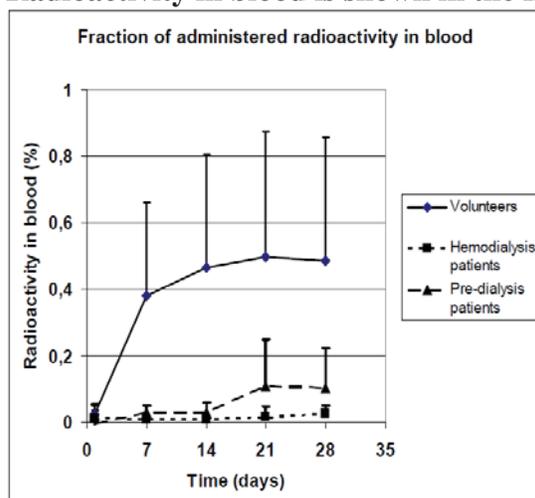
Notes: ESRD = End-stage renal disease; GFR = Glomerular filtration rate.

Source: Kidney Disease Outcomes Quality Initiative Guidelines [4].

- Renal function was determined via _C-G formula MDRD formula
- Renal function was determined at: Screening Baseline
- The control group is adequate Yes No
- The groups are matched by Age Sex Body Weight Smoking Status Race
No matching
- The selected dose is acceptable Yes No
- Dosing is long enough to obtain steady state Yes No Not Applicable
- Sample size was determined based on statistical analysis Yes No
- The overall study design acceptable: Yes No

Pharmacokinetics (Radioactivity)

Radioactivity in blood is shown in the figure and table below:



	Iron uptake	
	Median	Range
Healthy	0.43%	0.16 - 1.25%
HD	0.02%	0 - 0.04%
pre-dialysis	0.06%	0.008 - 0.44%

- The median radioactivity in the blood is 0.43%, 0.02% and 0.06 % for healthy subjects, hemodialysis patients and pre-dialysis patients, respectively.
- The radioactivity in the plasma is very low compared to that in the blood (data not shown here) implying the absorbed Fe distributed in the erythrocytes.

Pharmacodynamics

Mean changes on serum phosphate levels from baseline are shown in the table below:

	Serum phosphate
	Mean change on Day 8 from BL (mg/dL)
Healthy	- 0.25
HD	- 1.86
pre-dialysis	- 1.05

- Serum phosphate levels were decreased in pre-dialysis patients and hemodialysis patients on maintenance condition by 1.05 mg/dL and 1.86 mg/dL, respectively.
- Serum phosphate levels were not significantly changed in healthy subjects.
- No trend of changes was observed for serum levels of calcium, iron, ferritin, transferrin, transferrin saturation, intact parathyroid hormone (iPTH), vitamin D3 1, 25-OH and vitamin D3 25-OH (data not to be shown here).

Safety

Was there any death or serious adverse events? Yes No NA

One (1) SAE (myocardial infarction), which was considered as not related to the study medication by the investigator.

Diarrhea was the most commonly reported AE, seen in 38% of the treated subjects. Other gastrointestinal disorders reported were abdominal pain (reported by 17% of the treated subjects), flatulence (13%) and nausea (13%)

Conclusions

- The iron uptake after treatment with 10 g PA-21 was low. The median radioactivity in the blood is 0.43%, 0.02% and 0.06 % for healthy subjects, hemodialysis patents and pre-dialysis patients, respectively.

Reviewer's Comment:

- *Recovery of total radioactivity was not calculated. Samples of feces and urine were not collected for recovery assessment. Due to the insolubility of the product, it is reasonable to only track the potential absorbed portion. However, a recovery assessment would help support and confirm the study results. For example a >99% recovery of the radioactivity in the feces would be confirming the low absorption of < 0.5% and would resolve doubts on the assay validation that the low radioactivity in the blood is not a result of any instability or decay of the signal and etc.*

Study VIT-CI-01/02 (SAD, MAD)

Study Report # VIT-CI-01/02	Study period 2/2006 to 7/2006	
Title		
A Combined Single-Day and Multiple-Ascending Dose Study to Evaluate the Safety and Tolerability of the Oral Phosphate Binder PA21 in Healthy Male and Female Subjects		
Primary Objectives		
To evaluate the safety and tolerability of a single-day and multiple ascending doses of PA21 in healthy male and female subjects		
Study Type FTIH <input type="checkbox"/> SAD <input checked="" type="checkbox"/> MAD <input checked="" type="checkbox"/> MB <input type="checkbox"/>		
Study Design mono-centre, randomized, double-blind		
Doses 3.75, 5.0, 7.5, 8.75, 10.0, 11.25, 12.5 g/day (n=6 trt + 2 plc per dose group)		
On Day 1, a single-day treatment was performed at all dose levels. After a satisfying review of safety data until 24 hours post-dose, the multipledose treatment commenced in the same subjects on Day 3 and lasted until Day 9.		
Study medication		
	Chewable Tablet	Placebo Tablet
Dosage Form	Chewable Tablet	Placebo Tablet
Dosage Strength	1.25 g	-
Batch #.	525110B11	629000B11
Administration	Oral	Oral
Sampling schedules:		
Phosphate, calcium & creatinine (urine): 24-h urine collections: Day -1 to 1, Day 1 to 2 and Day 9 to 10		
Iron, Hb, ferritin, transferrin, transferrin saturation, calcium, phosphate, AP and PTH (blood): Screening, pre-dose Day 1 and in the morning of Day 10		
Vitamin A, D, E and K (blood): Pre-dose Day 1 (morning dose) and in the morning of Day 10		
Data Analysis Methods		
Descriptive statistics including changes from baseline (mean, SD, median and ranges, 95% confidence intervals) were obtained for all quantitative safety variables. If data for the target safety laboratory variables suggested a change from baseline, an ANCOVA with the factor treatment and the covariate "baseline value" was calculated.		

Study population

Enrolled/Completed/ Discontinued Due to AE	57/57/0
Age (range)	18 to 60 y
Male/Female	32/25
Race (Caucasian/other)	57/0

Results:**Phosphate levels**

- No consistent dose-related trend in phosphate levels in blood and urine were observed.

Table 12: Phosphate in Blood and 24-Hour Urine – Mean Changes (\pm SD) from Baseline and Paired T-Test Results on Day 10 (Target Population)

	Treatment Group PA21 [g] / Placebo							
	Placebo	3.75	5.0	7.5	8.75	10.0	11.25	12.5
Phosphate (blood) [mmol/L]								
Mean change	0.044	0.007	0.067	0.120	0.012	0.167	0.108	0.062
\pm SD	\pm 0.114	\pm 0.119	\pm 0.166	\pm 0.133	\pm 0.086	\pm 0.150	\pm 0.093	\pm 0.074
P-value	0.1684	0.8962	0.3697	0.0788	0.7528	0.0417 *	0.0355 *	0.0954
Phosphate (24-h urine) [mmol/day]								
Mean change	-4.16	-7.58	-5.83	-9.17	0.08	-1.47	-2.63	-9.42
\pm SD	\pm 8.65	\pm 8.84	\pm 11.23	\pm 4.20	\pm 17.60	\pm 13.37	\pm 5.13	\pm 13.71
P-value	0.0951	0.0896	0.2592	0.0031**	0.9912	0.7988	0.2644	0.1533

* p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001

Source: Appendix 16.5, Tables 3.3.6.1.2 and 3.3.6.4.1–3.3.6.4.2 (blood) and Tables 3.3.7.1.2 and 3.3.7.4.1–3.3.7.4.2 (urine).

Iron, Ferritin, Haemoglobin, Transferrin and Transferrin Saturation

- Although some data show significant changes, no dose-related trend was observed.

Table 14: Iron, Ferritin, Haemoglobin, Transferrin and Transferrin Saturation – Mean Changes (\pm SD) from Baseline and Paired T-Test Results on Day 10 (Target Population)

	Treatment Group PA21 [g] / Placebo							
	Placebo	3.75	5.0	7.5	8.75	10.0	11.25	12.5
Iron [μmol/L]								
Mean change	1.620	-2.402	-1.282	6.265	1.813	0.758	2.452	3.835
\pm SD	4.636	5.174	4.630	3.791	4.079	3.086	5.034	4.162
P-value	0.2137	0.3071	0.5278	0.0098 **	0.3258	0.5735	0.2864	0.0736
Ferritin [μg/L]								
Mean change	6.311	54.928	34.052	22.680	10.615	4.308	14.980	5.595
\pm SD	11.091	62.509	31.542	19.653	14.678	9.037	10.490	12.875
P-value	0.0529	0.0840	0.0457 *	0.0368 *	0.1367	0.2955	0.0173 *	0.3358
Haemoglobin [g/L]								
Mean change	2.2	1.8	4.2	-1.2	4.0	5.8	1.2	2.7
\pm SD	6.1	6.1	5.3	3.8	7.3	2.6	3.8	4.3
P-value	0.1978	0.4977	0.1105	0.4877	0.2384	0.0029 **	0.4819	0.1870
Transferrin [g/L]								
Mean change	0.112	-0.052	-0.042	0.155	0.107	0.057	-0.047	0.043
\pm SD	0.141	0.172	0.194	0.128	0.133	0.127	0.142	0.145
P-value	0.0108 *	0.4951	0.6216	0.0314 *	0.1065	0.3234	0.4585	0.4970
Transferrin saturation [%]								
Mean change	1.587	-3.528	-1.228	8.562	0.890	0.275	4.382	6.102
\pm SD	6.891	10.025	10.498	6.630	7.208	4.632	8.215	6.269
P-value	0.4045	0.4280	0.7859	0.0250 *	0.7745	0.8901	0.2483	0.0628

* p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001

Source: Appendix 16.5, Tables 3.3.8.1.2 and 3.3.8.4.1–3.3.8.4.2 (iron), Tables 3.3.9.1.2 and 3.3.9.4.1–3.3.9.4.2 (ferritin), Tables 3.3.1.1.2 and 3.3.1.4.1–3.3.1.4.2 (haemoglobin), Tables 3.3.10.1.2 and 3.3.10.4.1–3.3.10.4.2 (transferrin) and Tables 3.3.11.1.2 and 3.3.11.4.1–3.3.11.4.2 (transferrin saturation).

Calcium in Blood and 24-Hour Urine, AP and PTH

- Although some data show significant changes, no dose-related trend was observed.

Table 16: Calcium in Blood and 24-Hour Urine, AP and PTH – Mean Changes (\pm SD) from Baseline and Paired T-Test Results on Day 10 (Target Laboratory Population)

	Treatment Group PA21 [g] / Placebo							
	Placebo	3.75	5.0	7.5	8.75	10.0	11.25	12.5
Calcium (blood) [mmol/L]								
Mean change	0.038	-0.048	-0.007	0.062	0.030	0.027	0.040	0.037
\pm SD	0.089	0.088	0.079	0.060	0.048	0.040	0.055	0.048
P-value	0.1356	0.2382	0.8442	0.0546	0.1876	0.1663	0.1357	0.1229
Calcium (24-h urine) [mmol/day]								
Mean change	-1.725	-0.820	-1.912	-0.203	-0.508	-0.203	1.222	-1.070
\pm SD	1.351	1.154	1.533	1.279	2.453	2.291	1.332	2.281
P-value	0.0004 ***	0.1422	0.0283 *	0.7129	0.6334	0.8365	0.0746	0.3024
AP (37°C) [U/L]								
Mean change	4.38	1.93	7.40	11.12	-0.28	2.13	3.18	0.17
\pm SD	4.62	8.98	7.80	15.60	6.38	3.90	2.07	4.44
P-value	0.0036 **	0.6204	0.0678	0.1413	0.9176	0.2381	0.0130 *	0.9303
PTH [pg/mL]								
Mean change	2.62	2.18	4.27	-2.82	0.75	1.52	-1.47	0.52
\pm SD	6.57	5.27	2.41	2.67	3.99	9.23	3.01	5.67
P-value	0.1592	0.3564	0.0074 **	0.0492 *	0.6646	0.7040	0.2863	0.8321

* p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001

Source: Appendix 16.5, Tables 3.3.4.1.2 and 3.3.4.4.1–3.3.4.4.2 (calcium, blood), Tables 3.3.5.1.2 and 3.3.5.4.1–3.3.5.4.2 (calcium, 24-h urine), Tables 3.3.2.1.2 and 3.3.2.4.1–3.3.2.4.2 (AP) and Tables 3.3.3.1.2 and 3.3.3.4.1–3.3.3.4.2 (PTH).

Vitamins A, D [25(OH)D], D [1,25(OH)₂D], E and K

- There were a number of differences in vitamin levels between Day 10 and Day 1 with p-values <0.05. Most of the differences were not dose-related. However, the mean decreases in vitamin A (-436 μ g/L, p=0.0009) and vitamin E (-5.23 mg/L, p=0.0032) levels seen in the 12.5-g PA21 group were the largest among all treatment groups. A marked mean decrease was also observed for vitamin D [1,25(OH)₂D] (-14.6 pg/mL, p>0.05) in this group, but this difference showed a p-value >0.05.

Table 18: Vitamins A, D [25(OH)D], D [1,25(OH)₂D], E and K – Mean Changes (±SD) from Baseline and Paired T-Test Results on Day 10 (Target Population)

	Treatment Group PA21 [g] / Placebo							
	Placebo	3.75	5.0	7.5	8.75	10.0	11.25	12.5
Vitamin A [µg/L]								
Mean change	-64.6	-63.8	194.8	-164.7	315.2	-81.7	-60.2	-436.0
±SD	395.8	165.7	100.1	277.1	105.3	243.3	529.0	152.6
P-value	0.5521	0.3887	0.0050 **	0.2053	0.0007***	0.4483	0.7917	0.0009***
Vitamin D [25(OH)D] [ng/mL]								
Mean change	1.50	3.88	3.30	-0.57	-2.62	2.68	0.23	-0.43
±SD	2.56	1.23	2.80	3.37	1.15	2.25	2.29	1.96
P-value	0.0470 *	0.0006***	0.0344 *	0.6974	0.0025 **	0.0328 *	0.8127	0.6112
Vitamin D [1,25(OH)₂D] [pg/mL]								
Mean change	3.19	8.12	5.58	-1.78	-2.15	4.67	0.75	-14.60
±SD	22.58	14.06	3.69	6.61	4.15	5.27	13.81	26.80
P-value	0.6065	0.2166	0.0139 *	0.5377	0.2605	0.0822	0.8994	0.2396
Vitamin E [mg/L]								
Mean change	-0.70	-2.33	3.05	-0.67	1.33	0.67	-2.27	-5.23
±SD	5.37	1.86	1.34	3.44	1.37	3.39	5.00	2.43
P-value	0.6341	0.0278 *	0.0026 **	0.6554	0.0624	0.6500	0.3176	0.0032 **
Vitamin K [µg/L]								
N	9	0	6	5	2	3	6	5
Mean change	0.007	n.d.	0.373	-0.120	-0.020	1.363	0.217	-0.046
±SD	0.410	n.d.	0.126	0.198	0.170	1.705	0.136	0.074
P-value	0.9623	n.d.	0.0008***	0.2476	0.8949	0.3004	0.0114 *	0.2352

* p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001

n.d. = no data available

Source: Appendix 16.5, Tables 3.3.14.1.2 and 3.3.14.4.1–3.3.14.4.2 (Vitamin A), Tables 3.3.13.1.2 and 3.3.13.4.1–3.3.13.4.2 (Vitamin D [25(OH)D]), Tables 3.3.12.1.2 and 3.3.12.4.1–3.3.12.4.2 (Vitamin D [1,25(OH)₂D]), Tables 3.3.15.1.2 and 3.3.15.4.1–3.3.15.4.2 (Vitamin E) and Tables 3.3.16.1.2 and 3.3.16.4.1–3.3.16.4.2 (Vitamin K).

Safety

Death/SAE: **None**

- Adverse events with a probable drug relationship were confined to discoloured feces.
- Possibly drug-related gastrointestinal AEs such as flatulence and diarrhea increased at doses of 11.25 and 12.5 g PA21, while abdominal pain occurred predominantly after doses of 7.5 g PA21 and higher.
- Other AEs were infrequently observed without an apparent relation to the dose administered.

Conclusion

- Ascending single-day and multiple-dose administration of 3.75 to 12.5 g PA21 for eight days was safe and well tolerated in healthy male and female subjects.
- Changes in target laboratory safety parameters were, in general, not different between treatment with PA21 and placebo. The observations of lower vitamin A and E levels after 12.5 g were inconclusive, since there was no indication of a dose-dependency at the lower dose levels.

4.1.3 EXTRINSIC FACTORS

DDI- PA21 VS Losartan

Report # PA-DDI-001	Study Period 03/22/11 08/02/11	EDR Link \\cdsesub1\evsprod\nda205109\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\pa-ddi-001\pa-ddi-001-report-body-1.pdf	
Title	A Single-centre, Open-label, 3-period Study of the Pharmacokinetic Effect of PA21 on Losartan Potassium in Healthy Male and Female Adults		
Objectives	To assess the effect, if any, of PA21 on losartan or its active metabolite's (EXP 3174) exposure.		
Rationale: Losartan was shown to be adsorbed or to interact with PA21 in vitro. Therefore, this study is being conducted to assess the effect of PA21 on the pharmacokinetics of losartan or its active metabolite.			
Study Design Single-Dose Randomized Open-Label Crossover Single-Center 3-Period Healthy Vonuteers Subjects were admitted to the clinical facility on Day -2. Three periods are detailed below.			
Screening: -21days		Washout: 7 days	
Sequence	Treatment 123, or 231 or 312		
Treatments:			
Treatment Group	Period Dosing Schedule		
	1	2	3
Treatment 1	PA21 and losartan potassium with food	No PA21; losartan potassium with food	PA21 with food and losartan potassium 2 hours later
	2	3	1
Treatment 2	No PA21; losartan potassium with food	PA21 with food and losartan potassium 2 hours later	PA21 and losartan potassium with food
	3	1	2
Treatment 3	PA21 with food and losartan potassium 2 hours later	PA21 and losartan potassium with food	No PA21 losartan potassium with food
Study medication			
Drug name	PA21	Losartan Potassium	
Dosage Form	Chewable Tablets	Tablets	
Dosage Strength (Dose)	2.5 g (15 g/day)	100 mg (100 mg/day)	
Lot #	991200D11	G001380 and Z1351	
Administration	Oral	Oral	
PK Sampling (Blood)			
<u>Losartan and EXP 3174:</u> Pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24 and 48 hours post-dose of losartan administration on Days 1, 12 and 23			
Analytical Method			
The performance of the assay method during sample analysis is acceptable and is summarized below.			

Analyte	Losartan	EXP 3174 (Losartan carboxylic acid)
Method	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma
LOQ (ng/mL)	1.00	1.00
Range (ng/mL)	1.00 to 1500	1.00 to 1500
QCs (ng/mL)	3.00, 50.0, 600, 1200	3.00, 50.0, 600, 1200
Accuracy/Bias	-2.8 % to 1.7 %	0.0 % to 6.3 %
Precision (CV%)	3.4 % to 8.4 %	2.4 % to 8.7 %

Statistical Method: Point estimates and 90% confidence intervals for the ratios of the geometric means for losartan and EXP 3174 C_{max} and AUC (Trt 1/Trt 2 and Trt 3/Trt 2) were constructed. The bioequivalence criteria for log-transformed parameters were defined as 80-125%.

Study Population :

Enrolled/Completed/ Discontinued Due to AE	41/33/0
Age [Median (range)]	31.83 (20-50) yr
Male/Female	26/15
Race (White/Black/Asian/Other)	31/3/7/0

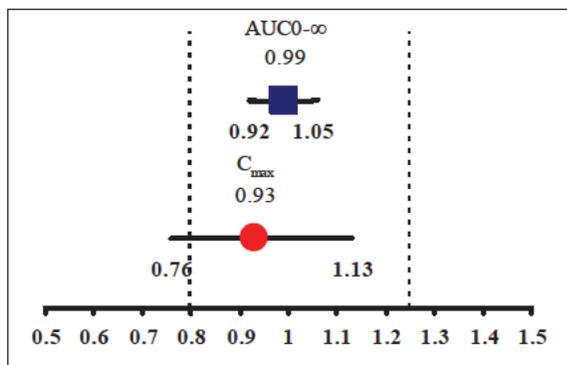
Results

Pharmacokinetics of losartan and its active metabolite (EXP 3174)

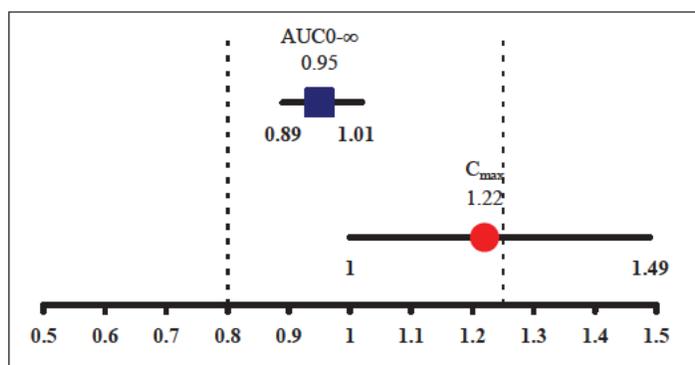
- Losartan C_{max} was not significantly altered when co-administered with PA21; however, losartan C_{max} increased by 22% when losartan was administered 2 hours after PA21 and breakfast and the upper bound (149%) of the 90% CI of the geometric mean ratio fell outside the bioequivalence range (80-125%); C_{max} of EXP 3174 was not altered by PA21.
- AUC of losartan and EXP 3174 were not changed whether administered immediately or 2 hours after PA21 and food.
- The T_{max} of losartan and EXP 3174 were significantly shorter when PA21 was administered with breakfast 2 hours prior to losartan compared to when losartan was administered immediately with PA21 and breakfast.
- The half-life of losartan and EXP 3174 were slightly decreased when losartan was co-administered with PA21 but not considered clinically significant.

Losartan

PA21 with meal+Losartan/Losartan with meal alone



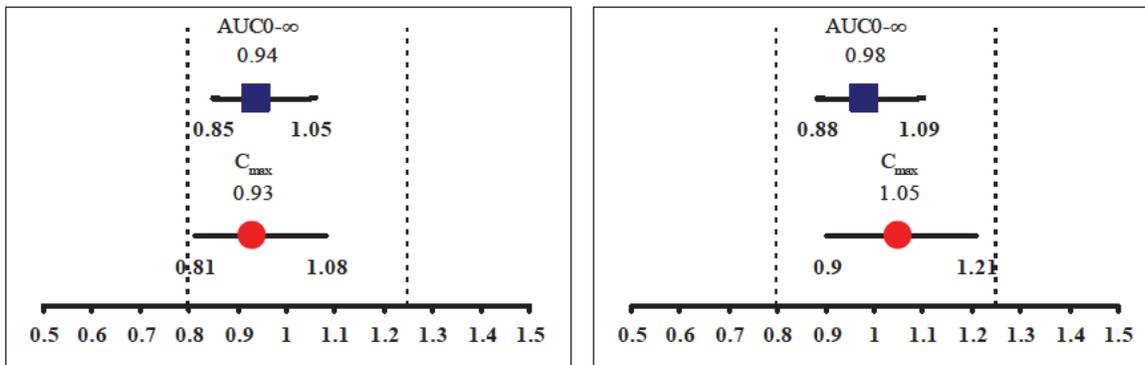
PA21 with meal+2h after Losartan/Losartan with meal alone



EXP 3174

PA21 with meal+Losartan/Losartan with meal alone

PA21 with meal+2h after Losartan/Losartan with meal alone



Reviewer's note: the increased Cmax of losartan is consistent with the known food effect of losartan where shortened Tmax was also found significant when losartan was taken 2 hours after meal. This finding is due to the study design and not an interaction between PA21 and losartan.

