CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202799Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	202-799
Submission Date:	23 May 2011
Brand Name:	Omontys®
Generic Name:	Peginesatide Injection
Formulation:	Single dose vials; Single dose pre-filled syringes; Multiple dose vials
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OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Hematology Products
Sponsor:	Affymax
Submission Type; Code:	Original NDA; 000
Dosing regimen:	Treatment initiation: 0.04 to 0.08 mg/kg once monthly (QM) Conversion from another ESA: QM dosing for amount derived from Epoetin or darbepoetin alfa
Indication:	For the treatment of anemia associated with chronic kidney disease in adult patients on dialysis

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1 EXECUTIVE SUMMARY

Peginesatide Injection is an erythropoiesis-stimulating agent (ESA). It is a synthetic, dimeric peptide covalently linked to polyethylene glycol (PEG). The current submission is the original NDA for peginesatide for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis.

The results of four phase 3 trials (two trials in patients with CKD on-dialysis and two trials in patients with CKD not on dialysis) have been submitted to support this NDA. The primary efficacy analysis for all trials was the mean change in hemoglobin between the baseline and the evaluation period. The efficacy analyses for the four phase 3 trials conclude that peginesatide is non-inferior to epoetin or darbepoetin. The CV safety outcomes in the on-dialysis trials (AFX01-12 and AFX01-14) appear similar for both treatment groups for the composite safety endpoint (CSE) and the major adverse cardiac events (MACE) endpoint. However, in the two non-dialysis trials (AFX01-11 and AFX01-13), there are differences in the safety outcomes, with results unfavorable for peginesatide.

An exploratory analysis was conducted for the non-dialysis population to evaluate the association between poor initial hemoglobin response, subsequent dose and CV outcomes. This analysis identified a subgroup of "slow" responders who had a poor initial response to peginesatide, required higher overall doses to reach the hemoglobin target, and had greater risk for CV events. However, it is not possible with the existing data to conclude that the increased CV risk in this subgroup is due to the higher doses. This subgroup of patients also had an increase in baseline CV risk factors compared to patients who had a better initial hemoglobin response. Similar findings for darbepoetin were reported for the TREAT study and are reflected in the ARANESP product label (sections 2.2, 5.1).

The CV risk in all dialysis patients has not been characterized in the application. The high-risk subgroup of "slow/poor" responders was not studied in the dialysis clinical trials. The on-dialysis trials only enrolled patients who, at baseline, were already on a stable epoetin doses and had hemoglobin within the target of 10–12 mg/dL. These patients were switched from epoetin to peginesatide to maintain hemoglobin within the target. However, the sponsor is seeking an indication for all dialysis patients, including initiation of treatment as well as converting from another ESA product.

The lower starting dose of 0.04 mg/kg is recommended for initiating treatment in dialysis patients. Based on a phase 2 study, the sponsor has proposed a starting dose range of 0.04 mg/kg to 0.08 mg/kg. In this study, the mean time course and mean hemoglobin for the 0.04 mg/kg and 0.08 mg/kg starting doses were similar. Furthermore, the average dose during the evaluation period was 0.05 for both dose groups. Because the 0.04 mg/kg had an adequate hemoglobin response and CV safety was not evaluated in this phase 2 study, starting doses greater than 0.04 mg/kg are not justified.

Peginesatide is not metabolized and it is not an inducer/inhibitor of CYP enzymes. Peginesatide does not bind to serum albumin or lipoproteins. Clinical development of peginesatide has primarily utilized a single-dose vial (SDV) formulation at a drug concentration of 10 mg/mL. Peginesatide concentrations from 2 to 12 mg/mL are planned for marketing as SDV, in addition to a multiple-dose vial (MDV) and a pre-filled syringe (PFS). Four phase 1 cross-over studies evaluated the bioequivalence of test formulations of SDV, MDV and PFS to the reference 10 mg/mL SDV formulation. These studies suggested equivalent PK and PD across the proposed range of commercial formulations.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology, Divisions of Clinical Pharmacology 5 and Pharmacometrics have reviewed the information contained in NDA 202799.

- We recommend limiting the indication to those dialysis patients studied in the phase 3 clinical trials. The CV safety for dialysis patients initiating peginesatide treatment has not been

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evaluated.

- If the FDA Office of New Drugs approves peginesatide for all dialysis patients, we recommend a starting dose of 0.04 mg/kg instead of the proposed dose range (0.04 mg/kg to 0.08 mg/kg) for patients initiating treatment.

Post Marketing Requirements

None

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations

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1.2 CLINICAL PHARMACOLOGY SUMMARY

Peginesatide is a synthetic, PEGylated dimeric erythropoietin receptor activating peptide that, unlike currently approved ESAs, has no homology to erythropoietin. Peginesatide is being developed for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

After IV administration, peginesatide attains C_{max} concentrations in approximately 15 minutes in both healthy subjects and subjects with CKD on dialysis. Plasma concentration of peginesatide increased slowly following SC administration and attained a broad peak with maximum concentration around 33 to 51 hours in healthy subjects, 48 to 168 hours in CKD subjects not on dialysis, and 47 to 73 hours in CKD subjects on dialysis. Absolute bioavailability of peginesatide between the SC and IV administrations may be estimated as approximately 40%. The decline in plasma concentrations of peginesatide after IV injection was monophasic or biphasic. Peginesatide stayed mainly in the systemic circulation, with a limited distribution to peripheral tissues. The distribution volume approximated that of the plasma volume. After multiple Q4W dosing at doses up to 0.15 mg/kg in hemodialysis patients, no accumulation of peginesatide has been observed.

Peginesatide is essentially not metabolized. Peginesatide and its related compounds, (b) (4) and potential degradants, are not inducers or inhibitors of CYP450 enzymes. In vitro protein binding studies in rat, monkey, and human sera demonstrated that peginesatide does not bind to serum albumin or lipoproteins.

Peginesatide increased Hgb in healthy subjects in phase 1 studies and increased and maintained Hgb levels in subjects with CKD on dialysis in phase 2 and 3 studies.

The dose of peginesatide when converting from an ESA is based on a log-linear correlation between the prior ESA dose (epoetin or darbepoetin) and the mean observed peginesatide dose, and fall within the range (0.005 – 1.0 mg/kg, or 0.35 – 70 mg for a 70 kg individual) of the doses studied in the phase 3 clinical trials. Dose titration in the phase 3 studies was sufficient to maintain average hemoglobin concentrations within the target range.

Exploratory analysis of data from the phase 3 non-dialysis studies revealed a subgroup of slow responding patients that have exhibited increased risk of CV events. Slow responders were defined as patients who had not achieved their target hemoglobin after three months on study treatment. These individuals were excluded from the phase 3 dialysis trials because patients enrolled were already on a stable epoetin dose and had met the target hemoglobin response. As CV safety data were not available for this population in patients on dialysis, we recommend limiting peginesatide use to the conversion to peginesatide from another ESA product in patients receiving dialysis.

If approved for the initiation of peginesatide therapy, the starting should be a fixed starting dose of 0.04 mg/kg. This dose appears to be sufficient for initiating a gradual hemoglobin response and the hemoglobin response for the 0.04 mg/kg starting is similar to a 0.08 mg/kg starting dose when hemoglobin-based dose adjustments are utilized.

The IRT review of the thorough QT study suggested that peginesatide has a low potential to prolong the QT interval. IRT proposed labeling has been added to the package insert.

Clinical development of peginesatide has primarily utilized a single-dose vial (SDV) formulation at a drug concentration of 10 mg/mL. Peginesatide concentrations from 2 to 12 mg/mL are planned for marketing as SDV, in addition to a multiple-dose vial (MDV) and a pre-filled syringe (PFS). Four phase 1 cross-over studies evaluated the bioequivalence of test formulations of SDV, MDV and PFS to the reference 10 mg/mL SDV formulation. These studies suggested equivalent PK and PD across the proposed range of commercial formulations.

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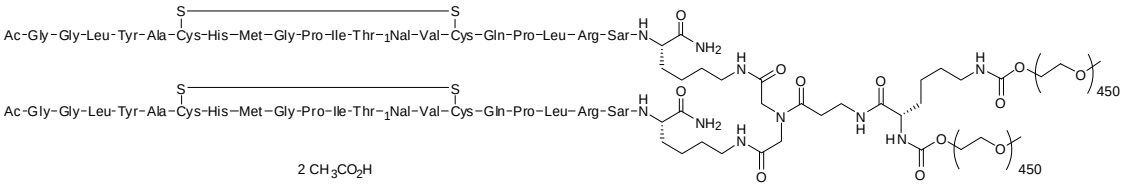
2 QUESTION BASED REVIEW

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?

Physico-chemical properties

1. Structural formula:



2. Established name: peginesatide
3. Molecular Weight: (b) (4)
4. Molecular Formula: $C_{2031}H_{3950}N_{62}O_{958}S_6$
5. Chemical Name: Poly(oxy-1,2-ethanediyl), α-hydro-ω-methoxy-, diester with 21N6,21'N6-[[(N2,N6-dicarboxy-L-lysyl-β-alanyl)imino]bis(1-oxo-2,1-ethanediyl)]bis[N-acetylglycylglycyl-L-leucyl-L-tyrosyl-L-alanyl-Lcysteinyl-L-histidyl-L-methionylglycyl-L-prolyl-L-isoleucyl-L-threonyl-3-(1-naphthalenyl)-L-alanyl-L-valyl-L-cysteinyl-L-glutaminyl-L-prolyl-L-leucyl-L-arginyl-N-methylglycyl-L-lysinamide] cyclic (6→15),(6'→15')-bis(disulfide), acetate (salt)

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

Peginesatide is an erythropoiesis-stimulating agent (ESA). It binds to and activates the human erythropoietin receptor and stimulates erythropoiesis in human red cell precursors in vitro in a manner similar to recombinant ESAs. The proposed indication is for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis.

2.1.3 What are the proposed dosage and route of administration?

The Sponsor's proposed initial dose of peginesatide in dialysis patients who are not currently treated with an ESA is 0.04 to 0.08 mg/kg, either intravenously or subcutaneously administered once monthly.

In patients receiving Epoetin alfa or darbepoetin alfa, the recommended peginesatide starting dose is derived from the patients previous ESA dose as outlined in Table 1.

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Table 1. Estimated peginesatide starting doses for patients based on previous ESA Dose

Previous Total Weekly Epoetin Alfa Dose (U/week)	Previous Weekly Darbepoetin Alfa Dose (mcg/week)	Peginesatide Dose Once Monthly (mg/month)
<2,500	<12	2
2,500 to <4,300	12 to <18	3
4,300 to <6,500	18 to <25	4
6,500 to <8,900	25 to <35	5
8,900 to <13,000	35 to <45	6
13,000 to <19,000	45 to <60	8
19,000 to <33,000	60 to <95	10
33,000 to <68,000	95 to <175	15
≥68,000	≥175	20

2.2 WHAT IS THE REGULATORY HISTORY OF THIS PRODUCT?

Peginesatide is considered an NME in the US. The initial IND was filed under IND 63,257 on March 25, 2005. FDA provided regulatory advice to the sponsor during the End of Phase 2 meeting held on February 23, 2007. FDA recommended that in order to consider approval for this drug, the sponsor would need to demonstrate that peginesatide is not importantly inferior in safety or efficacy to available products. Also, FDA recommended that results across studies show consistency with regard to safety and efficacy. Peginesatide was submitted under NDA 202-799 on May 23, 2011.

2.2.1 What is unique about peginesatide and are there are any other ESA products marketed?

There are currently three approved agents for use in treatment of anemia in patients with chronic kidney disease, Epogen/Procrit (epoetin alfa), Aranesp (darbepoietin alfa), and Mircera (pegylated epoetin alfa). Currently only Epogen/Procrit and Aranesp are marketed. Epogen/Procrit, Aranesp, and Mircera are erythropoietin analogs that act by binding to and activating the human erythropoietin receptor. Peginesatide is the first synthetic ESA and it does not have homology with endogenous erythropoietin.

Epoetin is administered up to three-times a week (TIW) and darbepoetin is administered once-weekly (QW) or once every two weeks (Q2W). The sponsor stated that given the limited ESA options available to providers and patients in the dialysis setting, peginesatide has been developed as an alternative ESA to be dosed every four weeks (Q4W).

2.2.2 What clinical and clinical pharmacology data is submitted to support the approval of peginesatide?

Clinical studies

The clinical development program for peginesatide includes 21 studies (six phase 1, ten phase 2, and four phase 3 studies, as well as one supportive phase 1 study conducted in Japanese patients). In support of this NDA, five randomized, active-controlled trials were conducted (Table 2). Although the efficacy of peginesatide was supported in the phase 3 studies for the treatment of anemia in subjects not on dialysis, there was difference in the outcomes for cardiovascular safety in this population, with results unfavorable for peginesatide. Therefore, the sponsor is seeking approval of peginesatide only for the chronic kidney disease patients who are on dialysis (AFX01-12, -14, and -15), and not for the chronic kidney disease patients who are not on dialysis (AFX01-11 and -13).

Table 2. Active controlled phase 2 and phase 3 trials

Study	Subjects	Comparator	Sample Size (peginesatide: control)	Region(s)
AFX01-11	Non-Dialysis CRF subjects not on an ESA (SC)	Darbepoetin alfa	326:164	US
AFX01-13	Non-Dialysis CRF subjects not on an ESA (SC)	Darbepoetin alfa	330:163	US and Europe
AFX01-12	Dialysis subjects previously treated with Epoetin (IV)	Epoetin alfa	524:269	US
AFX01-14	Dialysis subjects previously treated with Epoetin (IV/SC)	Epoetin alfa or beta	542:273	US and Europe
AFX01-15	Dialysis subjects not on an ESA (IV)	Epoetin alfa	76:38	Russia

Clinical Pharmacology studies

Clinical pharmacology program included 14 clinical studies as well as 7 in vitro studies (Table 3). The human PK studies consist of dose proportionality, single and multiple-dose PK, thorough QTc, BA/BE studies bridging the to-be-marketed formulation and clinical trial formulation, and a population PK analysis evaluating covariate effects of age, gender, race, ethnicity, renal and hepatic functions on the PK of peginesatide. AFX01-02 and AFX01-04 were not reviewed because these trials contain information irrelevant of the proposed indication.