Summary of Losartan and Losartan active metabolite (EXP 3174) PK parameters

Parameter (Units)	PA21 and Losartan with Food (Trt 1) (N=36)	No PA21; Losartan with Food (Trt 2) (N=34)	PA21 with Food; Losartan 2 Hours Later (Trt 3) (N=35)	
n, Geometric Mean (Geometric %CV)				
Losartan	C _{max} (ng/mL)	36 290.9337 (103.8)	33 330.0747 (68.9)	35 385.4816 (73.9)
	AUC ₀₋₂₄ (h*ng/mL)	35 787.6274 (36.0)	32 808.9614 (38.1)	35 739.0773 (43.0)
	AUC _{0-t} (h*ng/mL)	36 704.1338 (78.2)	33 800.9903 (37.2)	35 729.0036 (43.3)
	AUC _{0-infinity} (h*ng/mL)	35 788.6670 (36.1)	31 812.7578 (37.0)	35 740.3545 (43.1)
	C _{max} (ng/mL)	36 588.78813 (74.5)	33 656.60624 (45.4)	35 676.87107 (43.2)
EXP 3174	AUC ₀₋₂₄ (h*ng/mL)	36 3,920.4929 (54.4)	33 4,245.7244 (30.4)	35 4,139.3187 (28.7)
	AUC _{0-t} (h*ng/mL)	36 4,198.4982 (54.9)	33 4,612.9259 (28.1)	35 4,434.4000 (28.0)
	AUC _{0-infinity} (h*ng/mL)	36 4,236.1598 (53.1)	33 4,657.3419 (27.7)	35 4,466.6741 (27.8)

Statistical Analysis of the Effect of PA21 on Losartan and EXP 3174 Exposure						
Analyte	PK Parameter	No PA21; Losartan with Food (Trt 2) (Reference)	PA21 and Losartan with Food (Trt 1) (Test)	PA21 with Food; Losartan 2 Hours Later (Trt 3) (Test)	Geometric LS Mean Ratio Test/Reference	90% CI of Geometric Mean Ratio Test/Reference (%)
Losartan	C _{max} (ng/mL)	313.90	290.93	-	0.927	(0.761, 1.129)
		313.90	-	382.76	1.219	(1.000, 1.487)
	AUC ₀₋₂₄ (h*ng/mL)	782.00	773.60	-	0.989	(0.927, 1.056)
		782.00	-	742.27	0.949	(0.889, 1.013)
	AUC ₀₋₄ (h*ng/mL)	754.68	704.13	-	0.933	(0.827, 1.053)
754.68		-	733.65	0.972	(0.861, 1.098)	
AUC _{0-infinity} (h*ng/mL)	786.87	774.71	-	0.985	(0.923, 1.050)	
	786.87	-	743.86	0.945	(0.886, 1.009)	
EXP 3174	C _{max} (ng/mL)	631.26	588.79	-	0.933	(0.808, 1.077)
		631.26	-	659.77	1.045	(0.904, 1.208)
	AUC ₀₋₂₄ (h*ng/mL)	4,104.09	3,920.49	-	0.955	(0.857, 1.065)
		4,104.09	-	4,071.18	0.992	(0.889, 1.107)
	AUC ₀₋₄ (h*ng/mL)	4,452.49	4,198.50	-	0.943	(0.845, 1.052)
4,452.49		-	4,367.54	0.981	(0.878, 1.096)	
AUC _{0-infinity} (h*ng/mL)	4,500.93	4,236.16	-	0.941	(0.847, 1.046)	
	4,500.93	-	4,399.30	0.977	(0.878, 1.088)	

Note: LS - Least squares.

Statistical Analysis of the Effect of PA21 on Losartan and EXP 3174 T _{max} and t _{1/2}							
Analyte	PK Parameter	Medians			Median Difference Test/Reference	90% CI Median Difference Test/Reference (%)	Wilcoxon Signed Rank p-value
		No PA21; Losartan with Food (Trt 2) (Reference)	PA21 and Losartan with Food (Trt 1) (Test)	PA21 with Food; Losartan 2 hours Later (Trt 3) (Test)			
Losartan	T _{max} (h)	3.000	2.500	-	-1.000	(-1.250, -0.500)	0.0021
		3.000	-	2.000	-1.000	(-1.500, -0.735)	<0.0001
	t _{1/2} (h)	2.080	1.830	-	-0.245	(-0.460, -0.080)	0.0154
2.080		-	1.970	-0.123	(-0.470, 0.125)	0.4774	
EXP 3174	T _{max} (h)	5.000	4.515	-	-0.500	(-1.000, 0.000)	0.0810
		5.000	-	4.000	-1.000	(-1.500, -0.500)	0.0019
	t _{1/2} (h)	6.940	6.550	-	-0.345	(-0.625, -0.090)	0.0415
6.940		-	6.870	-0.187	(-0.495, 0.130)	0.3248	

Safety

Was there any death or serious adverse events? Yes No NA

Conclusion

PA21 co-administered with losartan or administered 2 hours earlier did not influence systemic exposure to losartan or its active metabolite, EXP 3174, and was generally well tolerated in healthy subjects.

DDI- PA21 VS Furosemide

Report # PA-DDI-002	Study Period 07/21/11 09/19/11	EDR Link \\cdsesub1\evsprod\nda205109\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\pa-ddi-002\pa-ddi-002-report-body-1.pdf	
Title	A Single-centre, Open-label, 3-period Study of the Pharmacokinetic Effect of PA21 on Furosemide in Healthy Male and Female Adults		
Objectives	To assess the effect, if any, of PA21 on furosemide exposure.		
Rationale:	Furosemide was shown to be adsorbed or to interact with PA21 in vitro. Therefore, this study is being conducted to assess the effect of PA21 on the pharmacokinetics of furosemide.		
Study Design	Single-Dose Randomized Open-Label Crossover Single-Center 3-Period Healthy Volunteers		
	Subjects were admitted to the clinical facility on Day -2. Three periods are detailed below.		
Screening: -21days	Washout: 7 days		
Sequence	Treatment 123, or 231 or 312		
Treatments:			
	Period Dosing Schedule		
	1	2	3
Treatment 1	PA21 and furosemide with food	No PA21; furosemide with food	PA21 with food and furosemide 2 hours later
	2	3	1
Treatment 2	No PA21; furosemide with food	PA21 with food and furosemide 2 hours later	PA21 and furosemide with food
	3	1	2
Treatment 3	PA21 with food and furosemide 2 hours later	PA21 and furosemide with food	No PA21 furosemide with food
Study medication			
Drug name	PA21	Furosemide	
Dosage Form	Chewable Tablets	Tablets	
Dosage Strength (Dose)	2.5 g (15 g/day)	40 mg (40 mg/day)	
Lot #	991200D11	BR4984	
Administration	Oral	Oral	
PK Sampling (Blood)			
<u>Furosemide</u> : Pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24 and 48 hours post-dose of furosemide administration on Days 1, 12 and 23			
Analytical Method			
The performance of the assay method during sample analysis is acceptable and is summarized below.			
	Analyte	Furosemide	
	Method	LC/MS/MS	
	Matrix	Plasma	
	LOQ (ng/mL)	10.0	
	Range (ng/mL)	10.0 to 10000	

	QCs (ng/mL)	30.0, 400, 4000, 8000
	Accuracy/Bias	-2.0 % to -0.6 %
	Precision (CV%)	3.6 % to 6.8 %

Statistical Method: Point estimates and 90% confidence intervals for the ratios of the geometric means for furosemide C_{max} and AUC (Trt 1/Trt 2 and Trt 3/Trt 2) were constructed. The bioequivalence criteria for log-transformed parameters were defined as 80-125%.

Study Population :

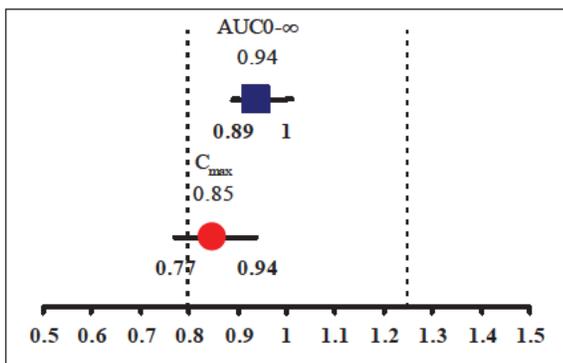
Enrolled/Completed/ Discontinued Due to AE	41/40/0
Age [Median (range)]	31.8 (20-50) yr
Male/Female	28/13
Race (White/Black/Asian/Other)	26/5/10/0

Results

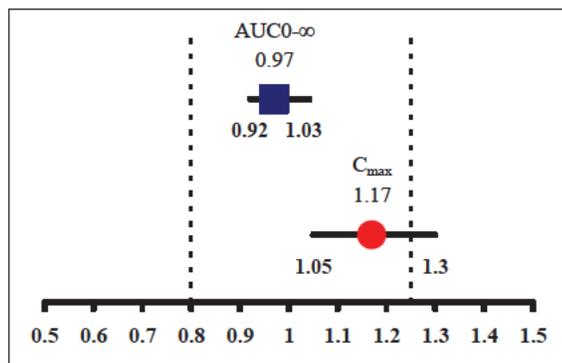
Pharmacokinetics of furosemide

- Furosemide C_{max} was not significantly altered by PA21. C_{max} was decreased by 15% when co-administered with PA21; but increased by 17% when furosemide was administered 2 hours after PA21 and breakfast.
- Furosemide AUC₀₋₂₄ and AUC_{0-infinity} were not changed whether administered immediately or 2 hours after PA21 and food.
- The T_{max} of furosemide was shorter when PA21 was administered with breakfast 2 hours prior to furosemide compared to when furosemide was administered immediately with PA21 and breakfast. This is consistent with known food effect with furosemide.
- The half-life of furosemide was increased when co-administered with PA21; but not changed when furosemide was administered 2 hours after PA21 and breakfast.

PA21 with meal+Furosemide/ Furosemide with meal alone



PA21 with meal+2h after Furosemide / Furosemide with meal alone



Summary of Furosemide PK parameters

Parameter (Units)	No PA21; Furosemide with Food (Trt 2) (N=41)	PA21 and Furosemide with Food (Trt 1) (N=41)	PA21 with Food; Furosemide 2 Hours Later (Trt 3) (N=40)		
n, Geometric Mean (Geometric %CV)					
C_{max} (ng/mL)	41 584.4116 (36.6)	41 496.2262 (40.3)	40 686.7510 (42.6)		
AUC_{0-24} (h*ng/mL)	41 2,084.417 (24.1)	41 1,849.033 (31.0)	40 2,009.286 (33.4)		
$AUC_{0-infinity}$ (h*ng/mL)	39 2,133.643 (24.3)	32 1,954.151 (30.9)	38 2,124.422 (35.8)		
n, Median (Minimum, Maximum)					
T_{max} (h)	41 3.000 (1.00, 6.00)	41 3.000 (1.00, 6.00)	40 2.000 (1.00, 5.00)		
$t_{1/2}$ (h)	39 2.880 (1.22, 19.73)	32 5.770 (1.99, 12.83)	38 2.835 (1.74, 16.79)		
Notes: CV = Coefficient of variation; Trt = Treatment group. Source: Section 14.2; Table 14.2.2.					
Statistical Analysis of the Effect of PA21 on Furosemide Exposure					
Parameter (Units)	Geometric LS Mean			Geometric LS Mean Ratio Test/Ref	90% CI of Geometric Mean Ratio Test/Ref (%)
	No PA21; Furosemide with Food (Trt 2) (Ref)	PA21 and Furosemide with Food (Trt 1) (Test)	PA21 with Food; Furosemide 2 Hours Later (Trt 3) (Test)		
C_{max} (ng/mL)	585.22	497.44	N/D	0.850	(0.766, 0.944)
	585.22	N/D	682.49	1.166	(1.050, 1.296)
AUC_{0-24} (h*ng/mL)	2,083.94	1,851.81	N/D	0.889	(0.844, 0.935)
	2,083.94	N/D	2,003.20	0.961	(0.913, 1.012)
$AUC_{0-infinity}$ (h*ng/mL)	2,159.70	2,030.60	N/D	0.940	(0.886, 0.998)
	2,159.70	N/D	2,103.79	0.974	(0.920, 1.031)
Notes: The C_{max} and AUC analyses were performed on log-transformed PK parameters using a linear mixed effects model with treatment, period, sequence, and subject within sequence as fixed effects. LS = Least squares; N/D = No data; PK = Pharmacokinetic; Ref = Reference; Trt = Treatment group.					

Statistical Analysis of the Effect of PA21 on Furosemide T_{max} and $t_{1/2}$						
Parameter	Medians			Median Difference Test/Ref	90% CI Median Difference Test/Ref (%)	Wilcoxon Signed Rank p-value
	No PA21; Furosemide with Food (Trt 2) (Ref)	PA21 and Furosemide with Food (Trt 1) (Test)	PA21 with Food; Furosemide 2 Hours Later (Trt 3) (Test)			
T_{max} (h)	3.000	3.000	N/D	-0.450	(-0.750, 0.000)	0.1004
	3.000	N/D	2.000	-1.250	(-1.715, -0.750)	<.0001
$t_{1/2}$ (h)	2.880	5.770	N/D	2.020	(0.795, 3.230)	0.0044
	2.880	N/D	2.835	0.215	(-1.310, 1.840)	0.7003

Notes: The T_{max} and $t_{1/2}$ analyses were performed using the Wilcoxon signed rank test on the median differences.
Ref = Reference; N/D = No data; Trt = Treatment group.

Safety
 Was there any death or serious adverse events? Yes No NA

Conclusion
 PA21 co-administered with furosemide or administered 2 hours earlier did not influence systemic exposure to furosemide and was generally well tolerated in healthy subjects.

DDI- PA21 VS Omeprazole

Report # PA-DDI-003	Study Period 09/14/11 12/18/11	EDR Link \\cdsesub1\evsprod\nda205109\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\pa-ddi-003\pa-ddi-003-report-body-1.pdf
Title	A Single-centre, Open-label, 3-period Study of the Pharmacokinetic Effect of PA21 on Omeprazole in Healthy Male and Female Adults	
Objectives	To assess the effect, if any, of PA21 on omeprazole exposure.	
Rationale:	Solubility of omeprazole was affected by PA21 in vitro. As the finding is difficult to interpret, this study is being conducted to assess the effect of PA21 on the pharmacokinetics of omeprazole.	
Study Design	Single-Dose Randomized Open-Label Crossover Single-Center 3-Period Healthy Volunteers	
	Subjects were admitted to the clinical facility on Day -2. Three periods are detailed below.	
Screening: -21days	Washout: 7 days	
Sequence	Treatment 123, or 231 or 312	
Treatments:		

Treatment Group	Period Dosing Schedule		
	1	2	3
Treatment 1	PA21 and omeprazole with food	No PA21; omeprazole with food	PA21 with food and omeprazole 2 hours later
Treatment 2	No PA21; omeprazole with food	PA21 with food and omeprazole 2 hours later	PA21 and omeprazole with food
Treatment 3	PA21 with food and omeprazole 2 hours later	PA21 and omeprazole with food	No PA21; omeprazole with food

Study medication

Drug name	PA21	Omeprazole
Dosage Form	Chewable Tablets	Tablets
Dosage Strength (Dose)	2.5 g (15 g/day)	40 mg (40 mg/day)
Lot #	097101B11	E007002
Administration	Oral	Oral

PK Sampling (Blood)

Omeprazole: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24 and 48 hours post-dose of omeprazole administration on Days 1, 12 and 23

Analytical Method

The performance of the assay method during sample analysis is acceptable and is summarized below.

Analyte	Omeprazole
Method	LC/MS/MS
Matrix	Plasma
LOQ (ng/mL)	10.0
Range (ng/mL)	10.0 to 1000
QCs (ng/mL)	30.0, 100, 400, 800
Accuracy/Bias	-3.0 % to 1.0 %
Precision (CV%)	2.6 % to 7.6 %

Statistical Method: Point estimates and 90% confidence intervals for the ratios of the geometric means for omeprazole C_{max} and AUC (Trt 1/Trt 2 and Trt 3/Trt 2) were constructed. The bioequivalence criteria for log-transformed parameters were defined as 80-125%.

Study Population :

Enrolled/Completed/ Discontinued Due to AE	43/38/0
Age [Median (range)]	31.42 (20-49) yr
Male/Female	22/21
Race (White/Black/Asian/Other)	30/5/7/1

Results

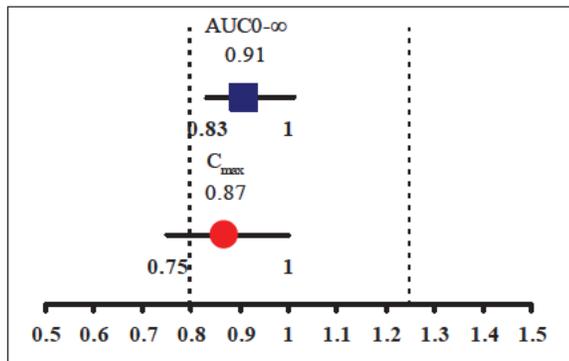
Pharmacokinetics of omeprazole

- Omeprazole C_{max} was not significantly altered when co-administered with PA21; however, omeprazole C_{max} increased by 30% when omeprazole was administered 2 hours after PA21 and

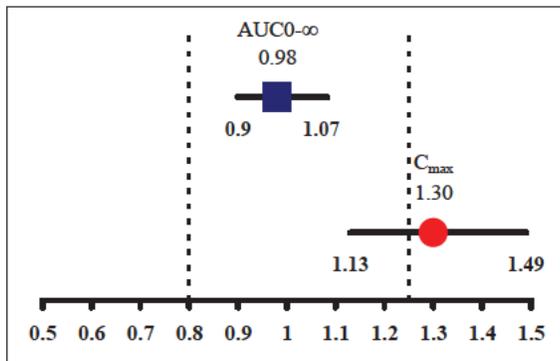
breakfast and the upper bound (149%) of the 90% CI of the geometric mean ratio fell outside the bioequivalence range (80-125%).

- Omeprazole AUC₀₋₈ and AUC_{0-infinity} were not significantly changed whether administered immediately or 2 hours after PA21 and food.
- The T_{max} of omeprazole was significantly shorter when PA21 was administered with breakfast 2 hours prior to omeprazole compared to when omeprazole was administered immediately with PA21 and breakfast.
- The half-life of omeprazole was not changed with or without co-administered with PA21.

PA21 with meal+Omeprazole/ Omeprazole with meal alone



PA21 with meal+2h after Omeprazole / Omeprazole with meal alone



Reviewer's note: the increased C_{max} of omeprazole is consistent with the known food effect of omeprazole where shortened T_{max} was also found significant when omeprazole was taken 2 hours after meal. This finding is due to the study design and not an interaction between PA21 and omeprazole.

Summary of Omeprazole PK parameters

Parameter (Units)	No PA21; Omeprazole with Food (Trt 2) (N=38)	PA21 and Omeprazole with Food (Trt 1) (N=39)	PA21 with Food; Omeprazole 2 Hours Later (Trt 3) (N=39)
n, Geometric Mean, (Geometric %CV)			
C _{max} (ng/mL)	38 569.9891 (70.4)	39 491.3757 (87.5)	39 736.0478 (67.7)
AUC ₀₋₈ (h*ng/mL) ⁽¹⁾	31 1,511.304 (70.3)	36 1,354.040 (70.6)	39 1,486.036 (79.5)
AUC _{0-infinity} (h*ng/mL)	18 1,983.074 (68.4)	18 1,783.147 (80.4)	37 1,591.461 (81.5)

¹ Although AUC₀₋₂₄ was planned, omeprazole levels were below the limit of quantitation in all subjects by 8-12 hours. Therefore, AUC₀₋₈ was calculated instead of AUC₀₋₂₄.

Notes: %CV = Coefficient of variation; N = The number of subjects dosed and included in the PK population for each treatment; PK = Pharmacokinetic; Trt = Treatment group.

Statistical Analysis of the Effect of PA21 on Omeprazole Exposure

PK Parameter (Units)	Geometric LS Mean			Geometric LS Mean Ratio Test/Ref	90% CI of Geometric Mean Ratio Test/Ref (%)
	No PA21; Omeprazole with Food (Trt 2) (Ref)	PA21 and Omeprazole with Food (Trt 1) (Test)	PA21 with Food; Omeprazole 2 Hours Later (Trt 3) (Test)		
C _{max} (ng/mL)	571.42	495.34	N/D	0.867	(0.754, 0.996)
	571.42	N/D	741.80	1.298	(1.130, 1.492)
AUC ₀₋₈ (h*ng/mL) ⁽¹⁾	1,295.43	1,255.25	N/D	0.969	(0.869, 1.080)
	1,295.43	N/D	1,491.18	1.151	(1.034, 1.282)
AUC _{0-infinity} (h*ng/mL)	1,620.82	1,479.14	N/D	0.913	(0.830, 1.003)
	1,620.82	N/D	1,592.40	0.982	(0.903, 1.069)

1 Although AUC₀₋₂₄ was planned, omeprazole levels were below the limit of quantitation in all subjects by 8-12 hours. Therefore, AUC₀₋₈ was calculated instead of AUC₀₋₂₄.

Notes: The C_{max} and AUC analyses were performed on log-transformed PK parameters using a linear mixed effects model with treatment, period, sequence, and subject within sequence as fixed effects.

LS = Least squares; N/D = No data; PK = Pharmacokinetic; Ref = Reference; Trt = Treatment group.

Statistical Analysis of the Effect of PA21 on Omeprazole T_{max} and t_{1/2}

Parameter	Medians			Median Difference Test/Ref	90% CI Median Difference Test/Ref (%)	Wilcoxon Signed Rank p-value
	No PA21; Omeprazole with Food (Trt 2) (Ref)	PA21 and Omeprazole with Food (Trt 1) (Test)	PA21 with Food; Omeprazole 2 Hours Later (Trt 3) (Test)			
T _{max} (h)	4.00	5.00	N/D	0.500	(0.000, 1.000)	0.2142
	4.00	N/D	2.50	-1.750	(-2.250, -1.250)	<0.0001
t _{1/2} (h)	1.00	1.09	N/D	0.002	(-0.130, 0.175)	1.000
	1.00	N/D	0.92	-0.013	(-0.110, 0.055)	0.6889

Notes: The T_{max} and t_{1/2} analyses were performed using the Wilcoxon signed rank test on the median differences.

Ref = Reference; Trt = Treatment group.

Safety

▪ Was there any death or serious adverse events? Yes No NA

Conclusion

PA21 co-administered with omeprazole or administered 2 hours earlier did not influence systemic exposure to omeprazole and was generally well tolerated in healthy subjects.

DDI- PA21 VS Digoxin

Report # PA-DDI-004	Study Period 11/10/11 01/02/12	EDR Link \\cdsesub1\EVSPROD\NDA205109\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\pa-ddi-004\pa-ddi-004-report-body-1.pdf	
Title	A Single-centre, Open-label, 3-period Study of the Pharmacokinetic Effect of PA21 on Digoxin in Healthy Male and Female Adults		
Objectives	To assess the effect, if any, of PA21 on digoxin exposure.		
Rationale:	Digoxin is a narrow therapeutic drug where alteration of its exposure would lead to significant consequences. Therefore, this study is being conducted to assess the effect of PA21 on the pharmacokinetics of digoxin.		
Study Design	Single-Dose Randomized Open-Label Crossover Single-Center 3-Period Healthy Volunteers Subjects were admitted to the clinical facility on Day -2. Three periods are detailed below.		
Screening: -21days	Washout: 7 days		
Sequence	Treatment 123, or 231 or 312		
Treatments:			
Treatment Group	Period Dosing Schedule		
	1	2	3
Treatment 1	PA21 and digoxin with food	No PA21; digoxin alone with food	PA21 with food and digoxin 2 hours later
	2	3	1
Treatment 2	No PA21; digoxin alone with food	PA21 with food and digoxin 2 hours later	PA21 and digoxin with food
	3	1	2
Treatment 3	PA21 with food and digoxin 2 hours later	PA21 and digoxin with food	No PA21; digoxin alone with food
Study medication			
Drug name	PA21		Digoxin
Dosage Form	Chewable Tablets		Tablets
Dosage Strength (Dose)	2.5 g (15 g/day)		0.25 mg (0.5 mg/day)
Lot #	097101B11		A78594
Administration	Oral		Oral
PK Sampling (Blood)			
<u>Digoxin</u> : Pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 hours post-dose of digoxin administration on Days 1, 12 and 23			
Analytical Method			
The performance of the assay method during sample analysis is acceptable and is summarized below.			
	Analyte	Digoxin	
	Method	LC/MS/MS	
	Matrix	Plasma	

LOQ (ng/mL)	0.100
Range (ng/mL)	0.100 to 50.00
QCs (ng/mL)	0.300, 2.5, 20.0, 40.0
Accuracy/Bias	-2.5 % to 1.0 %
Precision (CV%)	4.2 % to 7.0 %

Statistical Method: Point estimates and 90% confidence intervals for the ratios of the geometric means for digoxin C_{max} and AUC (Trt 1/Trt 2 and Trt 3/Trt 2) were constructed. The bioequivalence criteria for log-transformed parameters were defined as 80-125%.

Study Population :

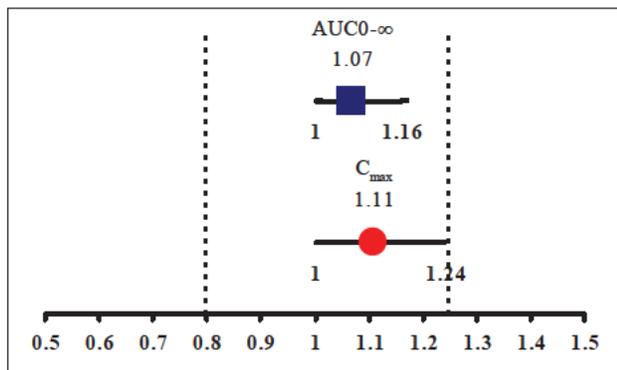
Enrolled/Completed/ Discontinued Due to AE	42/42/0
Age [Median (range)]	31.48 (20-49) yr
Male/Female	21/21
Race (White/Black/Asian/Other)	27/10/4/1

Results

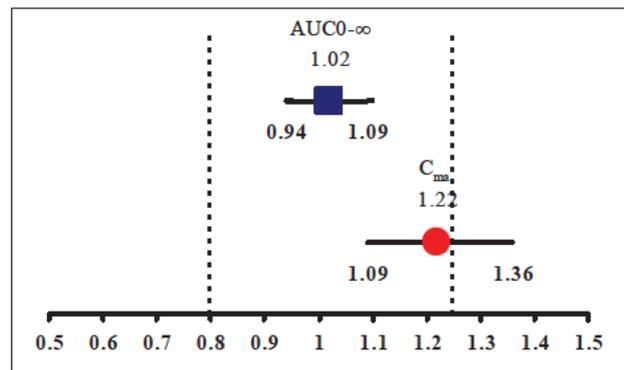
Pharmacokinetics of digoxin

- Digoxin C_{max} increased slightly when digoxin was administered 2 hours after PA21 and breakfast and the upper bound (135%) of the 90% CI of the geometric mean ratio fell outside the bioequivalence range (80-125%).
- Digoxin AUC₀₋₂₄ and AUC_{0-infinity} were not changed whether administered immediately or 2 hours after PA21 and food.
- The T_{max} of digoxin was slightly shorter when PA21 was administered with breakfast 2 hours prior to digoxin compared to when digoxin was administered immediately with PA21 and breakfast.
- The half-life of digoxin was not changed with or without co-administered with PA21.

PA21 with meal+Digoxin/Digoxin with meal alone



PA21 with meal+2h after Digoxin /Digoxin with meal alone



Reviewer's note: the slightly increased C_{max} of digoxin is considered not clinical significant due to following reasons: 1) digoxin AUC is more clinical relevant to describe digoxin exposure, 2) the comparison in this study is confounded by meal where some food effect might contributed to shorter T_{max} hence higher C_{max} as can be seen in the following table. The T_{max} distribution for the Treatment 3 where digoxin was taken without food is between 0.5-2.5 hours while the T_{max} range appears to be 1-4 hour and 0.5-4 hours with food in Treatment 2 and 1, respectively.

Summary of Digoxin PK parameters

Parameter (Units)	No PA21; Digoxin with Food (Trt 2) (N=42)	PA21 and Digoxin with Food (Trt 1) (N=42)	PA21 with Food; Digoxin 2 Hours Later (Trt 3) (N=42)		
n, Geometric Mean (Geometric %CV)					
	42	42	42		
C _{max} (ng/mL)	1.6229 (39.8)	1.8280 (46.1)	1.9759 (37.2)		
	42	42	42		
AUC ₀₋₂₄ (h*ng/mL)	11.1117 (36.2)	12.1084 (34.7)	12.1266 (28.2)		
	36	38	39		
AUC _{0-infinity} (h*ng/mL)	30.6390 (32.4)	33.1481 (28.3)	31.0519 (27.3)		
n, Median (Minimum, Maximum)					
	42	42	42		
T _{max} (h)	1.500 1.00, 4.00	2.000 0.50, 4.00	1.500 0.50, 2.50		
	36	38	39		
t _{1/2} (h)	39.520 21.80, 56.64	38.120 24.95, 66.87	35.930 24.70, 62.39		
Notes: AUC _{0-inf} was not captured if the coefficient of determination R ² was less than 0.8 and the extrapolated area was 20% or greater for the particular profile, per the SAP Geometric %CV is calculated as $\sqrt{\exp(\text{SD}^2)-1} * 100\%$, where SD is the standard deviation. %CV = Coefficient of variation; PK = Pharmacokinetic; SAP = Statistical Analysis Plan; Trt = Treatment group. Source: Section 14.2, Table 14.2.2.					
Statistical Analysis of the Effect of PA21 on Digoxin Exposure					
PK Parameter (Units)	Geometric LS Mean			Geometric LS Mean Ratio Test/Ref	90% CI of Geometric Mean Ratio Test/Ref (%)
	No PA21; Digoxin with Food (Trt 2) (Ref)	PA21 and Digoxin with Food (Trt 1) (Test)	PA21 with Food; Digoxin 2 Hours Later (Trt 3) (Test)		
C _{max} (ng/mL)	1.62	1.80	N/D	1.109	(0.995, 1.236)
	1.62	N/D	1.98	1.218	(1.093, 1.356)
AUC ₀₋₂₄ (h*ng/mL)	11.11	12.11	N/D	1.090	(1.014, 1.171)
	11.11	N/D	12.13	1.091	(1.015, 1.173)
AUC _{0-infinity} (h*ng/mL)	30.55	32.79	N/D	1.074	(0.998, 1.155)
	30.55	N/D	31.02	1.016	(0.944, 1.093)
Notes: The C _{max} and AUC analyses were performed on log-transformed pharmacokinetic parameters using a linear mixed model with treatment, period, sequence, and subject within sequence as fixed effects. LS = Least squares; N/D = No data; PK = Pharmacokinetic; Ref = Reference; Trt = Treatment group.					

Table 12 Statistical Analysis of the Effect of PA21 on Digoxin Exposure T_{max} and $t_{1/2}$

Parameter	Medians			Median Difference Test/Reference	90% CI Median Difference Test/Reference (%)	Wilcoxon Signed Rank p-value
	No PA21; Digoxin with Food (Trt 2) (Reference)	PA21 and Digoxin with Food (Trt 1) (Test)	PA21 with Food; Digoxin 2 Hours Later (Trt 3) (Test)			
T_{max} (h)	1.500	2.00	N/D	0.015	(0.000, 0.250)	0.2445
	1.500	N/D	1.500	-0.500	(-0.500, -0.250)	0.0006
$t_{1/2}$ (h)	39.520	38.120	N/D	-2.125	(-5.020, 1.255)	0.4022
	39.520	N/D	35.930	-2.795	(-5.320, -0.145)	0.0854

Notes: The T_{max} and $t_{1/2}$ treatment medians and p-value are from the Wilcoxon signed rank test. The T_{max} and $t_{1/2}$ median difference (test/reference) and 90% CI of the median difference are from Hodges-Lehmann estimate.
N/D = No data; Trt = Treatment group.

Source: Section 14.2; Table 14.2.3.2.

Safety

- Was there any death or serious adverse events? Yes No NA

Conclusion

PA21 co-administered with digoxin or administered 2 hours earlier did not influence systemic exposure to digoxin and was generally well tolerated in healthy subjects.

DDI- PA21 VS Warfarin

Report # PA-DDI-005	Study Period 11/09/11 02/08/12	EDR Link \\cdsesub1\evsprod\nda205109\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\pa-ddi-005\pa-ddi-005-report-body-1.pdf
Title	A Single-centre, Open-label, 3-period Study of the Pharmacokinetic Effect of PA21 on Warfarin in Healthy Male and Female Adults	
Objectives	To assess the effect, if any, of PA21 on warfarin exposure.	
Rationale:	Warfarin is a narrow therapeutic drug where alteration of its exposure would lead to significant consequences. Therefore, this study is being conducted to assess the effect of PA21 on the pharmacokinetics of warfarin.	
Study Design	Single-Dose Randomized Open-Label Crossover Single-Center 3-Period Healthy Volunteers	
	Subjects were admitted to the clinical facility on Day -2. Three periods are detailed below.	
Screening: -21days	Washout: 7 days	
Sequence	Treatment 123, or 231 or 312	
Treatments:		

Treatment Group	Period Dosing Schedule		
	1	2	3
Treatment 1	PA21 and warfarin with food	No PA21; warfarin alone with food	PA21 with food and warfarin 2 hours later
Treatment 2	No PA21; warfarin alone with food	PA21 with food and warfarin 2 hours later	PA21 and warfarin with food
Treatment 3	PA21 with food and warfarin 2 hours later	PA21 and warfarin with food	No PA21; warfarin alone with food

Study medication

Drug name	PA21	Warfarin
Dosage Form	Chewable Tablets	Tablets
Dosage Strength (Dose)	2.5 g (15 g/day)	10 mg (10 mg/day)
Lot #	097101B11	1E67414A
Administration	Oral	Oral

PK Sampling (Blood)

Warfarin: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours post-dose of warfarin administration on Days 1, 12 and 23

Analytical Method

The performance of the assay method during sample analysis is acceptable and is summarized below.

Analyte	R-Warfarin	S-Warfarin
Method	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma
LOQ (ng/mL)	10.0	10.0
Range (ng/mL)	10.0 to 1000	10.0 to 1000
QCs (ng/mL)	30.0, 110, 400, 800	30.0, 110, 400, 800
Accuracy/Bias	-0.3 % to 4.3 %	-0.5 % to 4.3 %
Precision (CV%)	4.9 % to 9.4 %	4.7 % to 9.3 %

Statistical Method: Point estimates and 90% confidence intervals for the ratios of the geometric means for warfarin C_{max} and AUC (Trt 1/Trt 2 and Trt 3/Trt 2) were constructed. The bioequivalence criteria for log-transformed parameters were defined as 80-125%.

Study Population :

Enrolled/Completed/ Discontinued Due to AE	43/42/1*
Age [Median (range)]	30.05 (20-50) yr
Male/Female	26/17
Race (White/Black/American Indian/Asian)	26/15/1/1

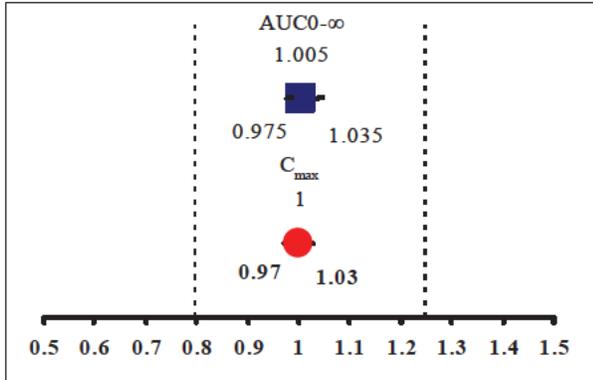
*: 1 subject with 1 TEAE during Trt 1 (rhabdomyolysis) that was considered both serious and severe but not related to study treatment. Study treatments were discontinued in this subject.

Results

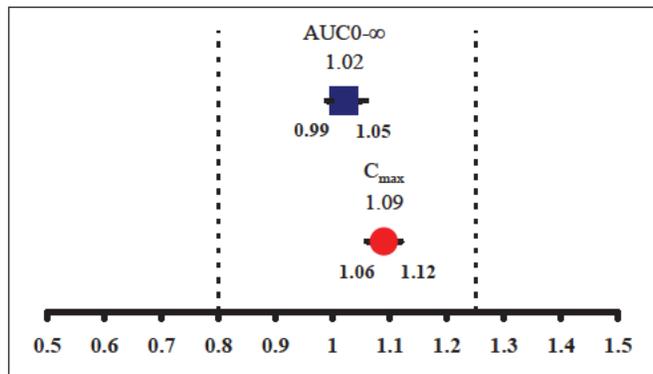
Pharmacokinetics of warfarin

- C_{max}, AUC₀₋₂₄ and AUC_{0-infinity} of both R- and S-warfarin were not changed whether administered immediately or 2 hours after PA21 and food. The 90% CI for all 3 parameters were within the equivalence range of 80-125%.
- The T_{max} of R- and S-warfarin was reached sooner when warfarin was administered 2 hours after PA21 with breakfast.
- The half-life of warfarin was not changed with or without co-administered with PA21.

PA21 with meal+Warfarin/Warfarin with meal alone



PA21 with meal+2h after Warfarin/Warfarin with meal alone



Summary of R-warfarin PK parameters

PK Parameter (Units)	No PA21; Warfarin with Food (Trt 2) (N=41)	PA21 and Warfarin with Food (Trt 1) (N=42)	PA21 with Food; Warfarin 2 Hours Later (Trt 3) (N=41)
n, Geometric Mean, (Geometric %CV)			
C _{max} (ng/mL)	41 1,083.232 (19.7)	42 1,081.186 (19.6)	41 1,178.980 (16.4)
AUC ₀₋₂₄ (h*ng/mL)	41 19,094.37 (18.9)	42 18,981.66 (18.0)	41 19,689.59 (16.7)
AUC _{0-infinity} (h*ng/mL)	40 68,411.02 (27.0)	42 68,603.59 (26.8)	41 69,725.68 (27.7)

Note: AUC_{0-inf} was not captured if the coefficient of determination R² was less than 0.8 and the extrapolated area was 20% or greater for the particular profile, per the SAP.
 Geometric %CV is calculated as $\sqrt{\exp(\text{SD}^2)-1} \times 100\%$.
 %CV = Coefficient of variation; PK = Pharmacokinetic; SAP = Statistical Analysis Plan;
 Trt = Treatment group.

Summary of S-warfarin PK parameters

PK Parameter (Units)	No PA21; Warfarin with Food (Trt 2) (N=41)	PA21 and Warfarin with Food (Trt 1) (N=42)	PA21 with Food; Warfarin 2 Hours Later (Trt 3) (N=41)		
n, Geometric Mean, (Geometric %CV)					
C _{max} (ng/mL)	41 1,028.710 (20.7)	42 1,032.264 (18.6)	41 1,166.021 (15.2)		
AUC ₀₋₂₄ (h*ng/mL)	41 15,706.44 (22.8)	42 15,722.26 (23.2)	41 16,103.34 (17.3)		
AUC _{0-infinity} (h*ng/mL)	40 44,216.19 (38.9)	42 45,512.21 (48.2)	41 45,728.93 (36.7)		
Note: AUC _{0-inf} was not captured if the coefficient of determination R ² was less than 0.8 and the extrapolated area was 20% or greater for the particular profile, per the SAP. Geometric %CV is calculated as $\sqrt{(\exp(\text{SD}^2)-1)*100\%}$. %CV = Coefficient of variation; PK = Pharmacokinetic; SAP = Statistical Analysis Plan; Trt = Treatment group.					
Statistical Analysis of the Effect of PA21 on Warfarin Exposure					
Geometric LS Mean					
PK Parameter (Units)	No PA21; Warfarin with Food (Trt 2) (Ref)	PA21 and Warfarin with Food (Trt 1) (Test)	PA21 with Food; Warfarin 2 Hours Later (Trt 3) (Test)	Geometric LS Mean Ratio Test/Ref	90% CI of Geometric Mean Ratio Test/Ref (%)
R-warfarin					
C _{max} (ng/mL)	1,084.79	1,084.43	N/D	1.000	(0.970, 1.030)
	1,084.79	N/D	1,179.19	1.087	(1.055, 1.120)
AUC ₀₋₂₄ (h*ng/mL)	19,061.33	19,049.28	N/D	0.999	(0.981, 1.018)
	19,061.33	N/D	19,726.65	1.035	(1.016, 1.054)
AUC _{0-infinity} (h*ng/mL)	68,552.25	68,867.47	N/D	1.005	(0.975, 1.035)
	68,552.25	N/D	69,945.84	1.020	(0.991, 1.051)
S-warfarin					
C _{max} (ng/mL)	1,033.36	1,035.07	N/D	1.002	(0.965, 1.040)
	1,033.36	N/D	1,168.21	1.130	(1.088, 1.174)
AUC ₀₋₂₄ (h*ng/mL)	15,836.22	15,801.93	N/D	0.998	(0.976, 1.021)
	15,836.22	N/D	16,202.49	1.023	(1.000, 1.047)
AUC _{0-infinity} (h*ng/mL)	46,174.66	45,824.90	N/D	0.992	(0.960, 1.026)
	46,174.66	N/D	46,277.24	1.002	(0.969, 1.036)
Notes: The C _{max} and AUC analyses were performed on log-transformed pharmacokinetic parameters using a linear mixed model with treatment, period, sequence, and subject within sequence as fixed effects. LS = Least squares; N/D = No data; PK = Pharmacokinetic; Ref = Reference; Trt = Treatment group.					

Statistical Analysis of the Effect of PA21 on Warfarin T_{max} and t_{1/2}

Parameter	Medians			Median Difference Test/Ref	90% CI Median Difference Test/Ref (%)	Wilcoxon Signed Rank p-value
	No PA21; Warfarin with Food (Trt 2) (Ref)	PA21 and Warfarin with Food (Trt 1) (Test)	PA21 with Food; Warfarin 2 Hours Later (Trt 3) (Test)			
R-warfarin						
T _{max} (h)	3.080	4.000	N/D	0.250	(-0.500, 0.750)	0.7835
	3.080	N/D	2.000	-1.500	(-2.250, -1.000)	<0.0001
t _{1/2} (h)	48.600	48.430	N/D	0.400	(-0.945, 1.825)	0.5520
	48.600	N/D	48.310	-0.322	(-1.565, 0.990)	0.6775
S-warfarin						
T _{max} (h)	3.000	3.510	N/D	0.250	(-0.250, 0.510)	0.4823
	3.000	N/D	1.500	-1.250	(-1.500, -1.000)	<0.0001
t _{1/2} (h)	40.100	40.550	N/D	0.300	(-0.320, 0.985)	0.3817
	40.100	N/D	40.440	-0.738	(-1.585, 0.295)	0.2612

Notes: The T_{max} and t_{1/2} treatment medians and p-value are from the Wilcoxon signed rank test. The T_{max} and t_{1/2} median difference (test-reference) and 90% CI of the median difference are from Hodges-Lehmann estimate.
N/D = No data; Ref = Reference; Trt = Treatment group.

Safety

- Was there any death or serious adverse events? Yes No NA

1 subject with 1 TEAE during Trt 1 (rhabdomyolysis) that was considered both serious and severe but not related to study treatment. Study treatments were discontinued in this subject.

Conclusion

PA21 co-administered with warfarin or administered 2 hours earlier did not influence systemic exposure to warfarin and was generally well tolerated in healthy subjects.

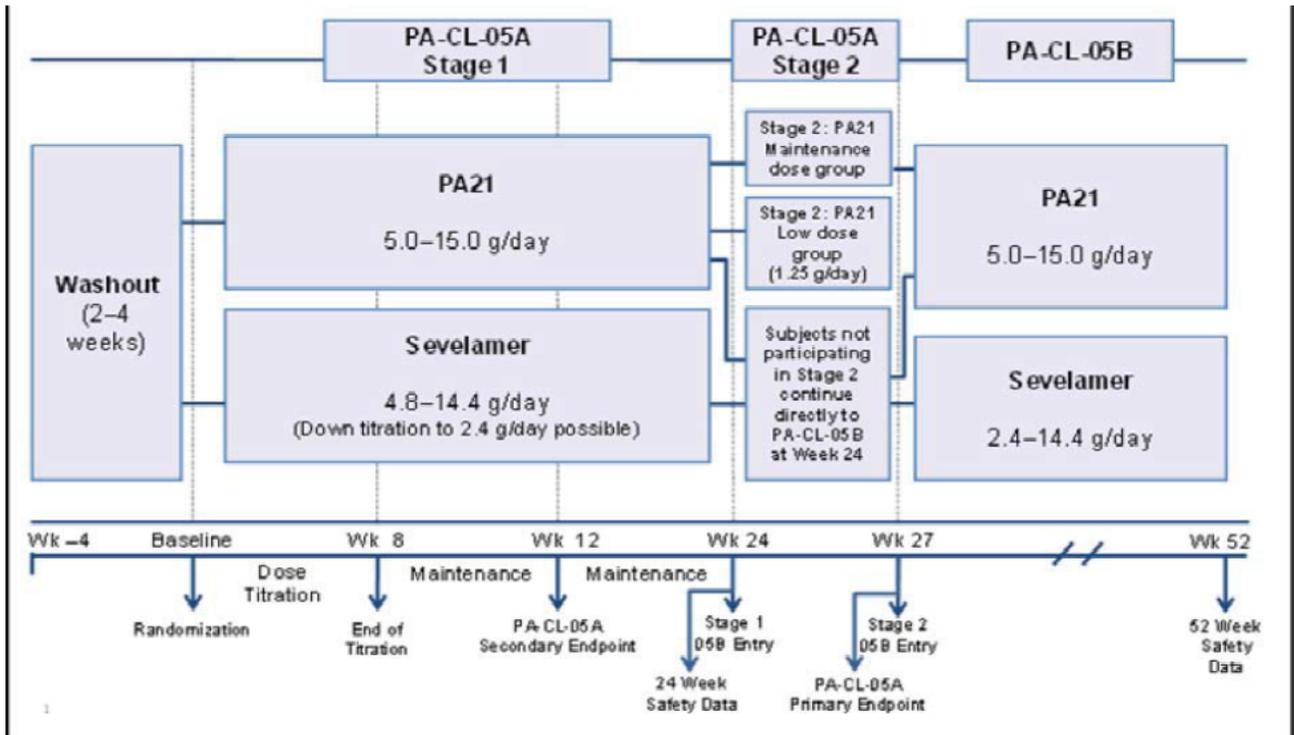
PD-DDI- PA21 VS Statins

Title	A Supplementary Post-hoc Report of Analyses to Assess for Pharmacodynamic Interaction of PA21 with HMG-CoA Reductase Inhibitors (Statins)
EDR Link	\\cdsesub1\evsprod\nda205109\0013\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\hyperphosphataemia\5354-other-stud-rep\statin-analysis\statin-analysis-report-body.pdf
Objectives	To explore and assess possible pharmacodynamic interactions between atorvastatin or simvastatin and PA21.

Rationale: Atorvastatin showed in vitro interaction with PA21. As statins were used in the pivotal trials and lipid-lowering effects were routinely measured, the aim of this analyses was to use pooled data from these 2 studies to determine if there are any pharmacodynamic interactions between PA21 and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (either atorvastatin, simvastatin, or other statins) administered concomitantly in ESRD patients. Specifically, the potential of PA21 to affect the lipid-lowering effects of these drugs was investigated.

Study Design

Pooled data from studies PA-CL-05A and PA-CL-05B were used for these integrated, post-hoc analyses. Design of the studies is shown below.



Source: PA-CL-05A/PA-CL-05B Clinical Study Report, Figure 1.

As part of the clinical chemistry safety analyses, the levels of LDL-C, Total-C, and triglycerides were determined at baseline (BL) and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, and at end of study/termination. In this report, 2 analysis populations were derived from the safety set in PA-CL-05A/PA-CL-05B: the atorvastatin set (AS) and the simvastatin set (SmS). Changes from BL over time in LDL-C (primary parameter), Total-C, and triglyceride levels were compared within the AS or SmS.

To avoid any changes in the lipid parameters by changes in the doses of statins, any change to the dose of statin, or any addition or deletion of a statin before the subject returned a post-BL evaluable LDL-C value led to exclusion from the AS or SmS.

Study Population :

Table 3 Summary of Analysis Populations for the Atorvastatin Set

Population	All Subjects in the PA-CL-05A/PA-CL-05B Safety Set (N=1,055)					
	PA21 (N=707)			Sevelamer (N=348)		
	BL Atorvastatin n (%)	Other BL Statin n (%)	No BL Statin n (%)	BL Atorvastatin n (%)	Other BL Statin n (%)	No BL Statin n (%)
05A/05B safety set	84 (100%)	185 (100%)	438 (100%)	45 (100%)	94 (100%)	209 (100%)
AS	76 (90.5%)	177 (95.7%)	424 (96.8%)	44 (97.8%)	87 (92.6%)	202 (96.7%)

Notes: AS = Atorvastatin set; BL = Baseline (in Study PA-CL-05A); 05A/05B = PA-CL-05A/PA-CL-05B.
Source: Section 5, Table 1.1.2.