Table 3. Overview of clinical pharmacology studies

	Study No. (location)	Study Objectives
PK studies	AFX01-102 (US)	IV BA of SDV and MDV formulations
	AFX01-103 (US)	SC BA/BE of SDV and MDV formulations
	AFX01-104 (US)	SC BA/BE of SDV formulations 10 mg/mL and 16 mg/mL
	AFX01-105 (US)	SC BA/BE of SDV formulations 2 mg/mL and 10 mg/mL
	AFX01-101 (US)	Thorough QTc study (IV)
PD studies	AFX01-0401 (UK)	Single IV dose escalation study (0.025, 0.05, 0.1 mg/kg) in healthy volunteers with dense PK
	CPH-001 (Japan)	Single IV & SC dose escalation study (0.0125, 0.025, 0.05, or 0.1 mg/kg) in healthy volunteers (IV, SC) with dense PK
	AFX01-02 (UK)	IV single dose-finding (0.025, 0.05, and 0.10 mg/kg) in ESA-naïve anemic subjects with CKD not on dialysis compared with placebo with dense PK
	AFX01-04 (EU)	IV/SC dose-finding in ESA-naïve anemic subjects with CKD not on dialysis with dense PK. Doses studied: Q4W × 6 doses, or Q2W × 12 doses; 0.025-0.075 mg/kg or 3.0 and 4.0 mg (fixed dose).
	AFX01-03 (US)	IV dose-finding in CKD hemodialysis patients with dense PK. Doses studied: Q4W × 6 doses; conversion factors mg/kg, tiered mg/kg (0.03-0.15 mg/kg) or tiered fixed mg.
	AFX01-07 (EU)	IV/SC dose-finding in CKD hemodialysis patients with dense PK. Doses studied: Q4W × 7 doses; tiered mg/kg
	AFX01-12 (US) AFX01-14 (US/EU)	Dose confirmation in CKD dialysis patients (AFX01-12 (IV), AFX01-14 (IV/SC)) Doses studied: 0.04, 0.08, 0.12, 0.16 mg/kg/Q4W for screening Epoetin dose (U/kg/week) <100, 100 to <200, 200 to <300, ≥ 300 U/kg/week) Sparse PK (AFX01-14 only)
	AFX01-15 (Russia)	28-week dose confirmation in CKD dialysis patients (IV) Doses studied: Peginesatide 0.04 mg/kg Q4W starting dose, Peginesatide 0.08 mg/kg Q4W starting dose, Epoetin 50 U/kg TIW starting dose
***In vitro* studies**	AF37702-10425	CYP Enzyme Identification
	AF37702-00024	CYP Inhibition potential of peginesatide
	F08-014	CYP Induction potential of AF37702
	A957-702-004 & AF37702-00025	CYP Induction potential of AF37702, (b) (4) (b) (4)
	AF08-013	CYP Inhibition potential of AF37702, (b) (4) (b) (4)
	AF09-010	plasma protein binding
	AF37702-10401	Red blood cells/plasma ratio

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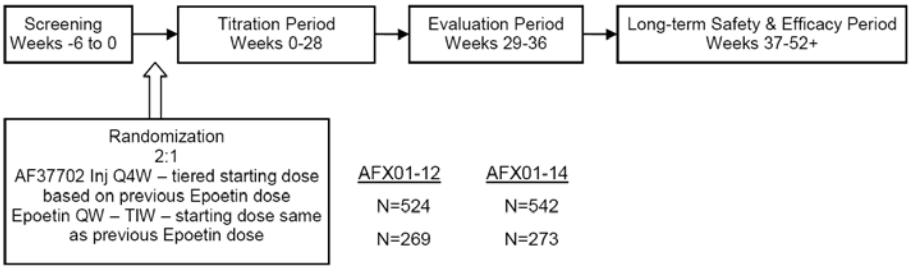
2.3 GENERAL CLINICAL PHARMACOLOGY

2.3.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In dialysis patients who are currently treated with epoetin alpha

The safety and efficacy of peginesatide in CKD dialysis patients were supported primarily by two phase 3 trials (AFX01-12 and AFX01-14). Data from these trials were used to select the dose of peginesatide when switching from epoetin alfa. Both studies were designed as randomized, active-controlled, open-label, multi-center trials. Study AFX01-12 was conducted in the US and Study AFX01-14 was conducted in the US and Europe. The studies included an initial Titration Period, an Evaluation Period, and a Long-term Safety and Efficacy (LTSE) Period (Figure 1).

Figure 1. Design of Phase 3 Dialysis Studies AFX01-12 and AFX01-14



Dose was based on the prescribed total weekly Epoetin dose during the last week of the Screening Period (Table 4) and was administered 1 week after the last Epoetin dose administered prior to randomization (during Week 1).

Table 4. Peginesatide Injection Starting Doses in Studies AFX01-12 and AFX01-14

Screening Epoetin Dose (U/kg/week)	AF37702 Injection Starting Dose (mg/kg/Q4W)
<100	0.04
100 to 199	0.08
200 to 299	0.12
≥300	0.16

Each subject's dose was titrated to achieve and maintain Hgb in the target range of 10-12 g/dL. The primary efficacy endpoint for each study was the mean change in Hgb between Baseline and the Evaluation Period. Non-inferiority of peginesatide to Epoetin was established if the lower limit of the two-sided 95% confidence interval (CI) for the difference between the two treatment groups in mean changes of Hgb from Baseline was ≥ -1.0 g/dL.

In dialysis patients who are currently treated with darbepoetin alpha

Data from phase 2 trial (AFX01-202, N=101) were used to determine the dose of peginesatide when switching from darbepoetin. Study AFX01-202 evaluated the efficacy of peginesatide, once-every 4 weeks, at starting doses of 0.04, 0.08, 0.12, or 0.16 mg/kg according to the screening darbepoetin alfa dose in both dialysis and non-dialysis CKD patients. This was a multi-center, open-label study which consisted of a screening period, enrollment, titration period (weeks 0 – 18), and evaluation period (weeks 19 – 24). Doses were titrated to maintain hemoglobin concentrations within the target range of 10-12 g/dL. The primary endpoint was mean change in hemoglobin between baseline and the evaluation period.

In dialysis patients who are not currently treated with an ESA

Data from a phase 2 trial (AFX01-15, N=114) was used to select the starting dose of peginesatide for

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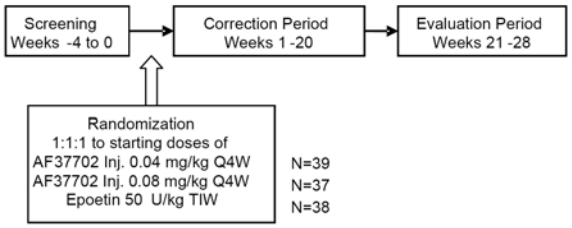
patients initiating ESA therapy. The study evaluated the dose response and safety of two starting doses of peginesatide. This was a phase 2, randomized, parallel design, active-controlled, open-label, multicenter study. The study included an initial Correction Period followed by an Evaluation Period (Figure 2).