Table 4 Summary of Analysis Populations for the Simvastatin Set

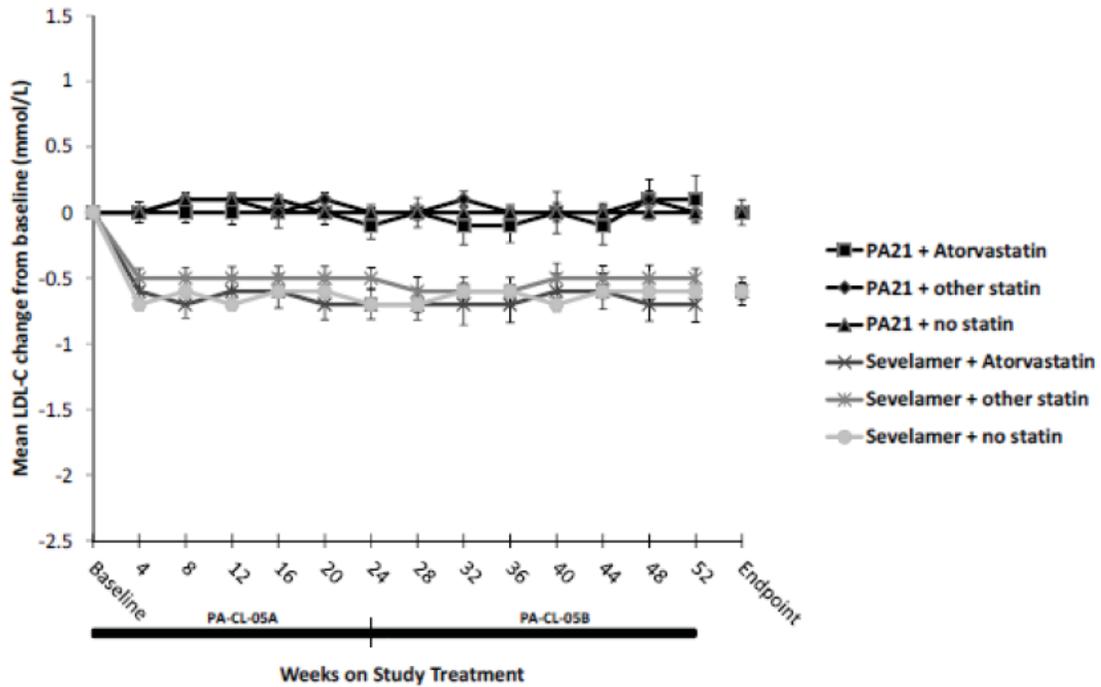
Population	All Subjects in the PA-CL-05A/PA-CL-05B Safety Set (N=1,055)					
	PA21 (N=707)			Sevelamer (N=348)		
	BL Simvastatin n (%)	Other BL Statin n (%)	No BL Statin n (%)	BL Simvastatin n (%)	Other BL Statin n (%)	No BL Statin n (%)
05A/05B safety set	131 (100%)	138 (100%)	438 (100%)	64 (100%)	75 (100%)	209 (100%)
SmS	126 (96.2%)	127 (92.0%)	424 (96.8%)	59 (92.2%)	72 (96.0%)	202 (96.7%)

Notes: BL = Baseline (in Study PA-CL-05A); 05A/05B = PA-CL-05A/PA-CL-05B; SmS = Simvastatin set.
Source: Section 5, Table 2.1.2.

Results

Atorvastatin

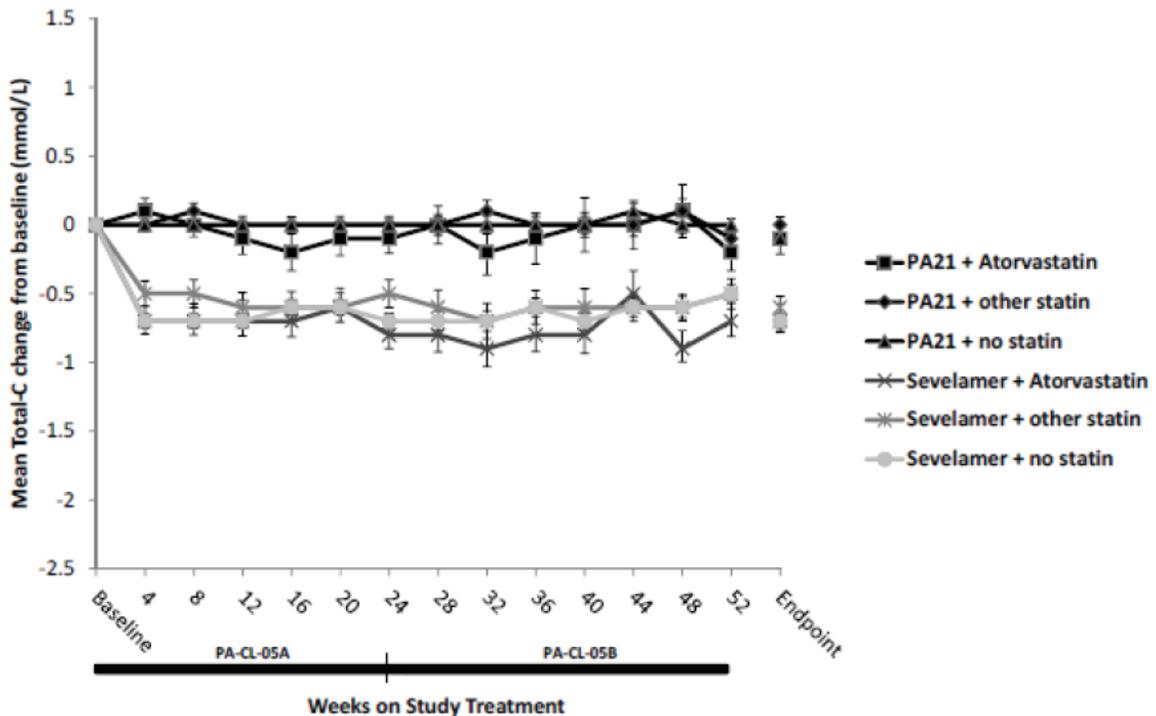
- LDL-C levels were not altered by PA21 over 52 weeks.
- LDL-C decreased by sevelamer regardless of whether receiving statins or not. This is a known effect of selevamer.
- Similar results were observed in Total-C.
- No changes were seen in triglycerides in both PA21 and sevelamer groups.

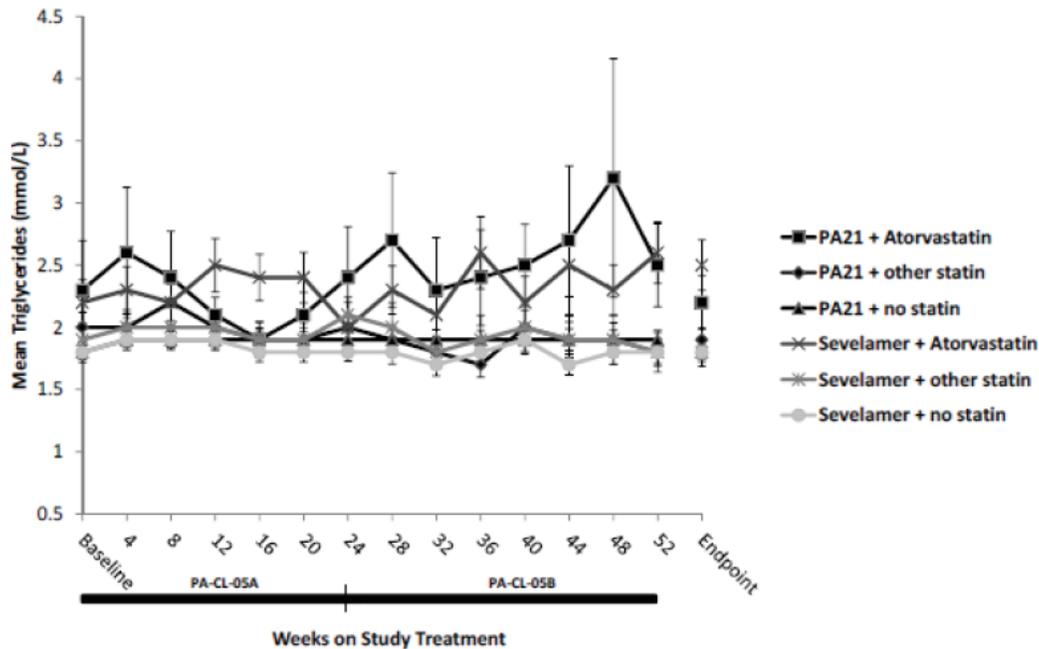


Notes: Baseline was defined as the latest evaluable value prior to the first study drug intake in PA-CL-05A. Endpoint was defined as the PA-CL-05B Week 28 value (i.e., Week 52 in combined PA-CL-05A/PA-CL-05B) or the latest non-missing evaluable value when 05B Week 28 is missing/not evaluable.

LDL-C = Low density lipoprotein cholesterol; SEM = Standard error of the mean.

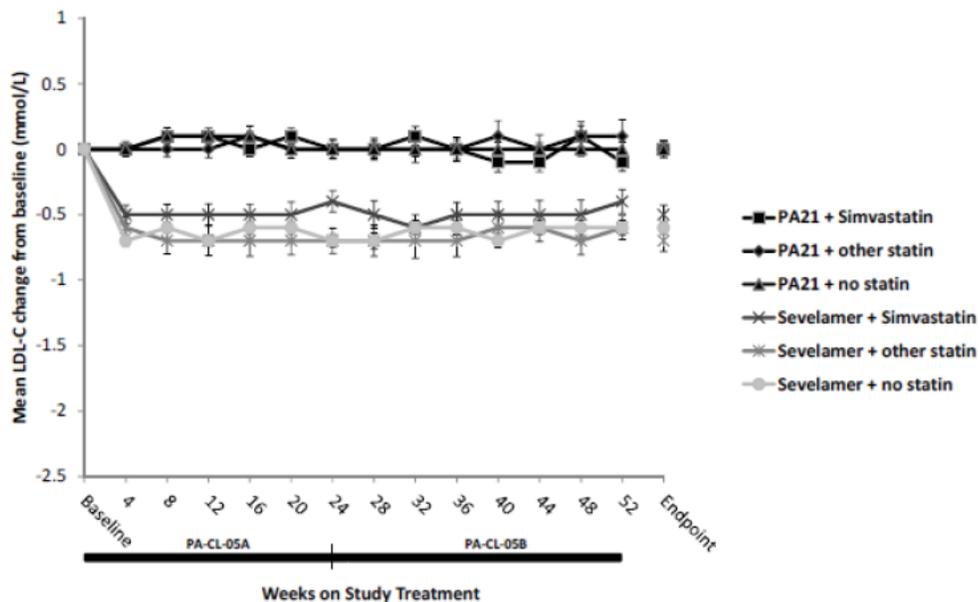
Source: Section 5, Table 1.4.1.1.





Simvastatin

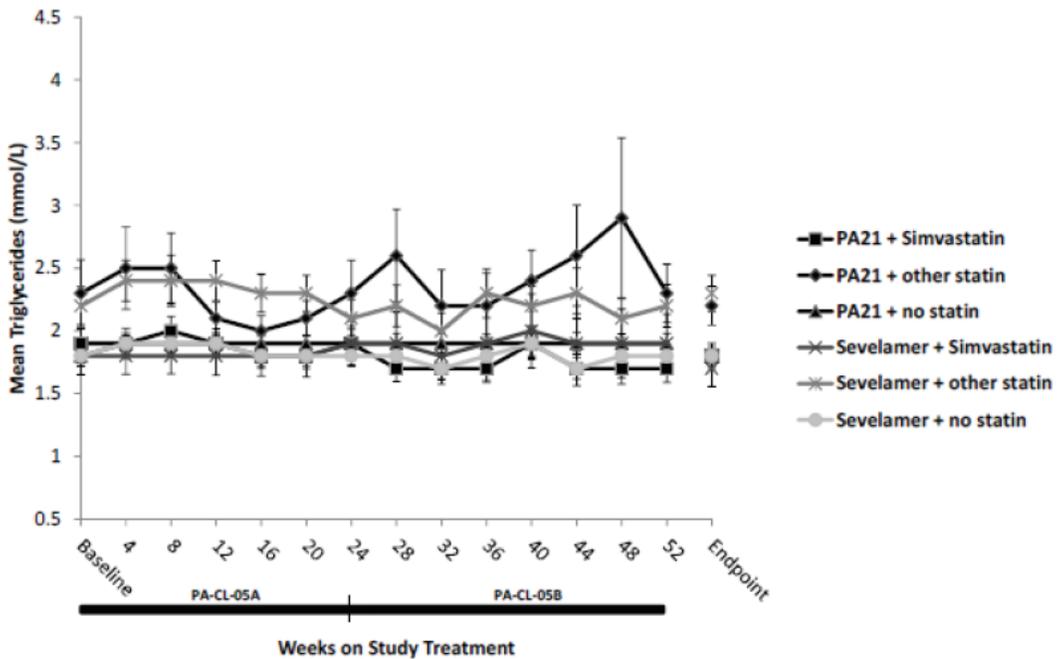
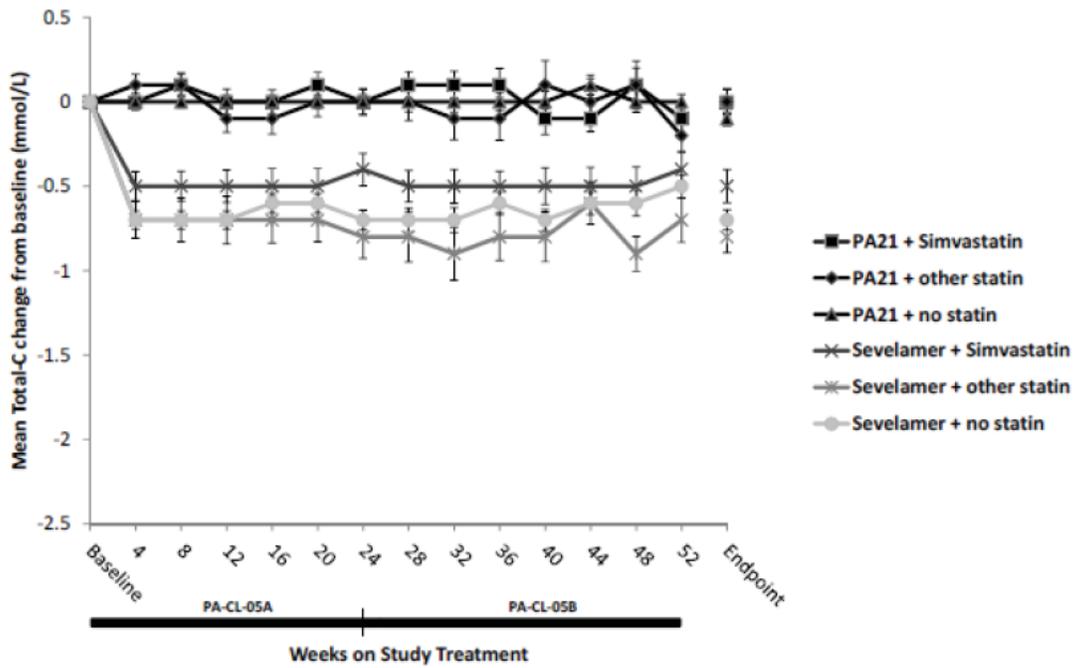
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- LDL-C decreased by sevelamer regardless of whether receiving statins or not. This is a known effect of sevelamer.
- Similar results were observed in Total-C.
- No changes were seen in triglycerides in both PA21 and sevelamer groups.



Notes: Baseline was defined as the latest evaluable value prior to the first study drug intake in PA-CL-05A. Endpoint was defined as the PA-CL-05B Week 28 value (i.e., Week 52 in combined PA-CL-05A/PA-CL-05B) or the latest non-missing evaluable value when 05B Week 28 is missing/not evaluable.

LDL-C = Low density lipoprotein cholesterol; SEM = Standard error of the mean.

Source: Section 5, Table 2.4.1.1.



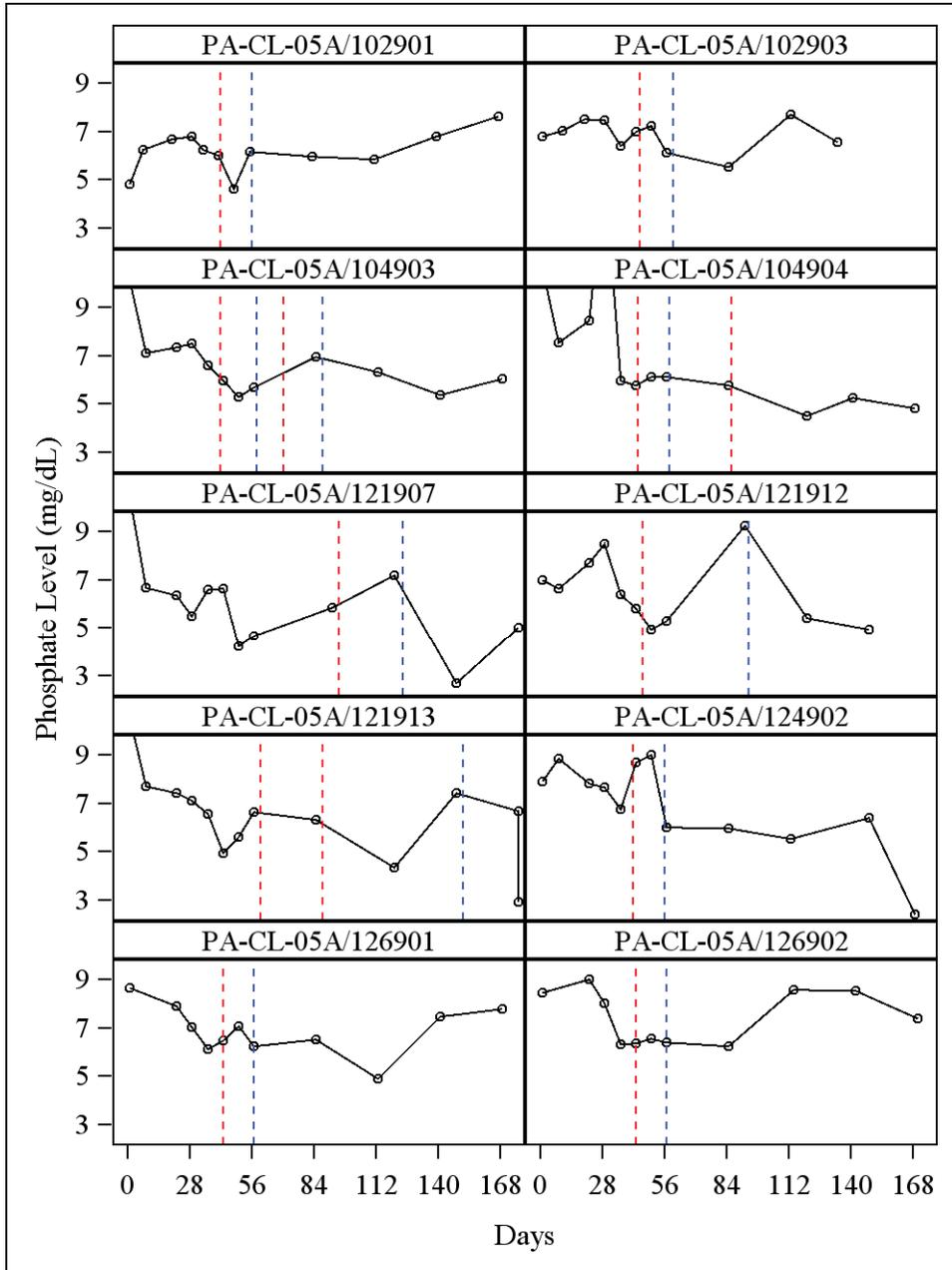
Conclusion

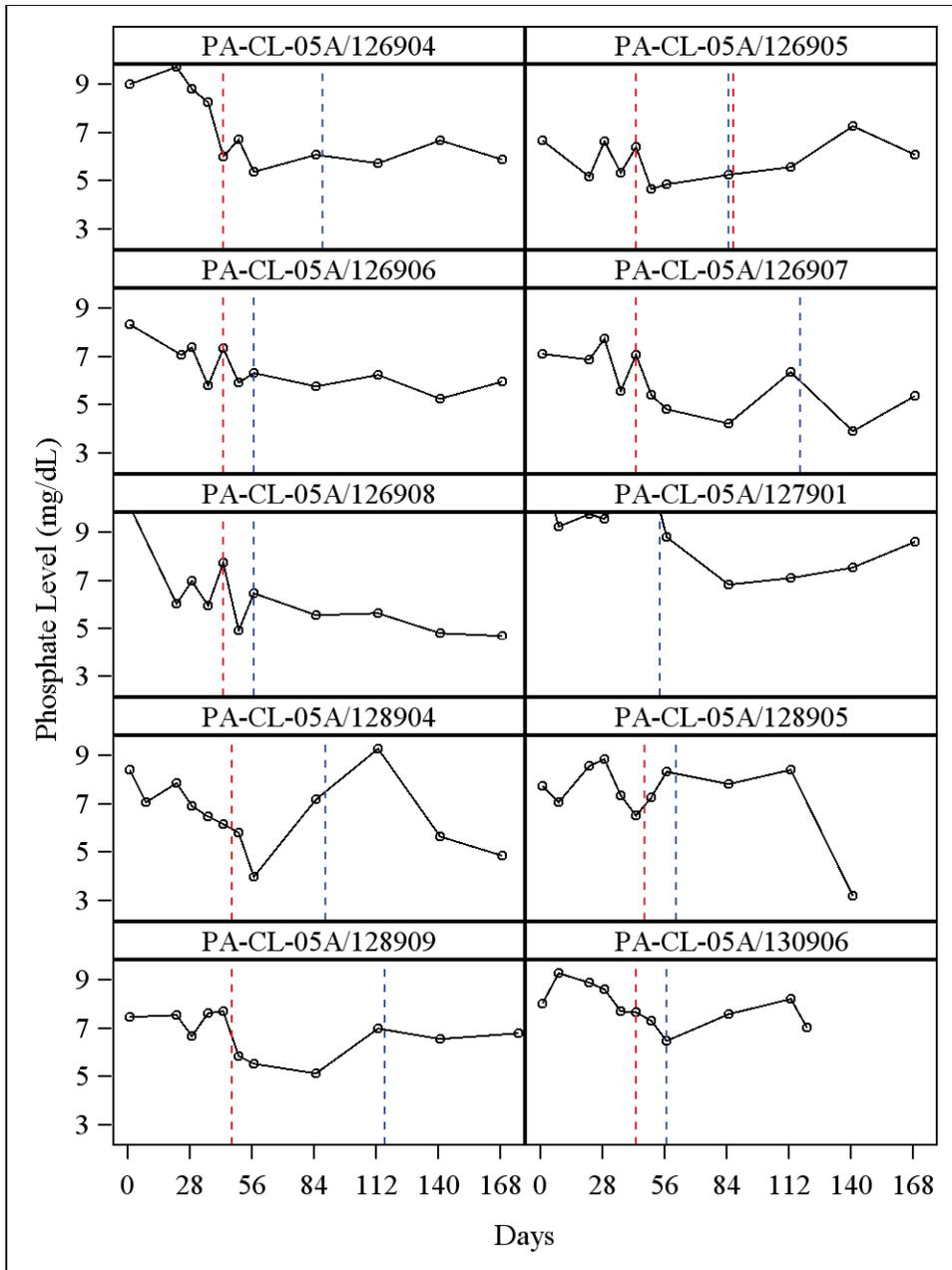
PA21 does not affect the lipid-lowering effects of HMG-CoA reductase inhibitors.

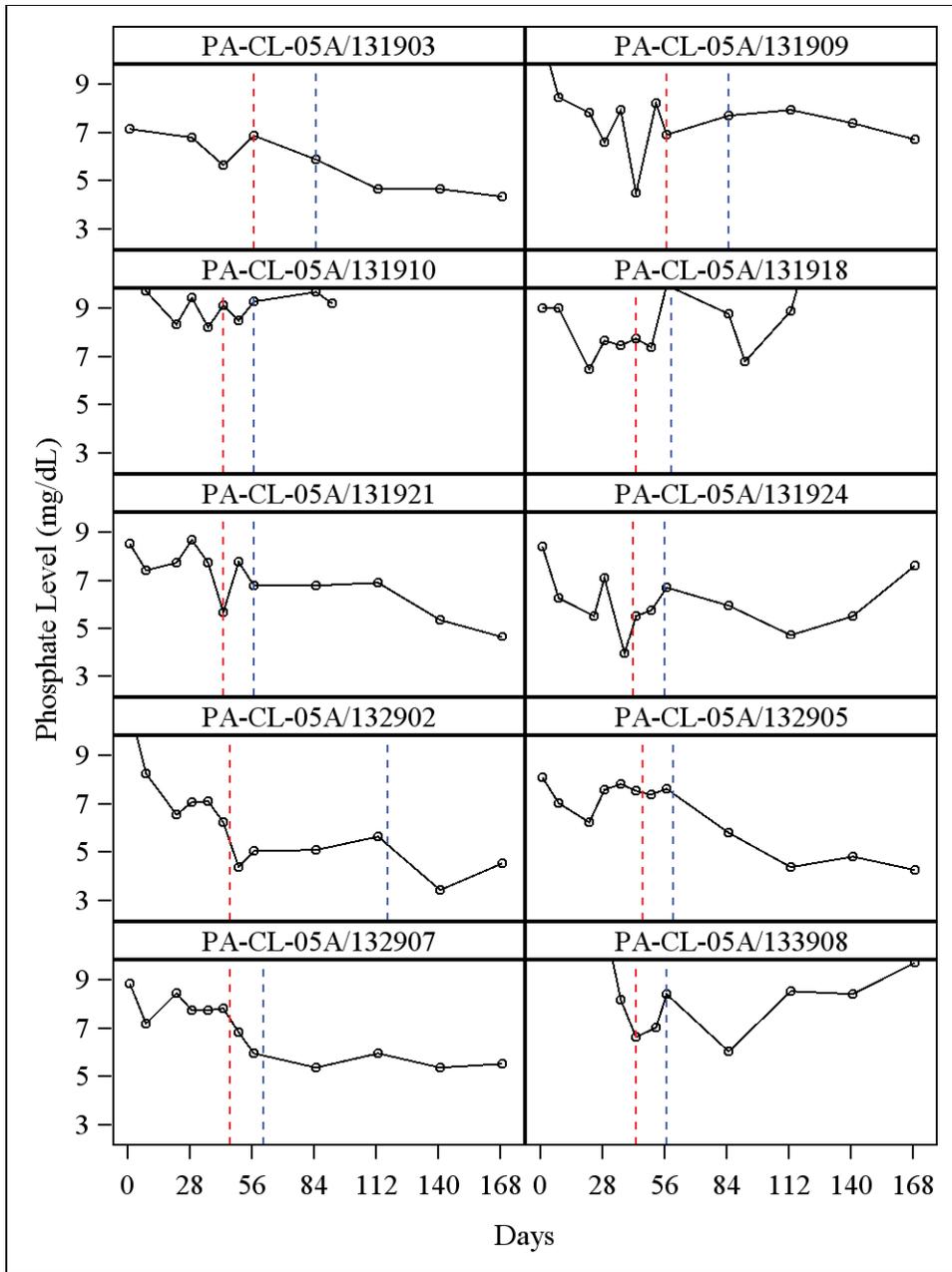
APPENDIX II INDIVIDUAL SERUM PHOSPHATE-TIME COURSE IN PATIENTS RECEIVED 12.5 G OR 15 G PA21 PER DAY

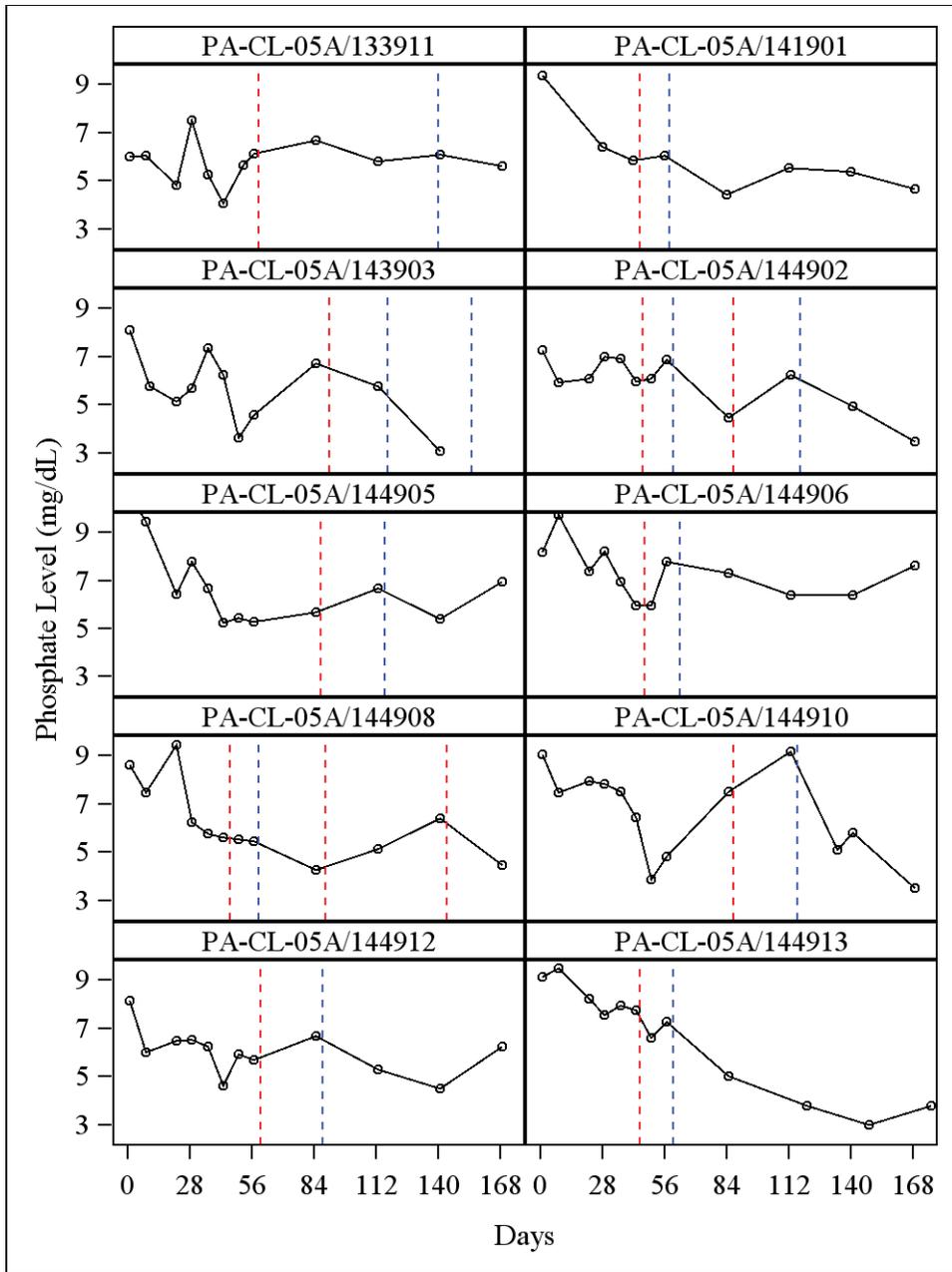
The graphs below show the serum phosphate values of individuals who got 12.5 or 15 g PA21/day as the maximum dose of this drug. There are several individuals who benefitted in terms control (reduction) of serum phosphate levels due to up-titration to 12.5 or further to 15 g PA21/day.

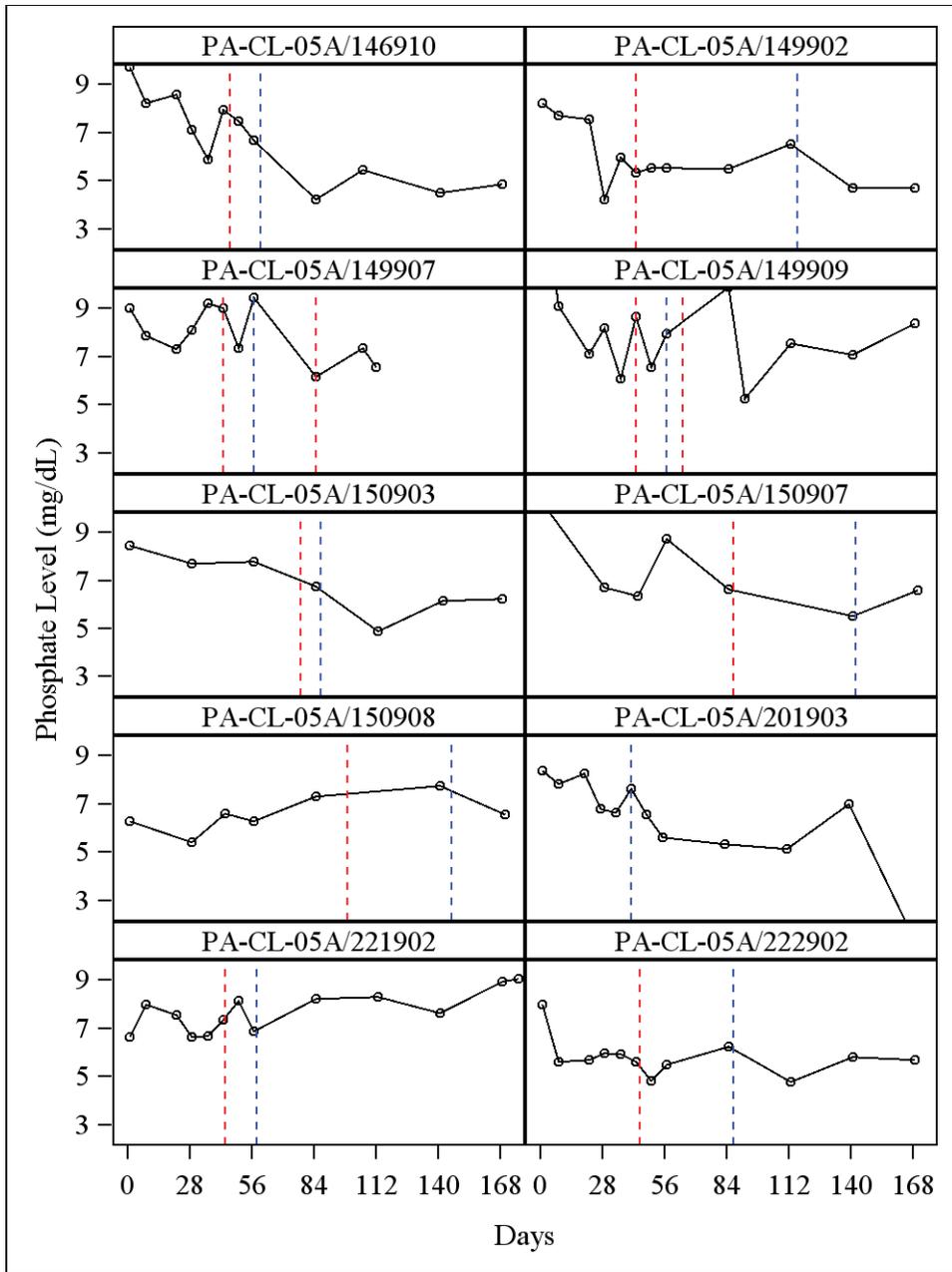
The red and blue dotted lines in the following graphs indicate dose change to 12.5 and to 15 g PA21/Day respectively. The black dots represent the measured serum phosphate values at specific visits, while the black line is drawn to aid the visualization of trend of measured serum phosphate values.