Figure 2. Design of Phase 2 Dialysis Study AFX01-15



Subjects were randomized in equal proportions to receive peginesatide at a starting dose of 0.04 mg/kg Q4W, peginesatide at a starting dose of 0.08 mg/kg Q4W, or Epoetin alfa IV at a starting dose of 50 U/kg TIW. Each subject's dose was titrated according to protocol-specified dose adjustment guidelines to achieve and maintain Hgb in a target range of 11-12 g/dL. The primary efficacy endpoint was the mean change in Hgb between the baseline and the evaluation Period.

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

Hemoglobin (Hgb) is an objectively measured biologic parameter and change in Hgb is well accepted as an appropriate parameter to reflect the mechanism of action of ESAs. Change in Hgb has been used as a primary endpoint in pivotal studies performed to support the marketing of current ESAs, including Epoetin alfa and darbepoetin alfa. In the phase 3 studies, each subject's dose of study medication was titrated to achieve and maintain Hgb according to the protocol-specified target range and protocol-specified dose adjustment guidelines. Hgb levels were obtained every 2 weeks. Hemoglobin levels used for dosing decisions were drawn 1 week prior to the next scheduled dose.

2.3.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

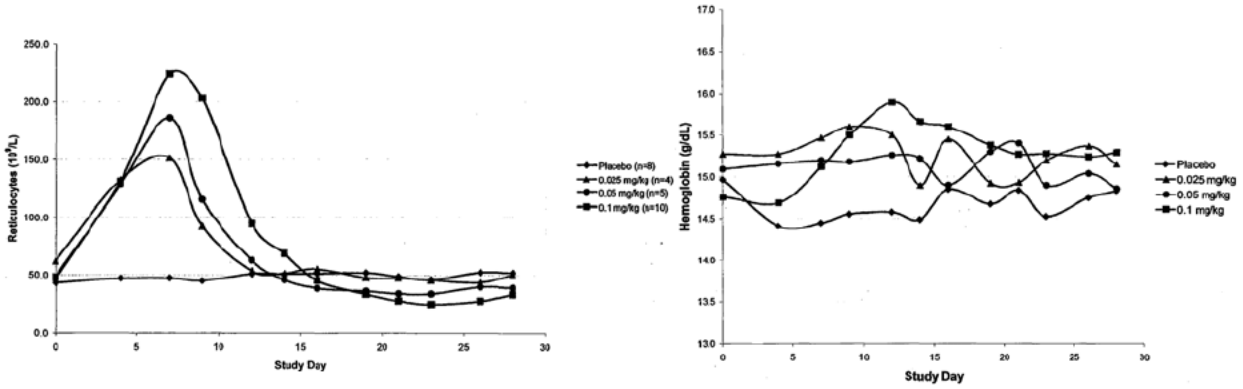
Yes. Please refer to Section 2.7 Analytical.

2.3.4 Exposure-response

2.3.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

In a phase 1 dose escalation study (AFX01-0401, N=28) in healthy volunteers, reticulocyte count showed a dose-dependent increase with increasing peginesatide dose (Figure 3 (left)). The hemoglobin response (Figure 3 (right)) also showed dose-dependent increases with increasing dose. This behavior is opposite that observed in the phase 3 clinical trials (See Section 2.3.4.2). Variability in disease accounts for this difference as patients with the lower hemoglobin and poor initial response required higher doses to achieve a similar hemoglobin response to patients with higher hemoglobin levels.

Figure 3. Dose-dependent reticulocyte response by dose group



The reticulocyte count responses were evaluated as a function of both magnitude and duration through assessment of peak response (C_{max}) and the AUC for the first 14 days post-dose as well as 28 days post-dose (Table 5). The results showed a higher peak response and increased AUC with higher peginesatide dose.

Table 5. Mean C_{max}, AUC_{0-14}, AUC_{0-28} reticulocyte count by dose group

Dose Group	Estimate	C_{max} (10^9/L)	AUC_{0-14} (10^9/L*Days)	AUC_{0-28} (10^9/L*Days)
Placebo (n_1=8)	Mean (SD)	61.1 (16.1)	661 (205)	1,367 (361)
0.025 mg/kg (n_2=4)	Mean (SD)	148.2 (38.8)	1,390 (439)	2,091 (763)
0.05 mg/kg (n_3=5)	Mean (SD)	186.5 (43.8)	1,502 (273)	2,028 (344)
0.1 mg/kg (n_4=10)	Mean (SD)	227.5 (40.4)	1,932 (416)	2,418 (520)
One-Way ANOVA				
F-test		34.2	20.3	6.87
p-value		<0.0001	<0.0001	0.0018

Since doses were adjusted based on hemoglobin levels in the pivotal trials, analysis for the exposure-response relationships for efficacy was not conducted.

2.3.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The cardiovascular (CV) primary composite safety endpoint (CSE) was evaluated in the phase 3 trials AFX01-11, -12, -13, and -14. However PK samples were not assayed in a sufficient number of patients to evaluate exposure response for CSE events based on pharmacokinetic concentrations. A dose-response relationship for cardiovascular (CV) events could not be identified because of the following limitations in the data:

- For an individual patient, the peginesatide (or darbepoetin) dose was titrated throughout the duration of the phase 3 trials to maintain hemoglobin in the range of 11 – 12 g/dL.
- The average dose of peginesatide (or darbepoetin) was inversely correlated with average hemoglobin levels.
- Patients who were not within the target hemoglobin by 3 months (*i.e.*, slow responders) were titrated to higher peginesatide (or darbepoetin) doses and had an increased risk of CV events.

- There was an imbalance of baseline CV risk factors between slow and normal responders.

To evaluate the dose-response relationship for CV events in trials AFX01-11 and AFX01-13, the average doses of darbepoetin and peginesatide were used instead of the randomized starting dose because patients' doses were titrated throughout the duration of the study to achieve target hemoglobin of 11 – 12 g/dL. Figure 4 shows an apparent trend for increased composite safety endpoint (CSE) events with increasing average dose quartile for both darbepoetin and peginesatide. However, as shown in Table 6 and Figure 5, hemoglobin is inversely correlated with dose. Therefore, it is difficult to tease out the contribution of dose or hemoglobin to CV risk.

Figure 4. Cardiovascular risk appears to be correlated with average study dose for both darbepoetin and peginesatide. Curves for the cumulative percentage of patients with a primary CSE are shown for each average dose quartile.