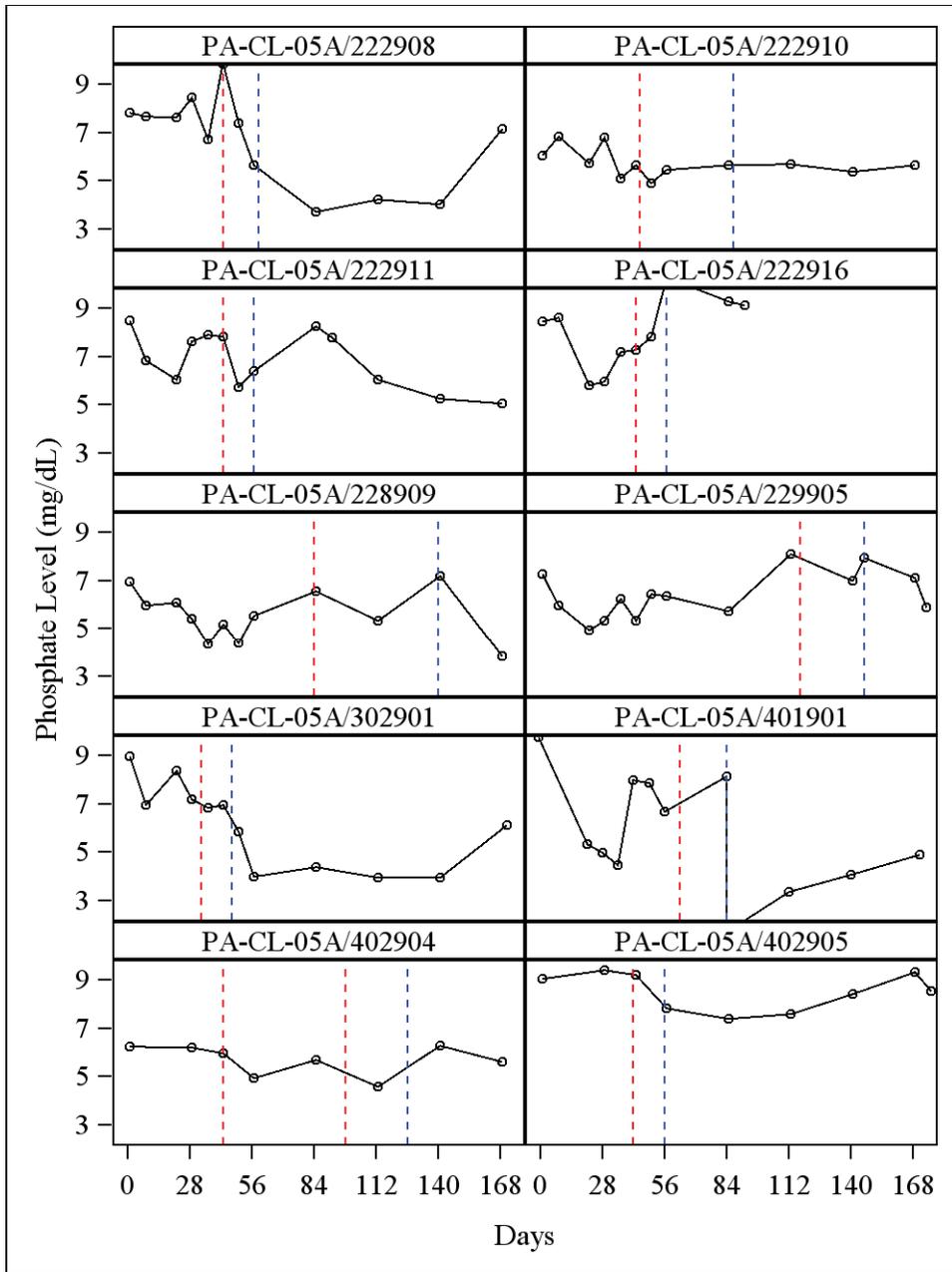


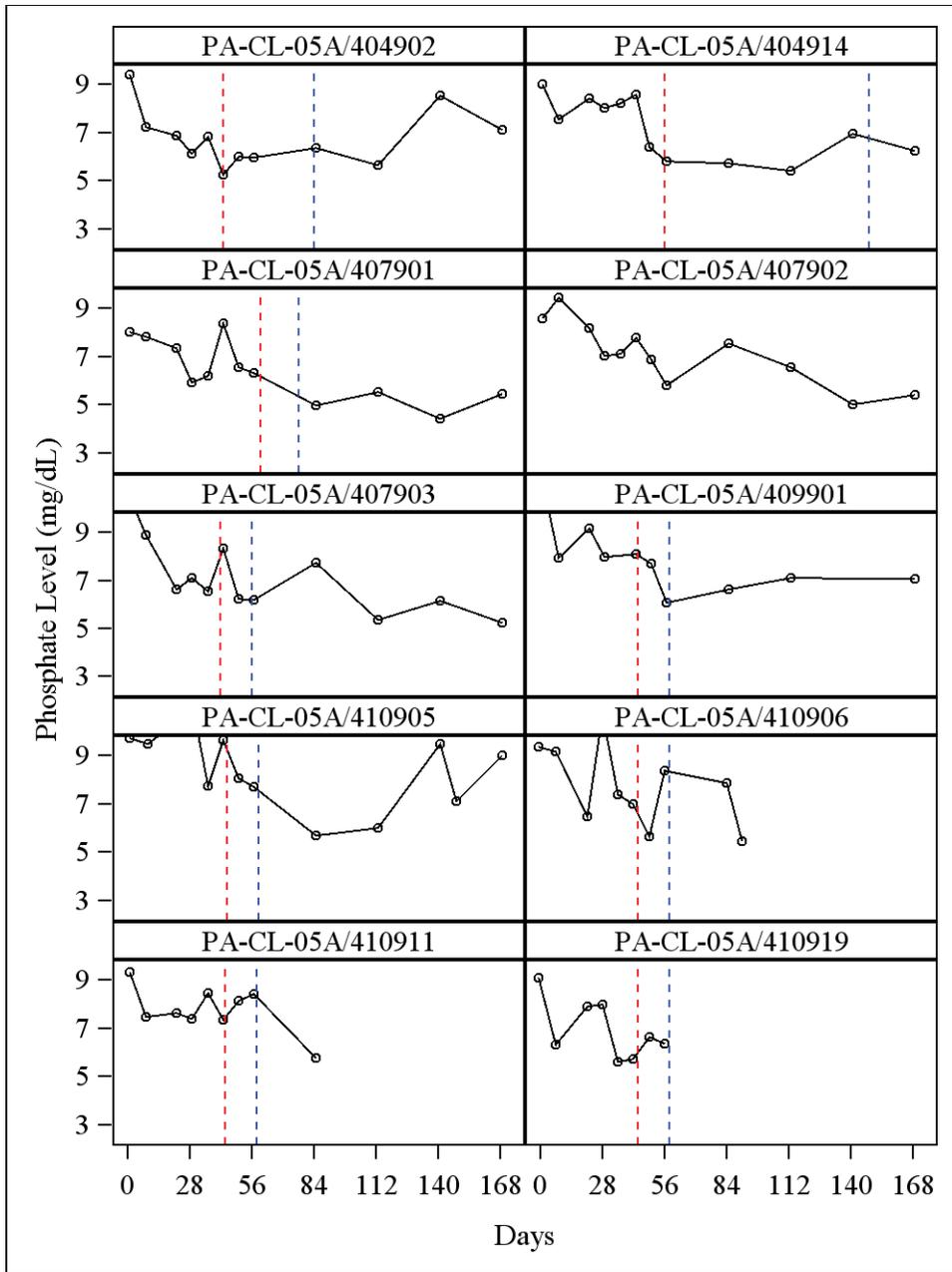


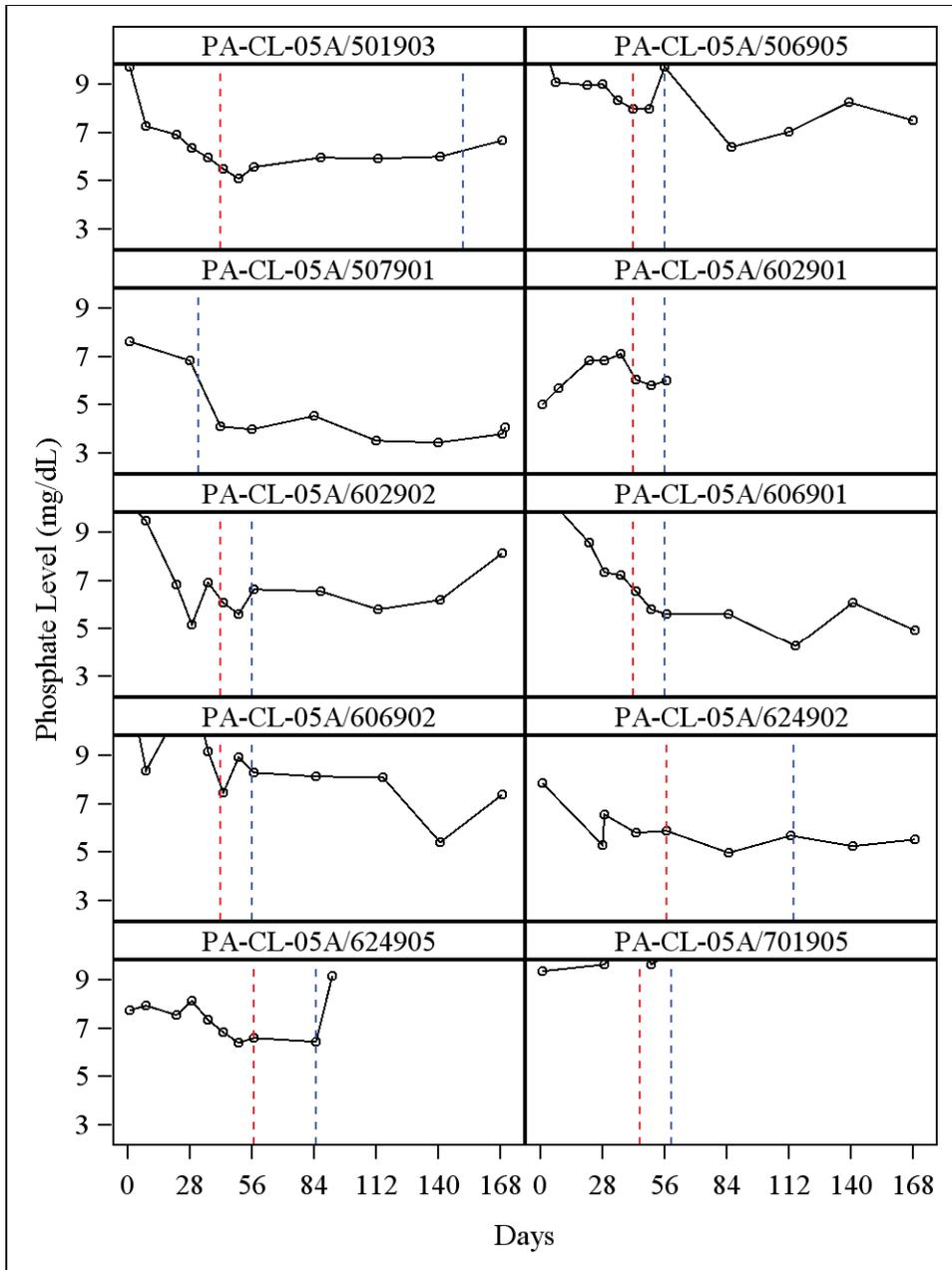


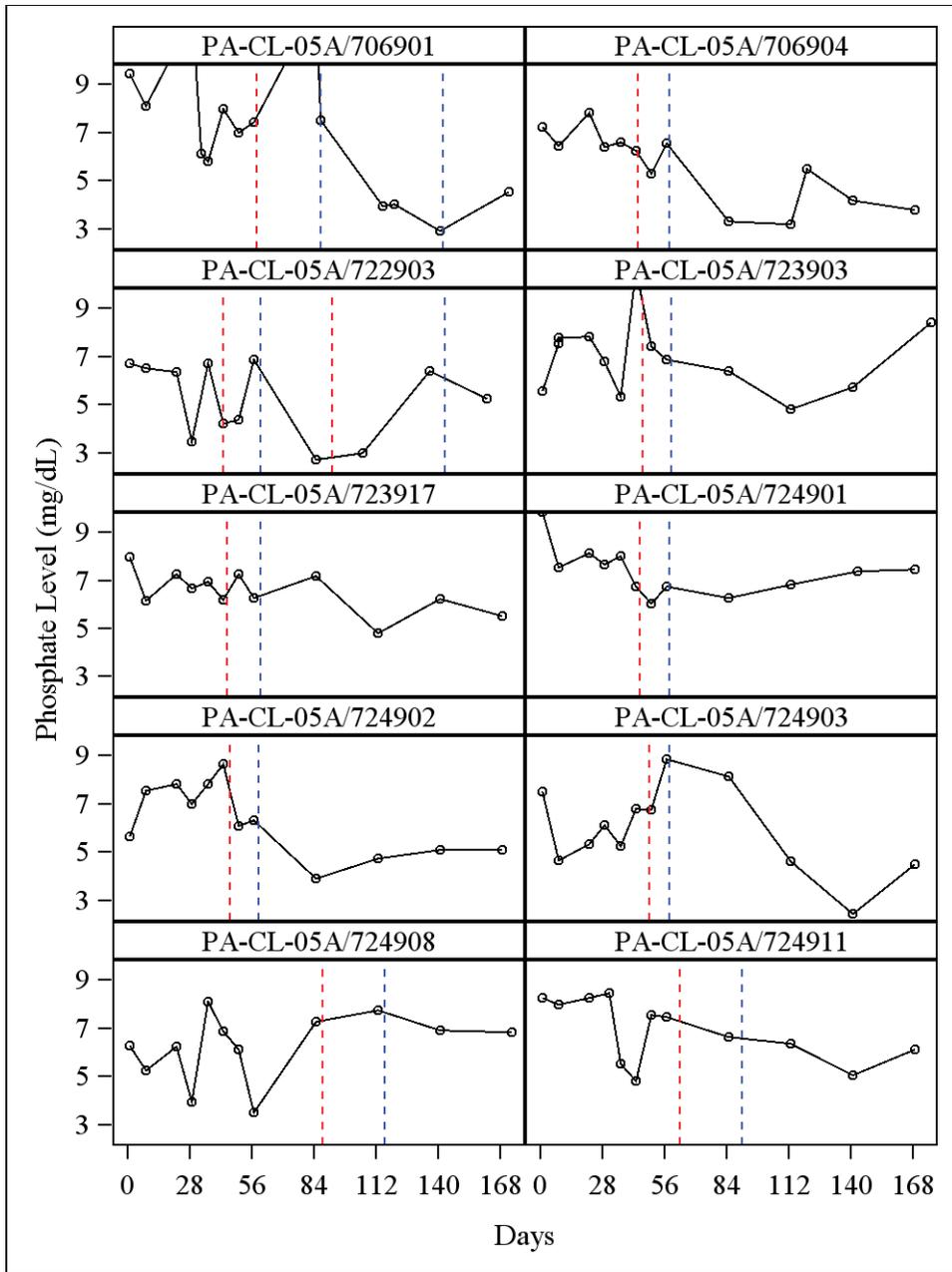


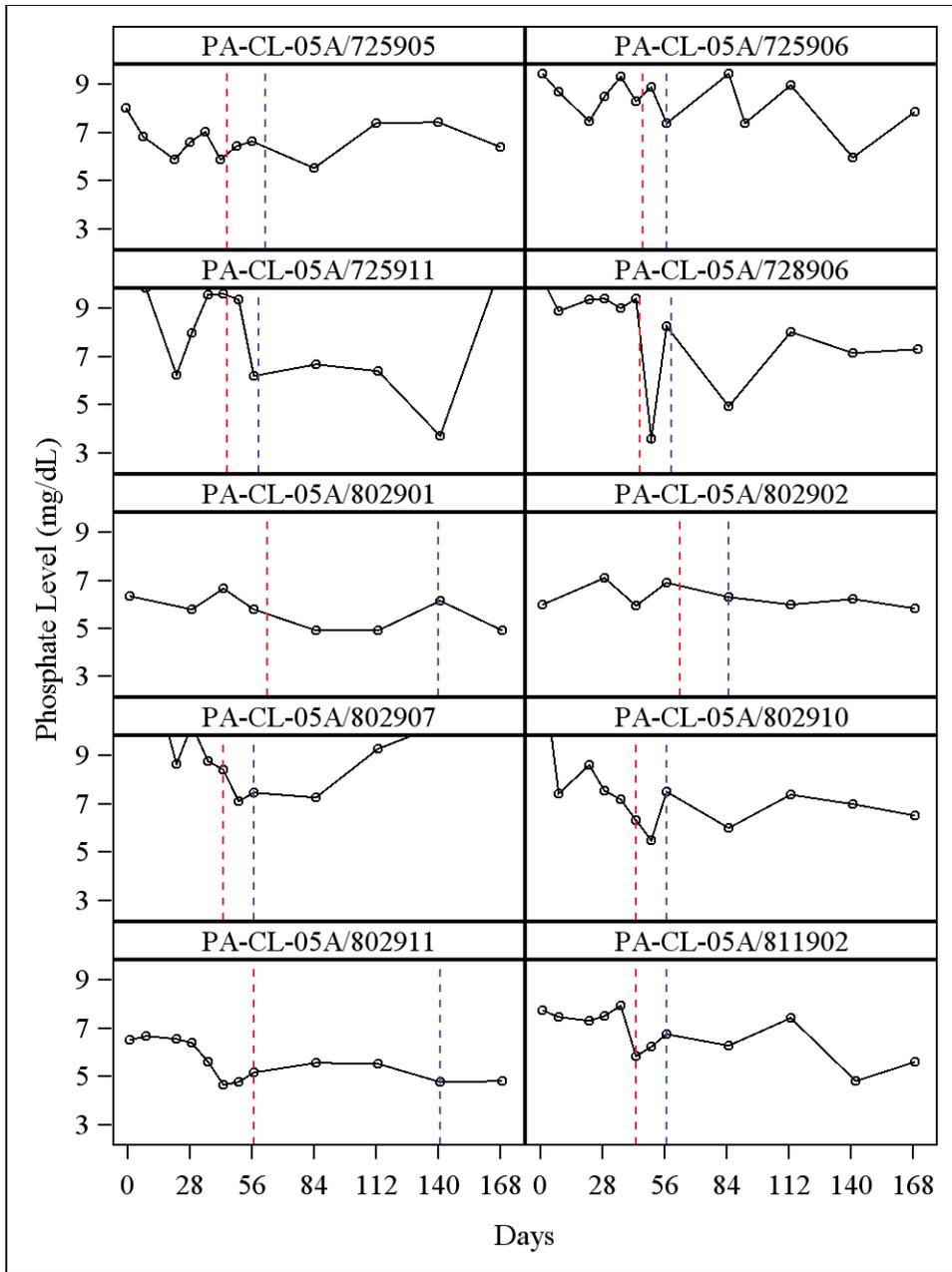


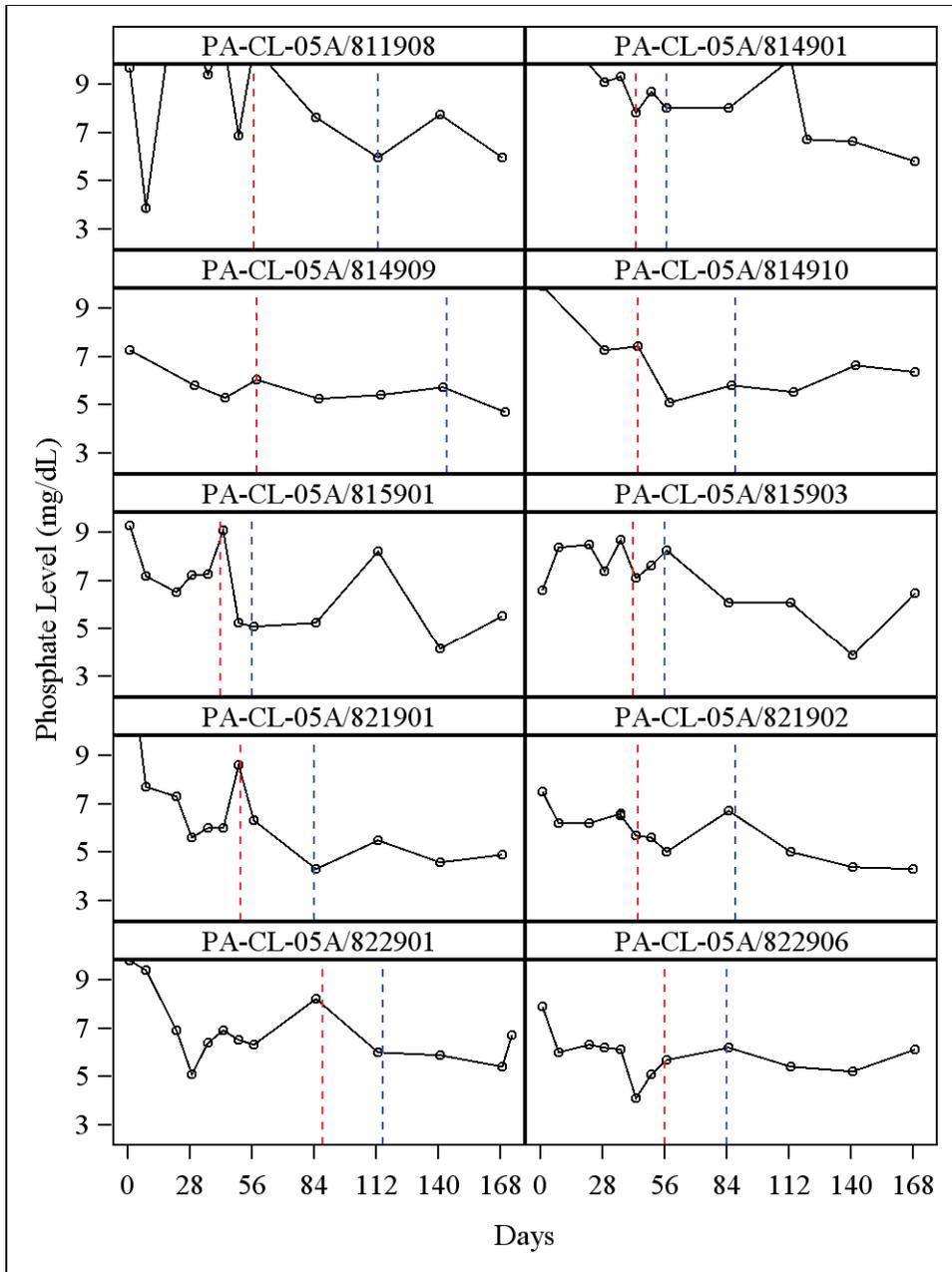


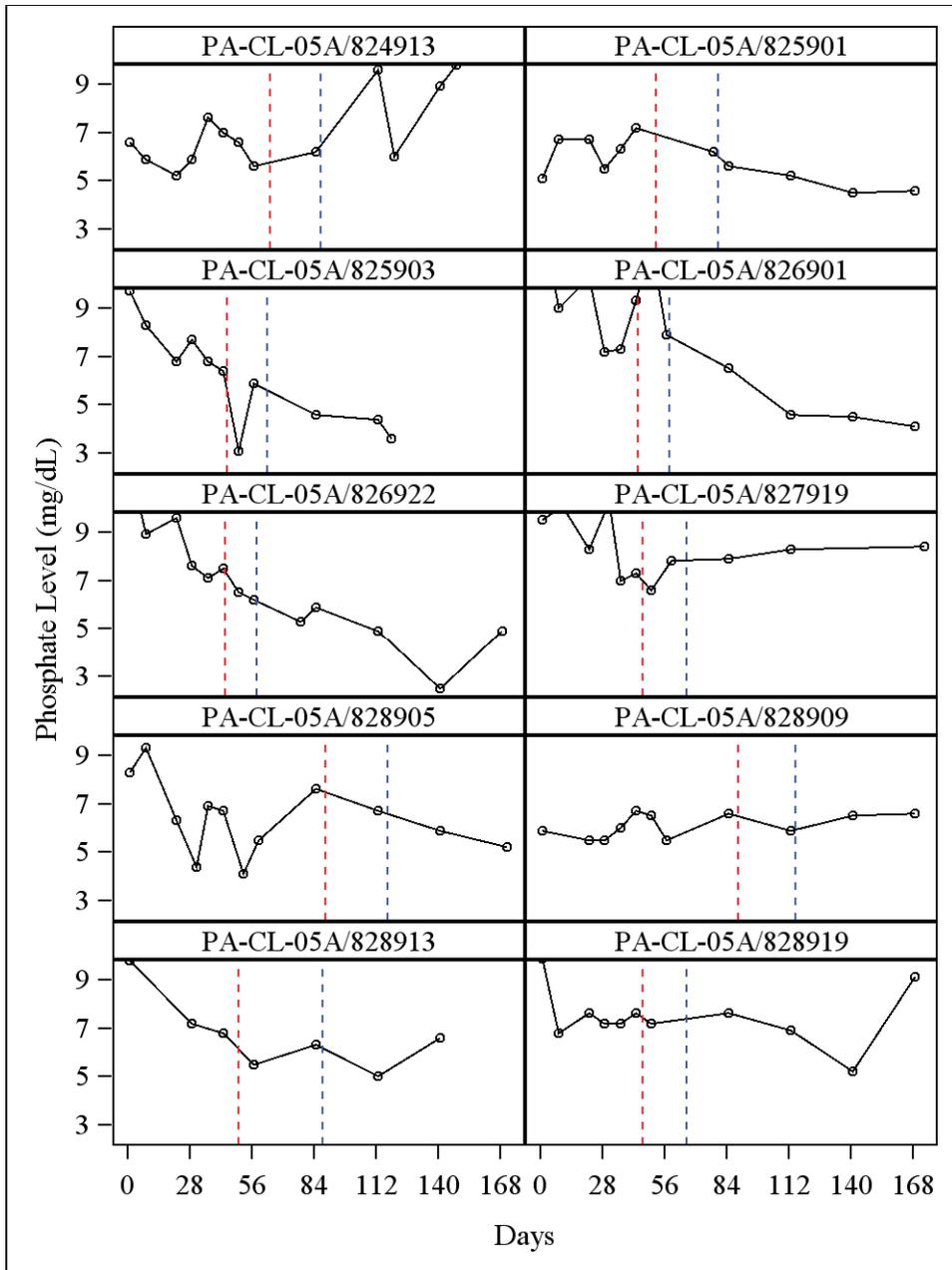


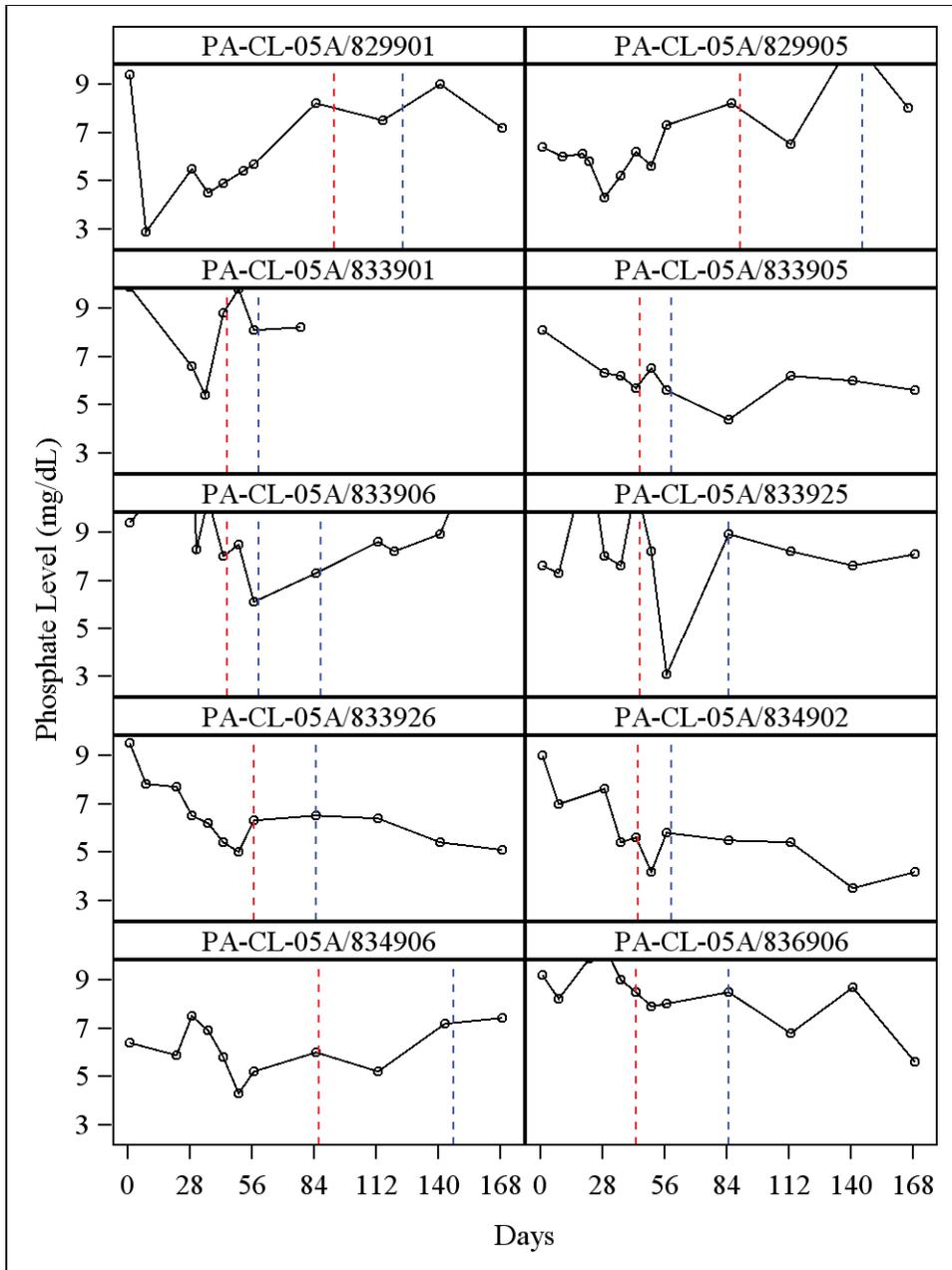


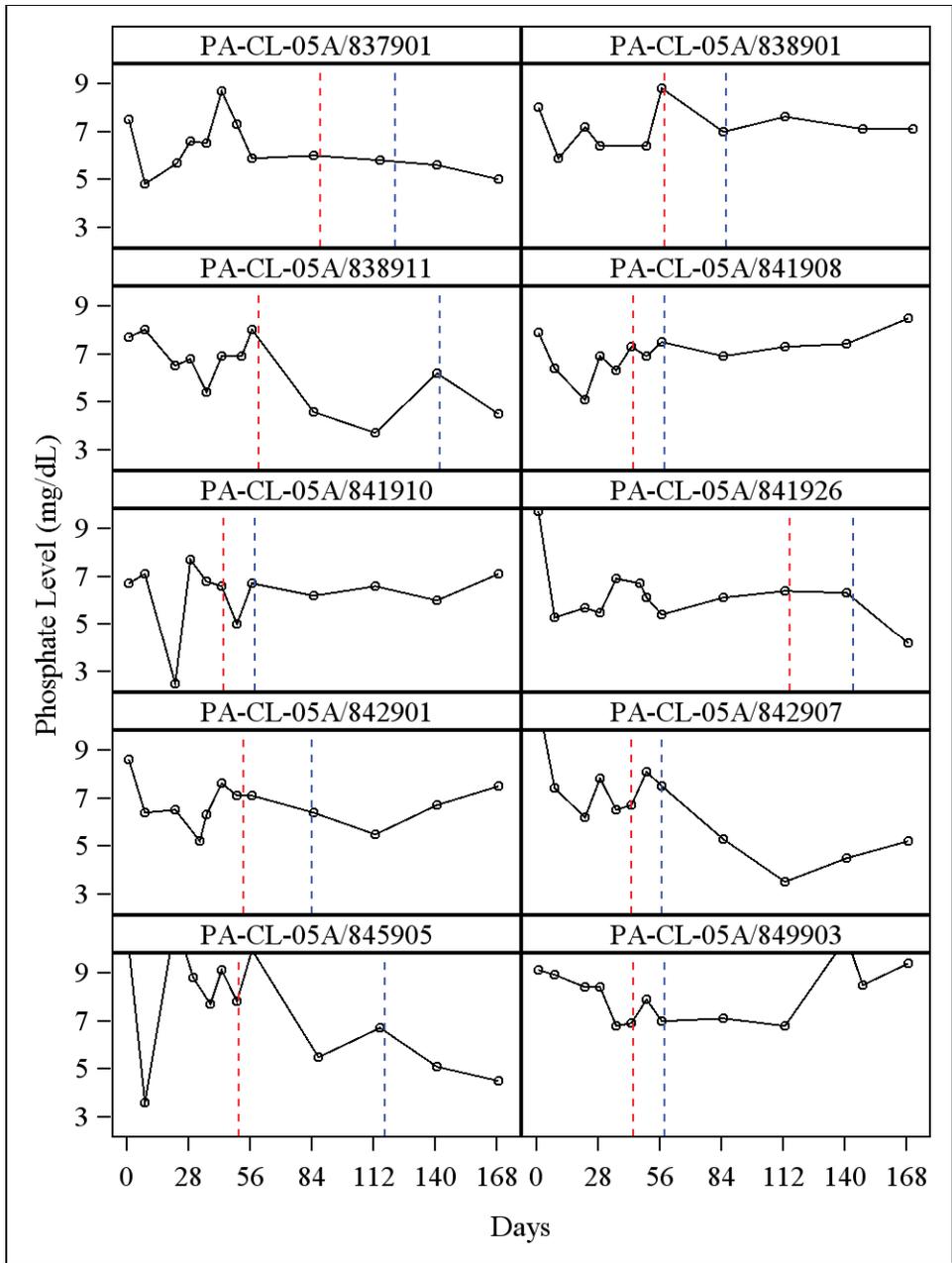


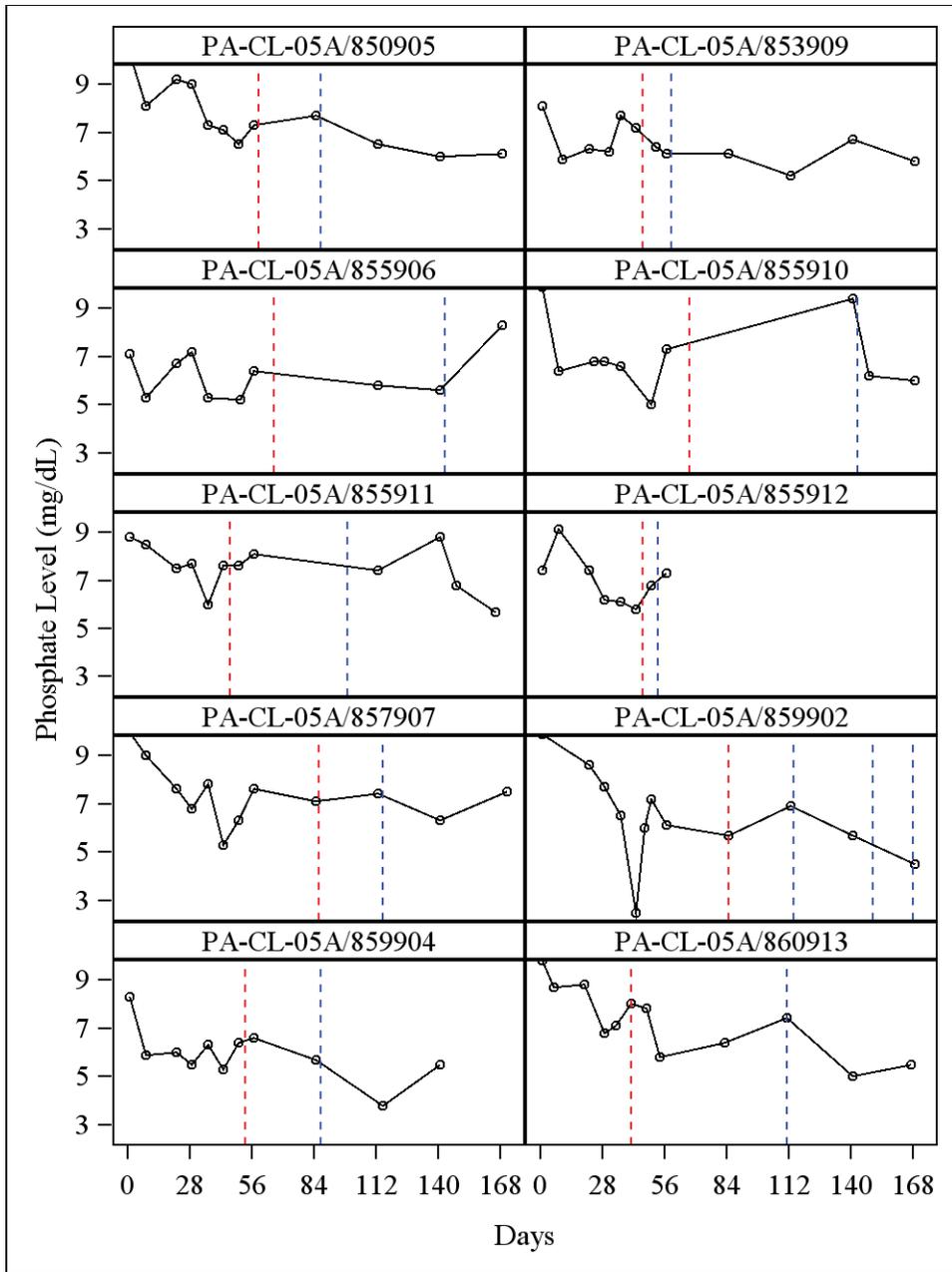


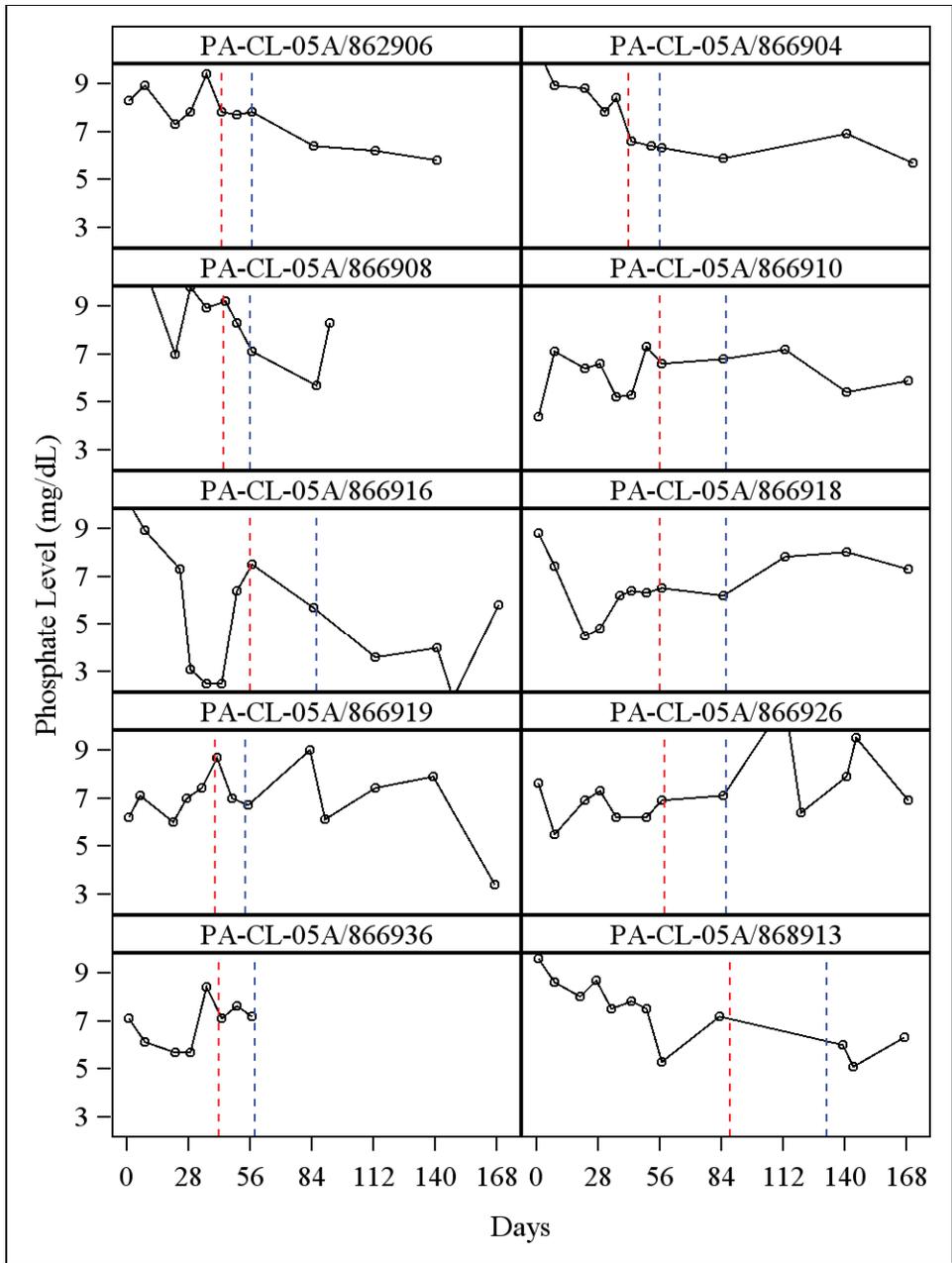


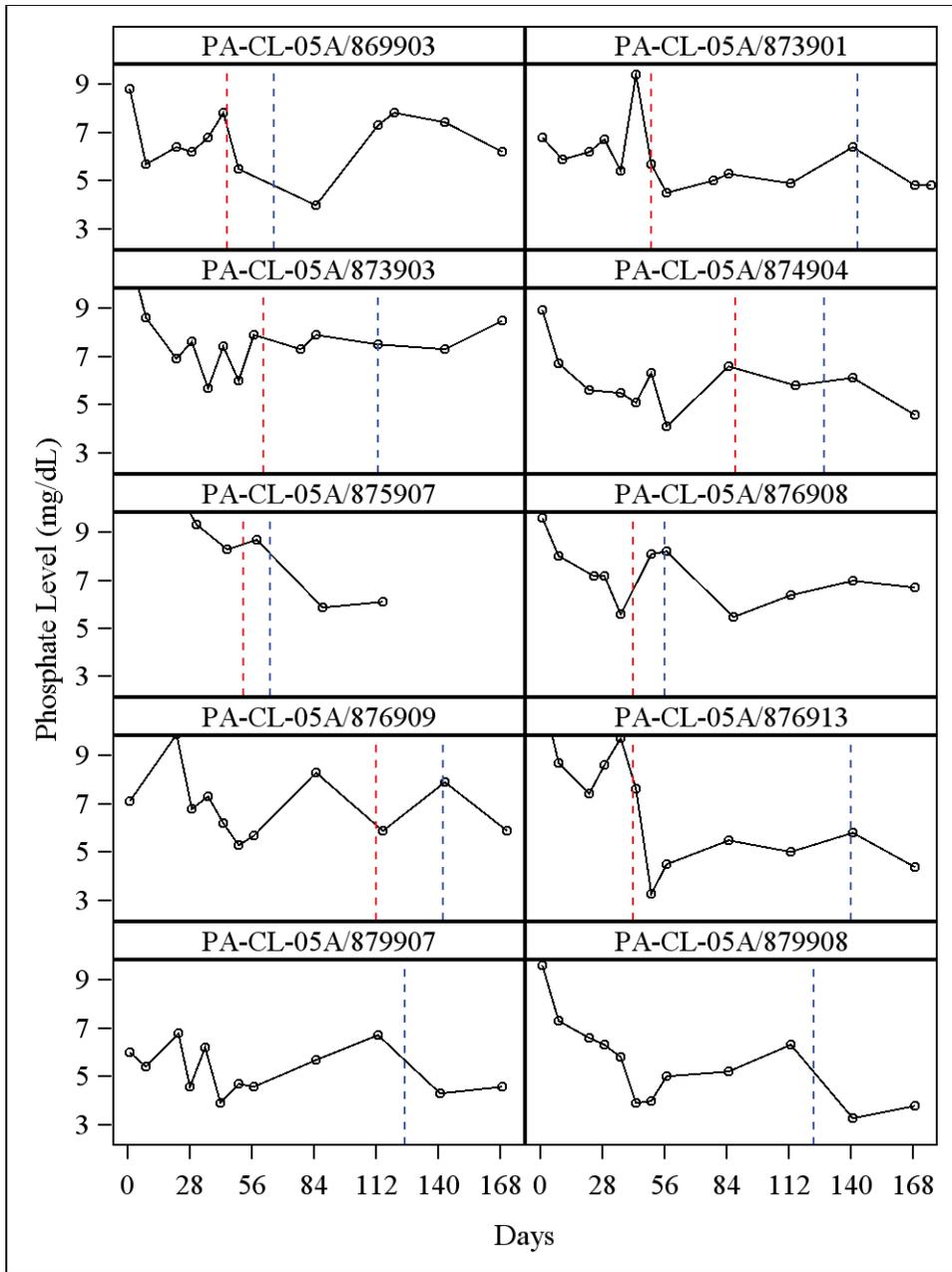


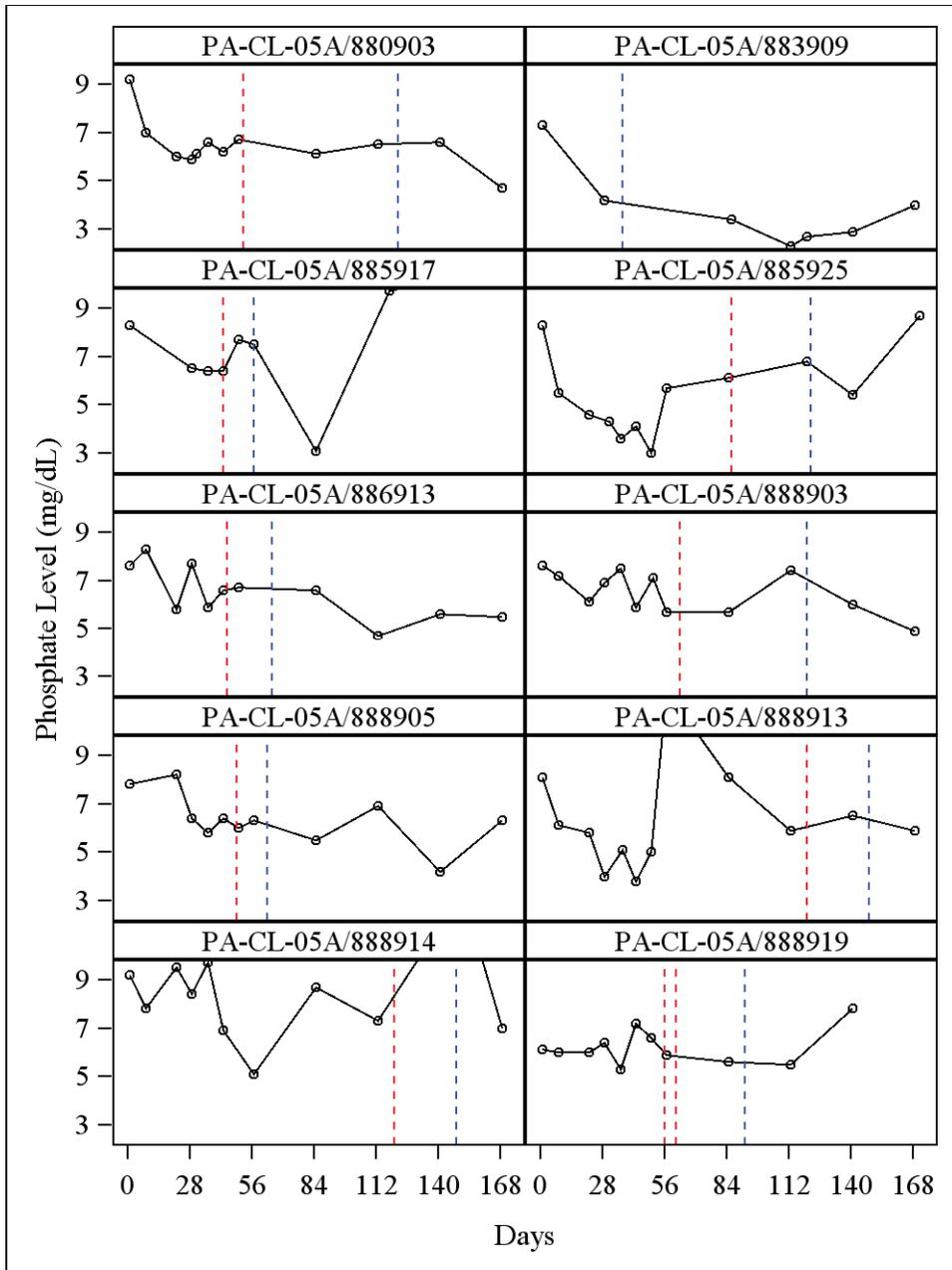


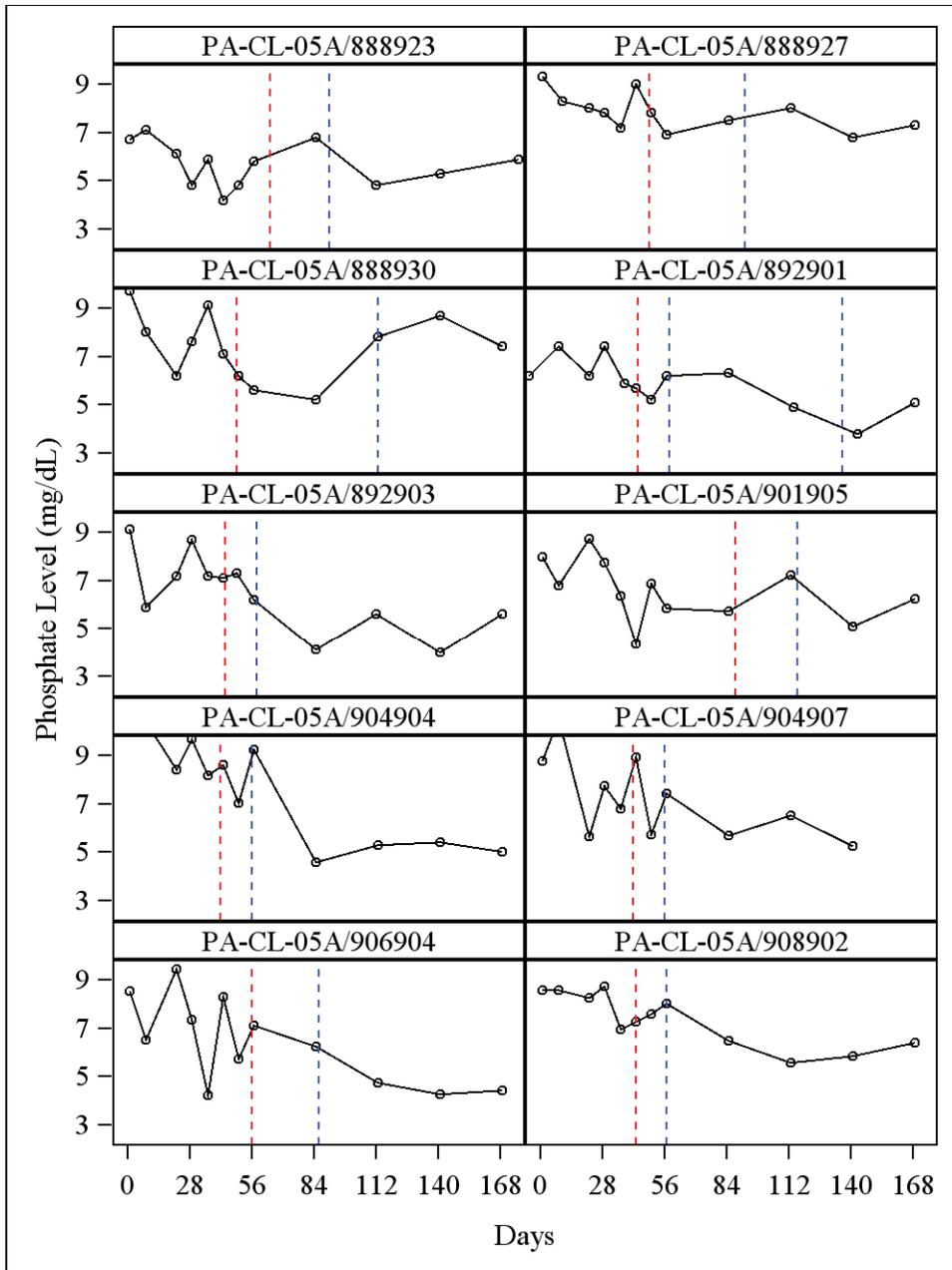


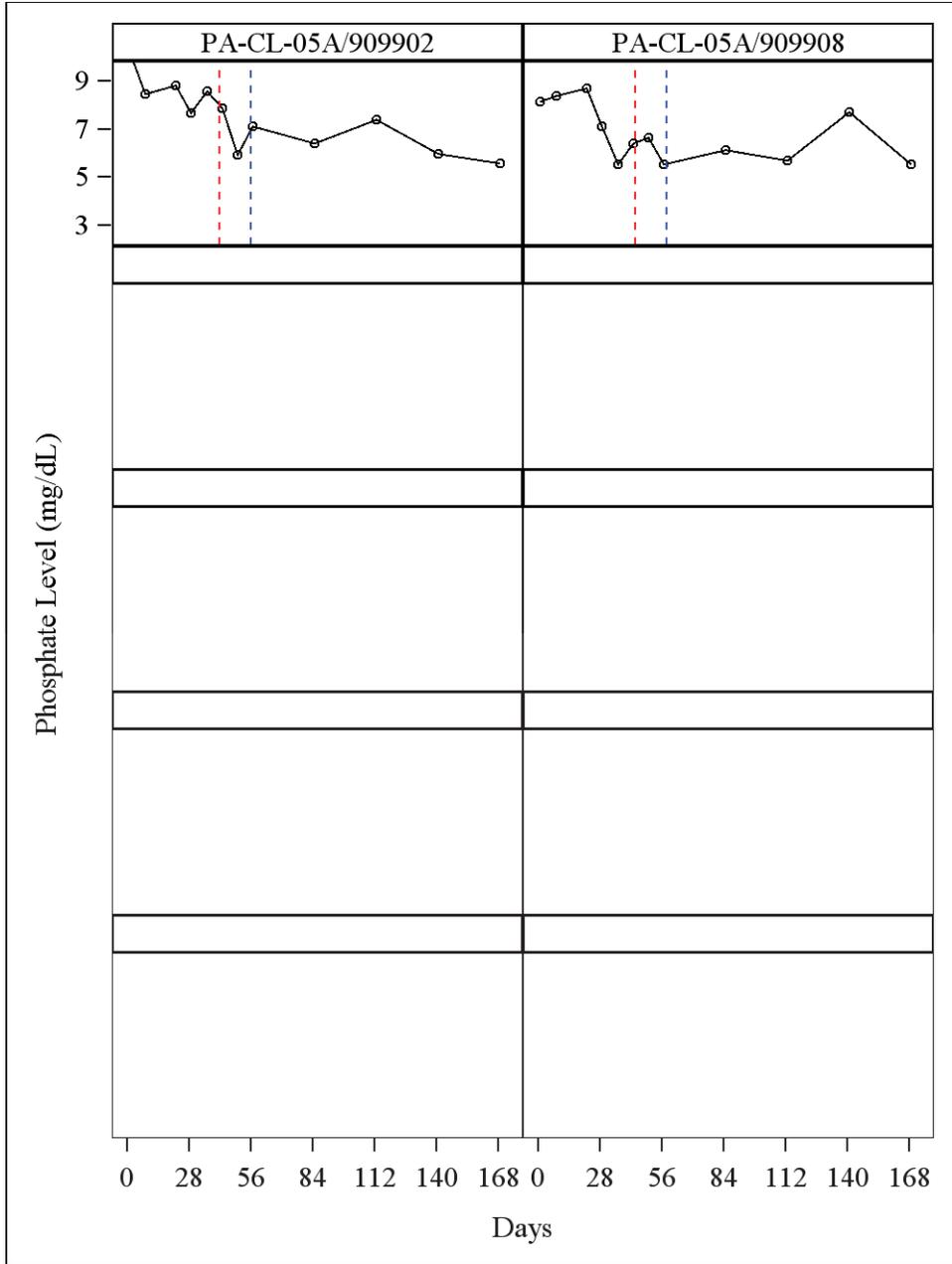












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/s/

JU PING LAI
10/22/2013

DHANANJAY D MARATHE
10/22/2013

YANING WANG
10/22/2013

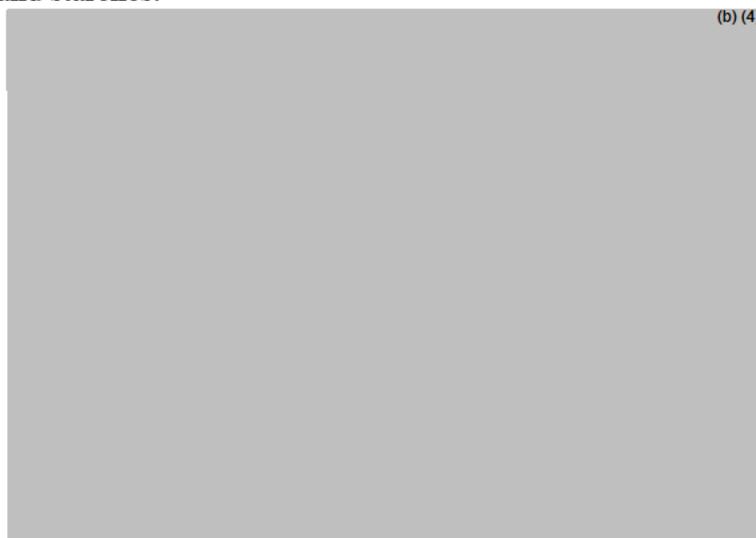
RAJANIKANTH MADABUSHI
10/22/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205109	Biopharmaceutics Reviewer: Elsbeth Chikhale, PhD	
Submission Date:	February 1, 2013		
Division:	Division of Cardio Renal Products	Biopharmaceutics Team Leader: Angelica Dorantes, PhD	
Applicant:	Vifor Fresenius Medical Care Renal Pharma	Acting Supervisor: Richard Lostritto, PhD	
Trade Name:	Velphoro™	Date Assigned:	October 10, 2012
Generic Name:	Sucroferric oxyhydroxide	Date of Review:	September 29, 2013
Indication:	to control hyperphosphataemia in patients with end-stage renal disease (ESRD)	Type of Submission: 505(b)(1) Original New Drug Application	
Dosage form/ strengths	Chewable tablets/ 500 mg elemental iron equivalent/tablet		
Route of Administration	Oral		

SUMMARY:

Submission:

The proposed drug product is a chewable tablet containing 2.5 g PA21 drug substance (equivalent to 500 mg iron). The drug substance, PA21, is a mixture of polynuclear iron(III)-oxyhydroxide (pn-FeOOH), sucrose and starches.