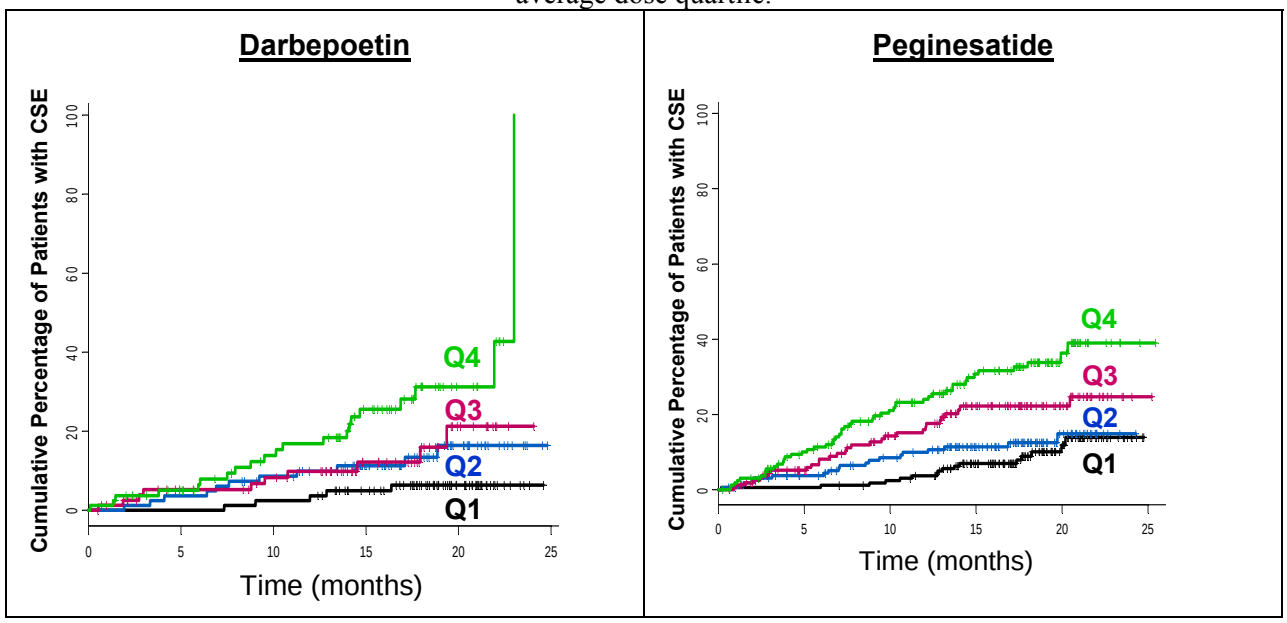
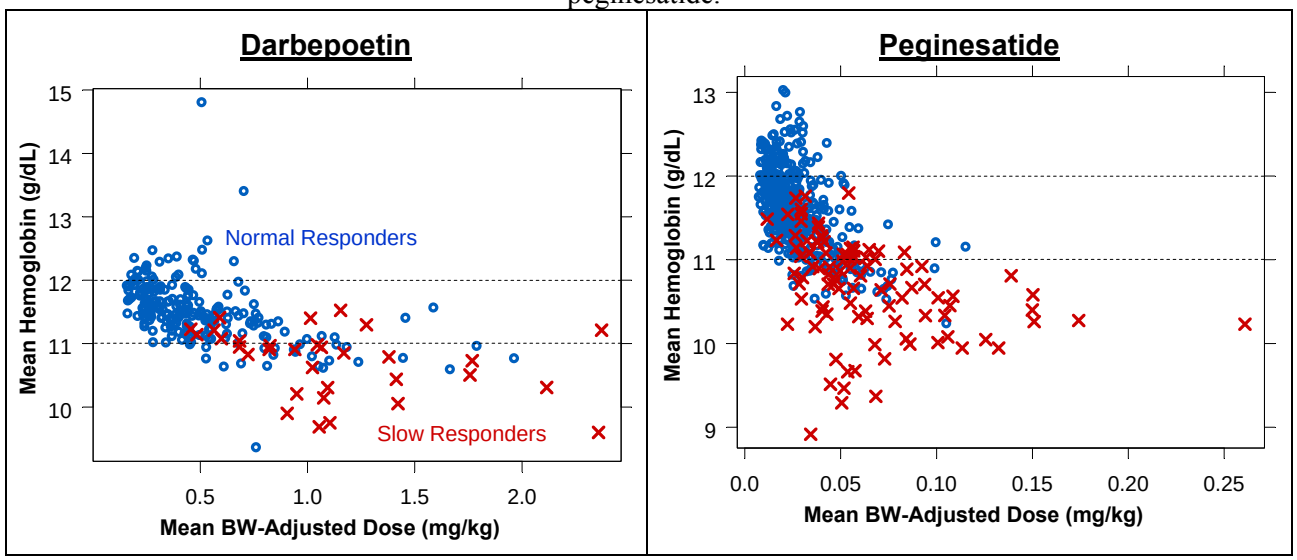


Table 6. Mean Hemoglobin is Inversely Correlated with Mean ESA Study Dose.

	Darbepoetin		Peginesatide	
Quartile	Mean Dose (mcg/kg)	Mean Hgb (g/dL)	Mean Dose (mcg/kg)	Mean Hgb (g/dL)
1	0.243	11.7	13.4	11.8
2	0.399	11.5	22.1	11.7
3	0.602	11.5	32.1	11.4
4	1.14	10.8	65.8	10.8

Figure 5. Individual mean hemoglobin is inversely correlated with average dose of darbepoetin and peginesatide.



There is a subgroup of patients that the sponsor identified as "poor responders" who exhibited an increased CV event rate (see Appendix 4.1, Section 3.3.1.). In the sponsor's analysis, poor responders were defined as individuals with a change from baseline hemoglobin value at one month that was in the lowest quartile of response. FDA Pharmacometrics reached the same conclusion with an approach that defined the this subgroup as individuals who had hemoglobin values at 3 months that were less than the lower limit of their target hemoglobin range. FDA referred to this subgroup as "slow responders" to differentiate it from the sponsor's definition. Not achieving the target hemoglobin was an important criterion because the individual's dose would continually be increased until the target hemoglobin was met. This definition was based on the primary efficacy endpoint (target hemoglobin range of 11 – 12 mg/dL) and the current ARANESP (darbepoetin) label that states, "For patients who do not respond adequately over a 12-week escalation period, increasing the Aranesp dose further is unlikely to improve response and may increase risks."

In trials AFX01-11 and AFX01-13, slow responders comprised 18% of the peginesatide treated subjects and 13% of the darbepoetin alfa treated subjects. As shown in Figure 6, the subgroup of slow responders received higher average doses of study drug compared to normal responders (Figure 6). Slow responders had higher CV risk. The cumulative percent of patients with CV events over time for slow and normal responders are shown in Figure 7 for CSE.

It is important to note that these results do not imply a causal relationship between hemoglobin, dose and CV risk. Slow responders were found to have a higher proportion of patients with underlying risk factors for CV events compared to normal responders as shown in Table 7.

Table 7. Baseline demographics of slow versus normal responders contain imbalances.

	Darbepoetin		Peginesatide	
Baseline Demographic	**Normal Responder**	**Slow Responder**	**Normal Responder**	**Slow Responder**
N (% of Treatment Group)	286 (87)	41 (13)	536 (82)	120 (18)
% Female	58	69	55	61
% NYHA Class II	16	13	16	27
Base Hgb (g/dL)	10.1	9.7	10.1	9.7
C-Reactive Protein (mg/L)	7	11	6	12
% w. Peripheral Vascular Disease	19	21	26	32
% w. Coronary Artery Disease	38	46	39	44
% w. Cardiovascular Disease	17	18	18	20
% w. Cardiac Arrythmia	13	15	14	26

Figure 6. Slow responders were titrated to higher doses than normal responders in both the darbepoetin (left panel) and peginesatide (right panel) treatment groups. Red and blue lines indicate the mean dose at the corresponding time for slow and normal responders, respectively. Data are presented as mean ±SEM.