The drug product is indicated for the control of hyperphosphataemia in patients with end-stage renal disease (ESRD). Following oral administration, PA21 adsorbs dietary phosphate in the GI

tract, preventing phosphate uptake into the blood, and thereby reducing the serum level of phosphorus. The phosphate bound to PA21 is subsequently eliminated in the feces. The drug is intended to work in the GI tract, and is not intended to be absorbed into the systemic circulation. Two slightly different PA21 drug formulations have been used to manufacture the PA21 chewable tablets used in the clinical studies. The original drug substance formulation, referred to as PA21-1, contains (b) (4). In the modified drug substance, referred to as PA21-2, (b) (4). This allows a direct compression of the active substance into chewable tablets, (b) (4) and thus reduced the number of tablets a patient is required to take while still delivering the same potential clinical benefit. Comparability of the 2 drug substance formulations was demonstrated by comparison of iron release, structure, oxidation state, hydration state, particle size and batch analysis and stability data. PA21-1 drug substance was used in the manufacture of the tablet utilized in the Phase 1 clinical studies (Q-24120 and VIT-CI-01/2) and PA21-1 chewable tablet was used in the Phase 2 study (PA-CL-03A) and as the low dose treatment in the Phase 3 study (PA-CL-05A). The PA21-2 drug substance was used to manufacture the chewable tablets used in the Phase 3 studies (PA-CL-05A and on-going study PA-CL-05B) and in the 5 in vivo drug-drug interaction studies (PA-DDI-001, PA-DDI-002, PA-DDI-003, PA-DDI-004 and PA-DDI-005).