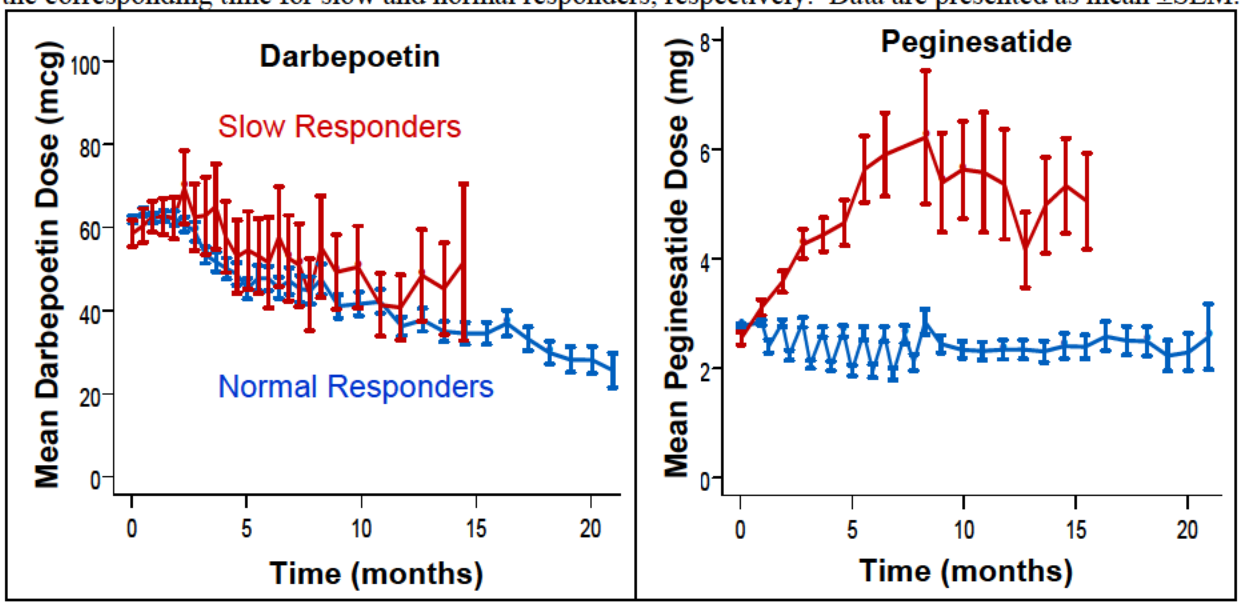


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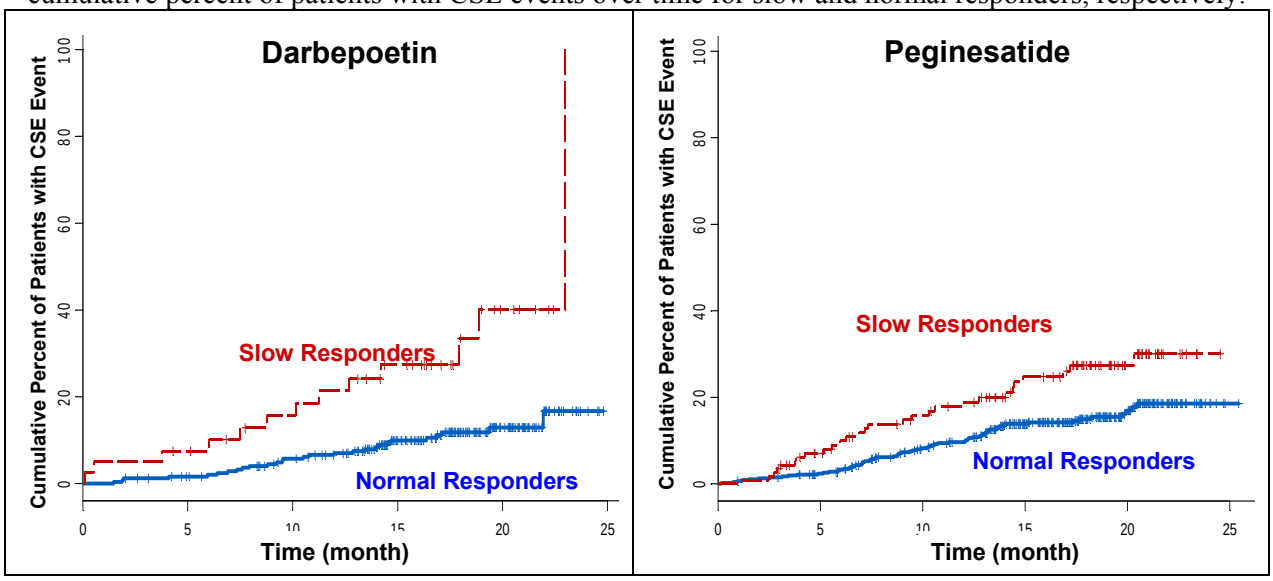
Figure 7. Slow responders appear to have increased CV risk in both the darbepoetin alfa (left panel) and peginesatide (right panel) treatment groups for the primary CSE. Red and blue lines depict the cumulative percent of patients with CSE events over time for slow and normal responders, respectively.



2.3.4.3 Does this drug prolong the QT or QTc interval?

According to the QT/IRT review, no significant QTc prolongation effect of peginesatide was detected in the thorough QT study AFX01-101. This study was a phase 1, single-dose, multi-center, randomized, double-blind, double-dummy, three-period crossover study. Sixty-five healthy subjects received peginesatide 0.1mg/kg, placebo, and moxifloxacin 400 mg. The overall summary of findings is presented in Table 8.

Table 8: The Point Estimates and the 90% CIs corresponding to the Largest Upper Bound for Peginesatide and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	ΔΔQTcF (ms)	90% CI (ms)
Peginesatide Injection	0.75	0.2	(-1.6, 1.9)
Moxifloxacin 400 mg*	3	12.3	(10.3, 14.2)
* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 9.6 ms.			

The largest upper bound of the 2-sided 90% CI for the mean differences between peginesatide and placebo of ΔΔQTcF was below 10 ms. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that assay sensitivity was established.

The dose tested was 0.1 mg/kg, however, the label indicates that doses up to approximately [redacted] (b) (4) can be recommended as a starting dose. Therefore, the current dose proposed [redacted] (b) (4) does not cover the highest therapeutic exposure. There have been no identified factors that can increase drug exposure and no accumulation anticipated since the half-life is approximately 24 hours and the drug is given once per month.

For more details please see the IRT review attached. The IRT had labeling recommendations which can be found in Section 3 – Detailed Labeling Recommendations.

2.3.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Peginesatide has a predictable, dose-related effect on reticulocyte and hemoglobin (Hgb) levels. A

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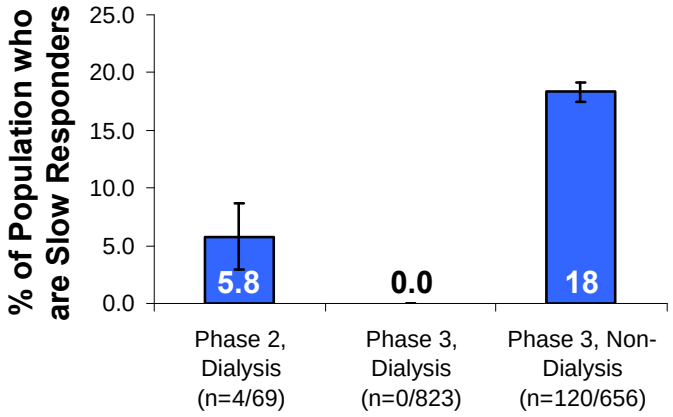
response-based titration regimen has been proposed to maintain hemoglobin levels in the range of 10-12 g/dL. The proposed dose for patients who are currently treated with an ESA is supported by the safety and efficacy results of study AFX01-12 and AFX01-14. However, CV data were not available for dialysis patients initiating peginesatide therapy.

The phase 3 dialysis trials did not enroll the slow responder subgroup which exhibited increased cardiovascular risk. The two phase 3 trials were conducted in dialysis patients who were previously receiving stable doses of epoetin and were randomized to either continue receiving their epoetin dose or convert to peginesatide. To be enrolled in the trials, dialysis patients were already on epoetin for > 8 weeks before randomization and baseline hemoglobin levels must have been in the target range of 10 – 12 g/dL for at least 4 weeks prior to study entry.

This is important because the sponsor is seeking an indication for all dialysis patients, not just those switching from a prior ESA. If a subgroup of slow responders exists for dialysis patients, it is in those individuals initiating treatment. However, the CV risk was not studied for dialysis patients initiating peginesatide treatment.

Figure 8 shows the percentage of slow responders in the peginesatide treated patients for both the dialysis and non-dialysis clinical trials. Trial AFX01-15 was a phase 2 trial conducted in subjects who were on dialysis and were initiating peginesatide treatment. From this small phase 2 study we expect that slow-responders are present in the dialysis population. However, the small number of peginesatide treated patients (n=69) and shorter trial duration (28 weeks) limited the ability to evaluate the cardiovascular safety in patients initiating treatment.

Figure 8. Slow responders are expected to be present in ESA treatment naive patients.



The CV risk for all dialysis patients has not been characterized. This includes both patients initiating treatment and those switching from a prior ESA. This is important because the sponsor is seeking the indication for all dialysis patients and the safety has only been characterized for those switching from another ESA.

If the FDA approves peginesatide for the initiation of ESA therapy for the correction of anemia, we recommend using 0.04 mg/kg peginesatide as the starting dose. Based on the phase 2 study AFX01-15, the sponsor has proposed a starting dose range of 0.04 mg/kg to 0.08 mg/kg. In this study, the mean time course and mean hemoglobin for the 0.04 mg/kg and 0.08 mg/kg starting doses were similar (Figure 9). Furthermore, the average dose during the evaluation period was 0.05 for both dose groups (Figure 10). From an efficacy standpoint, the 0.04 mg/kg dose appears to be an appropriate starting dose. Because the 0.04 mg/kg had an adequate hemoglobin response and CV safety was not evaluated in this phase 2 study, starting doses greater than 0.04 mg/kg are not justified.

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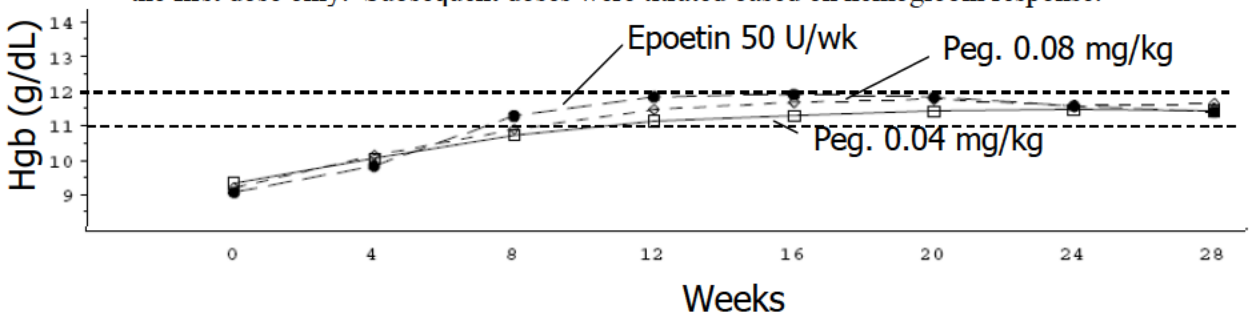
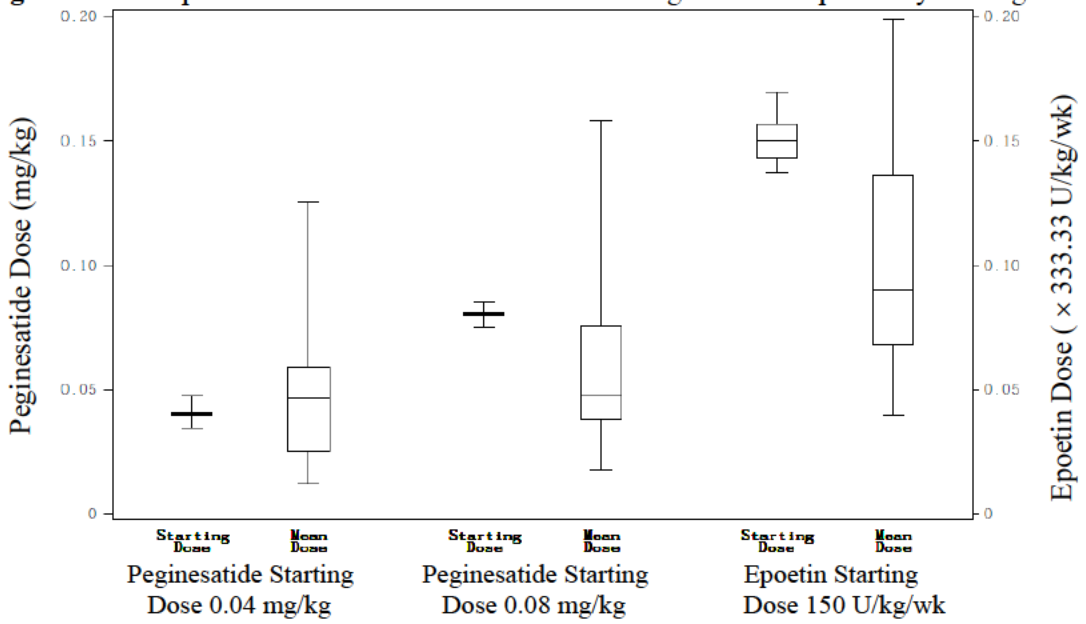
Figure 9. Mean hemoglobin value during 4-wk intervals of trial AFX01-15. The target hemoglobin range for this phase 2 study is indicated by the dashed lines. Dose amounts shown indicate the value of the first dose only. Subsequent doses were titrated based on hemoglobin response.



(Source: Sponsor's Clinical Efficacy Summary, Figure 12)

Figure 10. Comparison of first dose and mean dose during evaluation period by starting dose.



(Source: Sponsor's Clinical Efficacy Summary, Figure 32)

2.3.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.3.5.1 What are the single dose and multiple dose PK parameters?