Review:

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:

- 1) the dissolution methodology,
- 2) the dissolution acceptance criterion, and
- 3) the comparative dissolution profiles bridging the two manufacturing sites and the two PA21 drug substance formulations

RECOMMENDATION:

1. The following dissolution method is acceptable:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Dissolution Medium
Velphoro	Chewable Tablets	USP 2 (Paddle)	50	900 mL 0.1 N HCl at 37°C

2. Based on the discriminating capability of the dissolution method and the overall dissolution data from the clinical and registration batches, the proposed acceptance criterion of $Q = (b) (4)$ at 45 minutes is not acceptable and a dissolution acceptance criterion of $Q = (b) (4)$ at 30 minutes is recommended for this product.
3. The above dissolution acceptance criterion recommendation was conveyed to the Applicant in a teleconference held on 9/25/13. However, the Applicant was concerned that the proposed drug product would fail this criterion during stability and therefore they will not get the desired shelf life of (b) (4) for their product. During this teleconference, FDA agreed that the Applicant could have a wider dissolution acceptance criterion for their product if the results from in vitro phosphate adsorption/binding studies comparing

an old failed batch (b) (4) of drug product with a slower dissolution rate vs. a new acceptable fresh batch of drug product with a faster dissolution rate, demonstrated that the phosphate adsorption and binding between these product are equivalent. The Applicant committed to provide the supportive in vitro phosphate adsorption/binding data by October 16, 2013.

4. The proposed change in the drug product manufacturing site is supported by comparative dissolution profile data and is acceptable.
5. The change in drug substance formulation from PA21-1 to PA21-2 could not be supported by comparative dissolution profile data due to the fact that the drug products using PA21-1 drug substance are more than 5 years old and expired. However, since the Phase 3 clinical and drug-drug interaction studies were conducted with the proposed PA 21-2 drug substance, the bridging between the drug products using PA21-1 and PA21-2 is not an issue.

Since at this time of the review process, the submission of essential in vitro phosphate adsorption/binding data needed for the final determination on the acceptability the dissolution acceptance criterion is pending, from the Biopharmaceutics perspective an approval recommendation cannot be given for NDA 205109 for Velpore (sucroferric oxyhydroxide) Chewable Tablets.

Note that the additional in vitro phosphate adsorption/binding data are expected to be submitted on October 16, 2013. After these data are submitted and reviewed, Biopharmaceutics will revise their recommendation on the approvability of this NDA as appropriate.

Elsbeth Chikhale, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.

Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES

BIOPHARMACEUTICS INFORMATION:

Composition of the proposed drug product capsules:

Component	Function	Quantity per Tablet (mg)	Quantity per Tablet (%)
PA21 drug substance (iron(III)-oxyhydroxide, sucrose, and starches)	Active ingredient	2,500.00 ⁽¹⁾ (iron equivalent 500.00)	(b) (4)
Woodberry flavour ⁽²⁾			(b) (4)
Neohesperidin dihydrochalcone			
Magnesium stearate ⁽⁴⁾			
Silicon dioxide, colloidal			

DISSOLUTION METHOD:

The Applicant originally proposed (b) (4)

The following comments were sent to the Applicant in an information request dated 3/20/13:

As discussed previously during the Pre-NDA meeting on 12/7/12, your proposal (b) (4)

To continue the dissolution method development for your product, we recommend that you test additional paddle speeds (50 rpm (b) (4) and evaluate if (b) (4), is appropriate for your product.

1. *Submit a revised dissolution method development report with the updated information. The dissolution method development report should include the following:*
 - a. *Solubility data for the drug substance covering the pH range;*
 - b. *Detailed description of the dissolution test being proposed for the evaluation of your proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). Include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (i.e., 15, 20, 30, 45, & 60 minutes) and cover at least (b) (4) of drug release of the label amount or whenever a plateau (b) (4) is reached. We recommend that at least twelve samples be used per testing variable;*
 - c. *Provide the complete dissolution profile data (individual, mean, SD, profiles). The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim); and*

d. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

For the setting of the dissolution acceptance criteria of your product, the following points should be considered:

- e. The dissolution profile data (i.e., 15, 20, 30, 45, & 60 minutes) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your proposed drug product.
 - f. The *in vitro* dissolution profile should encompass the timeframe over which at least (b) (4) of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
 - g. The selection of the specification time point should be where $Q =$ (b) (4) dissolution occurs. However, if you have a slowly dissolving product or includes a BCS-Class 2, poor-soluble drug, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where $Q =$ (b) (4) dissolution occurs.
 - h. The dissolution acceptance criterion should be based on average dissolution data ($n=12$).
2. The dissolution data that you collect during your stability study should cover the complete dissolution profile (i.e., 15, 20, 30, 45, & 60 minutes). Please provide these data. If you have not collected these dissolution data at all appropriate time points, you should start collecting these data and submit to the NDA.

The Applicant provided a partial response on 3/29/13 and a complete response on 4/29/13.

The response contained the following proposed dissolution method:

Rotating paddle apparatus (apparatus 2)

Dissolution medium: 0.1 N HCl

Volume: 900 ml

Temperature: 37.0 °C

Agitation speed: (b) (4)

The provided dissolution development report (submitted 4/29/13, section 3.2.P.5.2.1) describes the selection of the dissolution test conditions as shown below.

Selection of dissolution apparatus:

Due to the dimensions of PA21 chewable tablet with a diameter of 20 mm and a thickness of approximately 6 mm, the choice of the apparatus is limited to Apparatus 2. (b) (4)

Therefore, Apparatus 2 was identified as being the most appropriate dissolution apparatus for PA21 chewable tablets.

Selection of dissolution medium:

The drug substance, PA21, is practically insoluble in water and has a pH-dependent solubility profile with poor solubility at higher pH and good solubility in acidic pH. The solubility cannot be increased by [REDACTED] (b) (4)

The solubility of PA21 at different pH values:

[REDACTED] (b) (4)

Based on the drug substance solubility, 0.1N HCl was selected as the proposed dissolution medium. Note that a neutralizing reaction takes place and the pH rises slightly during the dissolution testing. At pH 1.0 the structure of the polynuclear iron(III)-oxyhydroxide is destroyed, but iron as the analyte in the form of $[\text{Fe}(\text{H}_2\text{O})_6]^{3+}$ is stable in the test medium.

Selection of volume:

The solubility of PA21 at [REDACTED] (b) (4) is [REDACTED] (b) (4). The amount of iron per chewable tablet is 500 mg. Therefore, the minimum volume in order to achieve full dissolution, i.e., the saturation volume is [REDACTED] (b) (4). In order to achieve [REDACTED] (b) (4) the volume has been set to 900 mL.

Selection of agitation speed:

[REDACTED] (b) (4)

Discriminating power of the method:

The Applicant provided the following data to demonstrate the discriminating power of the dissolution procedure.

Three batches of PA21 chewable tablets (b) (4) were manufactured on production scale equipment and the following test results were obtained:

Batch Number	Hardness (Mean) (N)	Friability (%)	Abrasion (mm)	Thickness (mm)	Disintegration Time (min)
(b) (4)					

Another drug product batch (ROR3059) using PA21 (b) (4)

batches (b) (4) The dissolution test results of those 4 batches (b) (4) are shown here:

(b) (4)					
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Additionally, in order to provide samples of an iron(III)-oxide composed chewable tablet with a similar quantitative composition (mixture of iron(III)-oxide, sugar, starches, excipients) to that of PA21 chewable tablets, chewable tablets were manufactured (b) (4)

(b) (4)

Reviewer's Initial Assessment of the proposed dissolution method: Not Acceptable

The proposed rotation speed of (b) (4) is not acceptable. A rotation speed of 50 rpm provides better results and the dissolution method will have more discriminating power.

The following information request was sent to the Applicant on 7/11/13:

1. Revise the agitation speed of your proposed dissolution method from (b) (4) to 50 rpm, and

- provide appropriate updates to section P.5.1 and P.5.2 of your NDA.*
- 2. Provide dissolution profile data using 50 rpm (individual, mean, SD, tables and figure) for your clinical (156001A11, 014011B11, 014011C11) and stability/registration batches.*
 - 3. Provide comparative dissolution profile data using 50 rpm (individual, mean, SD, tables and figure), including f_2 testing, for drug product batches made at Vifor and (b) (4)*
 - 4. Provide comparative dissolution profile data using 50 rpm (individual, mean, SD, tables and figure), including f_2 testing, for drug product batches manufactured using PA21-1 and PA 21-2.*
 - 5. Provide comparative dissolution profile data using 50 rpm (individual, mean, SD, tables and figure), for drug product batches with different tablet hardness (b) (4)*

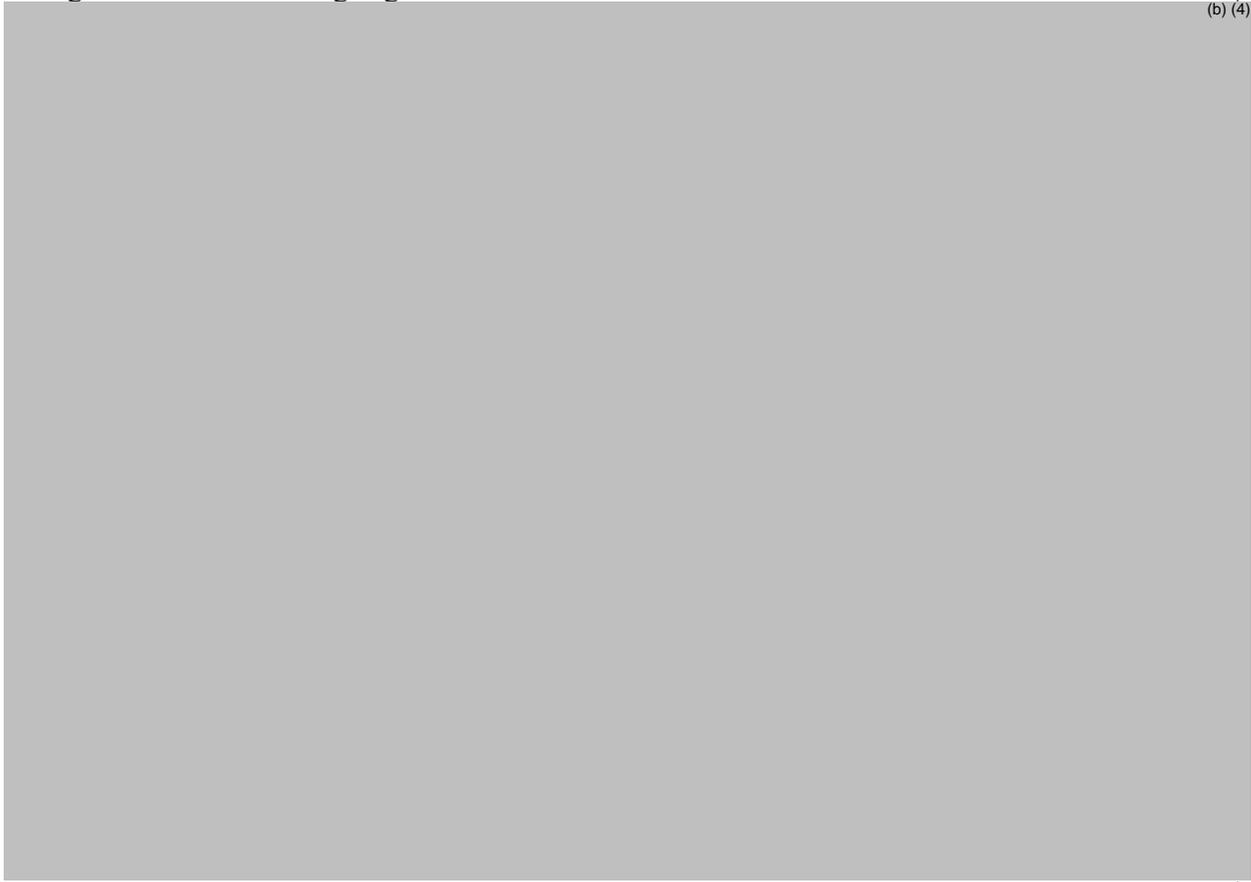
Applicant's Response dated 8/29/13:

1. Section 3.2.P.5.1 and Section 3.2.P.5.2 of the NDA have been updated to reflect the change from (b) (4) to 50 rpm.
2. The in vitro dissolution profiles from 3 clinical batches were measured with an agitation speed of 50 rpm (N=12). All clinical batches were manufactured at the manufacturing site (b) (4). The tested PA21 chewable tablets were stored at room temperature (RT) for 26 months (batch 156001A11) or 31 months (batches 014011B11 and 014011C11) (proposed expiry is at (b) (4)). The results are given in the following Figure:



The in vitro dissolution profiles of 3 primary stability batches manufactured at two manufacturing sites (b) (4) Germany and Vifor SA, Villars-sur-Glâne, Switzerland) were determined with an agitation speed of 50 rpm (N=12). The tested PA21

chewable tablets were stored at 30°C/65% relative humidity for 18 months. The results are given in the following Figure:



3. See Figure with dissolution profiles of drug product batches from Vifor SA and (b) (4) above. The mean values and differences in means for each site are summarized below:



4. The last PA21-1 drug substance batch was produced in 2007 and the last chewable tablets batches with PA21-1 drug substance were manufactured in 2008. Thus, the only available samples of PA21 chewable tablets containing PA21-1 drug substance expired several

years ago and are significantly older than the intended shelf-life of (b) (4). The tested PA21 chewable tablets were stored at RT for (b) (4). Because this dissolution test was introduced only recently, no dissolution data are available from the time of release. As PA21-1 and PA21-2 batches of PA21 chewable tablets differ significantly in their age, the similarity factor (f2) was not calculated. The obtained dissolution data on PA21-1 chewable tablets are as follows:



5. Three different batches of PA21 chewable tablets of different hardness, were analyzed. The results are shown in the following Figures:

Using 50 rpm (submitted in amendment dated 8/29/13):

(b) (4)



Using  (submitted in amendment dated 4/29/13):

(b) (4)



Note that the same batches were used to generate the two Figures above. The age of the batches and the storage conditions at the time of the dissolution test were not indicated in the NDA.

Reviewer's Overall Assessment on the proposed dissolution method: Acceptable

The revised dissolution method using a rotation speed of 50 rpm is acceptable. The discriminatory power of the revised dissolution method has been demonstrated.

DISSOLUTION ACCEPTANCE CRITERION:

The proposed acceptance criterion is:

(b) (4) (Q) after 45 minutes

The Applicant states that the proposed acceptance criterion for the proposed drug product is based on the USP monograph of other iron (b) (4) dosage forms that require (b) (4) % of (b) (4) % (Q) dissolved in 45 (b) (4) minutes.

Reviewer's Initial Assessment of the proposed dissolution acceptance criterion: Not Acceptable

Based on the provided dissolution data for the proposed drug product clinical batches and the stability dissolution profile data, an acceptance criterion of $Q = (b) (4)$ at 30 minutes is appropriate for the drug product.

A telephone conference was held between FDA and the Applicant on September 25, 2013, during which the rationale for the (b) (4) of the dissolution acceptance criterion to $Q = (b) (4)$ at 30 minutes was discussed. The Applicant was concerned that the proposed drug product would fail this dissolution acceptance criterion on stability and their desired shelf life of (b) (4) would not be feasible. Therefore, the Applicant proposed to (b) (4)

Reviewer's Overall Assessment of the proposed dissolution acceptance criterion: PENDING

The acceptability of the dissolution acceptance criterion is pending additional supportive in vitro phosphate adsorption/binding data that are expected to be submitted to the NDA by 10/16/13.

COMPARATIVE DISSOLUTION PROFILES BRIDGING THE TWO MANUFACTURING SITES AND THE TWO PA21 FORMULATIONS:

Based on the comparative dissolution profile data (see figure and table on page 8 of this review) the two drug product manufacturing sites (Vifor SA and (b) (4)) produce PA21 drug products with similar ($f_2 > 50$) dissolution profiles.

The similarity in dissolution between drug products using PA21-1 and PA21-2 drug substance could not be verified because the last drug product batches using PA21-1 drug substance is more than 5 years old (is expired) (b) (4). Since the Phase 3 clinical and drug-drug interaction studies were conducted with the proposed PA 21-2 drug substance, the bridging between the drug products using PA21-1 and PA21-2 is not an issue.

RECOMMENDATION:

- The applicant's dissolution methodology, as summarized below, is acceptable:
USP Apparatus II (paddle)
Temperature: 37 °C
Rotation speed: 50 rpm
Medium: 900 mL 0.1 N HCl
- Dissolution acceptance criterion:
The acceptability of the dissolution acceptance criterion is pending.
- Change in drug product manufacturing sites and change in drug substance formulation:
The change in drug product manufacturing site is supported by comparative dissolution profile data. The change in drug substance formulation could not be supported by comparative dissolution profile data due to the fact that the drug products using PA21-1 drug substance are more than 5 years old and expired.

At this time of the review process, from the Biopharmaceutics perspective the recommendation on the approvability of NDA 205109 for Velphore (sucroferric oxyhydroxide) Chewable Tablets containing 500 mg elemental iron (equivalent to 2,500 mg sucroferric oxyhydroxide complex) per tablet is PENDING (due to lack of complete information). The additional in vitro phosphate adsorption/binding data are expected to be submitted on October 16, 2013.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELSBETH G CHIKHALE
09/29/2013

ANGELICA DORANTES
09/29/2013

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	205109
Submission Date	2/1/13
Product name, generic name of the active	(b) (4) Tablets
Dosage form and strength	Chewable tablet – 500 mg iron equivalent/tablet
Route of Administration	Oral
Applicant	Vifor Fresenius Medical Care Renal Pharma
Clinical Division	Division of Cardio Renal Products
Type of Submission	Original NDA – 505(b)(1)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		The Applicant is in the process of developing a dissolution method. The application contains very limited dissolution data.
2.	Is the dissolution test part of the DP specifications?		x	The Applicant has proposed (b) (4) Dissolution should be included in the DP specifications.
3.	Does the application contain data to support the proposed dissolution acceptance criteria		x	The Applicant is not proposing dissolution acceptance criteria.
4.	Does the application contain the dissolution method development report?	x		Addition information on the dissolution method development needs to be requested.
5.	Does the application contain data on the discriminating ability of the dissolution method	x		Addition information on the dissolution method development need to be requested
6.	Is there a validation package for the analytical method and dissolution methodology?		x	Once finalized, the analytical and dissolution methods need to be validated.
7.	Does the application include a biowaiver request?		x	
8.	Does the application include an IVIVC model?		x	Not applicable
9.	Is information such as BCS classification mentioned, and supportive data provided?		x	Not applicable

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

10.	Is information on mixing the product with foods or liquids included?		x	Not applicable
11.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		The BA/BE information will be evaluated by OCP.
12.	Does the application include <i>in vitro</i> alcohol interaction studies?		x	Not needed

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
13.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		
14.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable
15.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable
16.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		x	See information request below sent to the Applicant on 3/20/13

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Biopharmaceutics Summary

General Summary

The proposed drug product is a chewable tablet containing 2.5 g PA21 drug substance (equivalent to 500 mg iron). The drug substance, PA21, is a mixture of polynuclear iron(III)-oxyhydroxide (pn-FeOOH), sucrose and starches.



The iron moiety in the drug substance contains



The tablet also contains small amounts of the excipients silica, magnesium stearate, neohesperidin dihydrochalcone, and woodberry flavor.

The drug product is indicated for the control of hyperphosphataemia in patients with end-stage renal disease (ESRD). Following oral administration, PA21 adsorbs dietary phosphate in the GI tract, preventing phosphate uptake into the blood, and thereby reducing the serum level of phosphorus. The phosphate bound to PA21 is subsequently eliminated in the feces. The drug is intended to work in the GI tract, and is not intended to be absorbed into the systemic circulation. As iron binds phosphate and its content in the tablet is quantitatively assayed and controlled, it was decided to express the strength of the PA21 tablet as the iron content. This reference to the iron content is more pharmacologically correct and is consistent with the phosphate binder lanthanum carbonate.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Two slightly different PA21 drug formulations have been used to manufacture the PA21 chewable tablets used in the clinical studies. The original drug substance formulation, referred to as PA21-1, (b) (4) In the modified drug substance, referred to as PA21-2, (b) (4) reduced the number of tablets a patient is required to take while still delivering the same potential clinical benefit. Comparability of the 2 drug substance formulations was demonstrated by comparison of iron release, structure, oxidation state, hydration state, particle size and batch analysis and stability data. PA21-1 drug substance was used in the manufacture of the tablet utilized in the Phase 1 clinical studies (Q-24120 and VIT-CI-01/2) and PA21-1 chewable tablet was used in the Phase 2 study (PA-CL-03A) and as the low dose treatment in the Phase 3 study (PA-CL-05A). The PA21-2 drug substance was used to manufacture the chewable tablets used in the Phase 3 studies (PA-CL-05A and on-going study PA-CL-05B) and in the 5 in vivo DDI studies (PA-DDI-001, PA-DDI-002, PA-DDI-003, PA-DDI-004 and PA-DDI-005).

Biopharmaceutics Filing Comments

The following comments were sent to the Applicant in an information request dated 3/20/13:

As discussed previously during the Pre-NDA meeting on 12/7/12, your proposal (b) (4) is not acceptable. To continue the dissolution method development for your product, we recommend that you test additional paddle speeds (50 rpm (b) (4)

1. Submit a revised dissolution method development report with the updated information. The dissolution method development report should include the following:
 - a. Solubility data for the drug substance covering the pH range;
 - b. Detailed description of the dissolution test being proposed for the evaluation of your proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (*i.e.*, *selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). Include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (*i.e.*, 15, 20, 30, 45, & 60 minutes) and cover at least (b) (4) of drug release of the label amount or whenever a plateau (*i.e.*, no increase over 3 consecutive time-points) is reached. We recommend that at least twelve samples be used per testing variable;
 - c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*). The

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and

- d. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

For the setting of the dissolution acceptance criteria of your product, the following points should be considered:

- e. The dissolution profile data (*i.e., 15, 20, 30, 45, & 60 minutes*) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your proposed drug product.
- f. The in vitro dissolution profile should encompass the timeframe over which at least (b) (4) of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- g. The selection of the specification time point should be where $Q = (b) (4)$ dissolution occurs. However, if you have a slowly dissolving product or includes a BCS-Class 2, poor-soluble drug, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (*i.e., 15-20 minutes*) and the second time point should be where $Q = (b) (4)$ dissolution occurs.
- h. The dissolution acceptance criterion should be based on average dissolution data (n=12).
2. The dissolution data that you collect during your stability study should cover the complete dissolution profile (*i.e., 15, 20, 30, 45, & 60 minutes*). Please provide these data. If you have not collected these dissolution data at all appropriate time points, you should start collecting these data and submit to the NDA.

RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed NDA 205109 for filing purposes and we found this NDA filable from a Biopharmaceutics perspective. The sponsor has submitted a reviewable submission.

{See appended electronic signature page}

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

3/25/13
Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

3/25/13
Date

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/s/

ELSBETH G CHIKHALE
03/25/2013

ANGELICA DORANTES
03/25/2013

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205109	Brand Name	TBD
OCP Division (I, II, III, IV, V)	I	Generic Name	PA21
Medical Division	Cardio-Renal	Drug Class	Drugs for treatment of hyperphosphataemia
OCP Reviewer	Ju-Ping Lai	Indication(s)	Control of serum phosphorus levels in patients with end-stage renal disease (ESRD)
OCP Team Leader	Rajnikanth Madabushi	Dosage Form	Chewable tablets
Pharmacometrics Reviewer	Dhananjay Marathe	Dosing Regimen	Starting dose: 3 tablets (1,500 mg) per day; (1 tablet 3 times daily with meals) Titration: start as early as 1 week in decrements or increments of 1 tablet per day – until serum phosphorus level is ≤ 5.5 mg/dL.
Date of Submission	1/31/2013	Route of Administration	Oral
Estimated Due Date of OCP Review	10/1/2013	Sponsor	Vifor
Medical Division Due Date	11/15/2013	Priority Classification	Standard
PDUFA Due Date	12/1/2013		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		Radiolabelled PA21 to evaluate potential iron uptake
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	1		
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:				
multiple dose:	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	5		
In-vitro:	X	22		Screening for potential DDIs
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	X	1(+1 supportive)		
Phase 3:	X	1		
PK/PD -				
Phase 1 and/or 2, proof of concept:		(1 supportive)		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		33		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Not absorbed
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		Not absorbed, no concentrations available
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		Not absorbed, no concentrations available
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

___ Yes ___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Please provide study report and datasets for the Japanese study (PA1201) to allow adequate Dose-Response relationship analysis.

Ju-Ping Lai	03/14/13
Reviewing Clinical Pharmacologist	Date
Raj Madabushi	03/14/13
Team Leader/Supervisor	Date

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/s/

JU PING LAI
03/15/2013

RAJANIKANTH MADABUSHI
03/15/2013