Single Dose

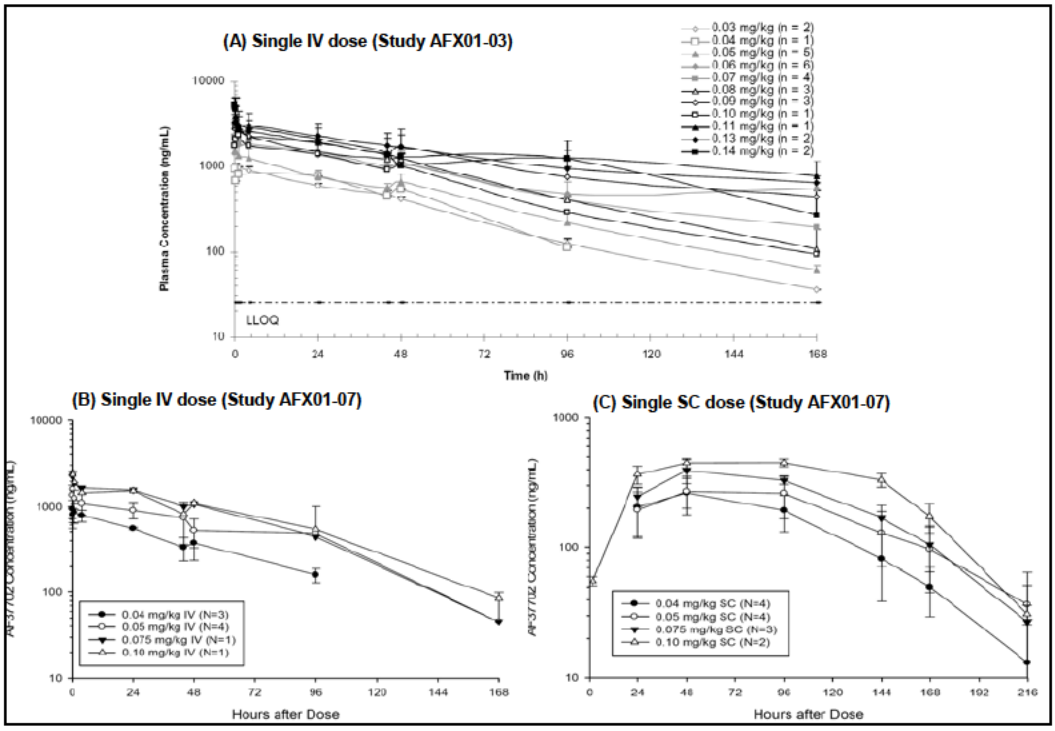
PK data for peginesatide from phase 2 studies in which a starting dose of peginesatide 0.05 to 0.14 mg/kg was administered by IV (AFX01-03 and AFX01-07) or 0.04 to 0.1 mg/kg was administered by SC (AFX01-07) to patients with CKD on dialysis were pooled by the sponsor.

Table 9. Mean peginesatide PK parameters for patients with CKD on dialysis following a single IV or SC dose of peginesatide: pooled data from AFX01-03 and AFX01-07

	C_{max}/Dose (µg/mL)/(mg/kg)	$AUC_{0\text{-}inf}$/Dose (µg·h/mL)/(mg/kg)	$t_{1/2}$ (h)	CL (mL/h·kg)	Vd (mL/kg)
Mean (CV%) (IV, N=30)	34.1 (38.9%)	2097 (35.2%)	47.9 (34.5%)	0.5 (38%)	34.9 (39.6%)
Mean (CV%) (SC, N=13)	5.79 (28.3%)	711 (26.9%)	34.3 (25.7%)	1.5 (26.7 %)	73.8 (40.8%)

The mean (±SD) peginesatide plasma concentrations vs. time data are displayed in Figure 11. Metabolites (peptide fragments) were not determined.

Figure 11. Mean (±SD) plasma concentration versus time profiles



Multiple Dose

Full PK profiles were not obtained after multiple doses. In a dose-finding study (AFX01-03) pre-dose plasma concentrations collected on weeks 5, 9, 13, 17, and 21 from patients requiring no subsequent dose adjustments were used to determine the extent of accumulation following Q4W dosing. All pre-dose samples were below the assay's limit of quantification. Further examination of pre-dose plasma concentrations collected on weeks 5, 9, 13, 17, and 21 from patients who had undergone either upward or downward dose adjustments per study protocol also showed non-detectable plasma levels of peginesatide except for 1 sample from Patient #08059. The week 9 pre-dose sample gave a concentration of 30 ng/mL that was close the LLOQ of the assay (25 ng/mL) and was considered to be low and almost non-quantifiable. Similar results were obtained in another dose-finding study (AFX01-07). The observed lack of systemic accumulation is consistent with a dosing interval that is greater than four or five half-lives of the drug.

2.3.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The PK data for peginesatide from phase 1 study in healthy subjects and phase 2 studies in non-dialysis

and dialysis patients who received a single dose of peginesatide 0.05 mg/kg by IV administration (Table 10).

Table 10. Mean peginesatide PK parameters for healthy subjects (AFX01-401), CKD patients not on dialysis (AFX01-02) and CKD patients on dialysis (AFX01-03) following a single IV dose of 0.05 mg/kg peginesatide

Population	Healthy subjects	Non-dialysis patients	Dialysis patients
study	AFX01-401, N=5	AFX01-02, N=7	AFX01-03, N=4-5
C_{max} (ng/mL)	1192 (49.1)	2932 (2742)	1612 (518.5)
$AUC_{0\text{-}inf}$ (ng·h/mL)	56161 (9017)	83165 (26051)	81308 (13172)
CL (mL/hr)	72.1 (15.8)	47.9 (12.8)	44 (5.62)
Vd (mL)	1914.8 (244.8)	2927 (590.8)	2535 (871.5)
$T_{1/2}$ (hr)	18.9 (3.75)	43.6 (6.37)	35.92 (5.42)

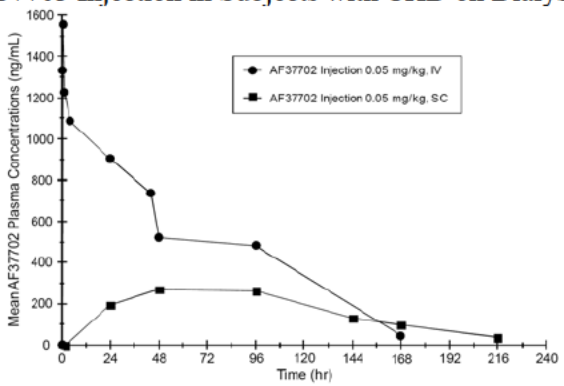
After IV administration, peginesatide attains C_{max} levels in approximately 15 minutes in both healthy subjects and patients with CKD. The $t_{1/2}$ values of peginesatide were 19 hours, 44 hours, and 36 hours in healthy subjects, patients with CKD not on dialysis, and dialysis patients, respectively. The mean clearance rate (CL) was 72.1 mL/hr in healthy subjects which is faster than in patients with CKD not on dialysis or on dialysis (Table 10.). With little or no kidney function, it is expected that patients with CKD on dialysis have decreased clearance of peginesatide when compared with healthy subjects. Accordingly, the peginesatide exposure was higher in patients with CKD compared to healthy subjects.

2.3.5.3 What are the characteristics of drug absorption?

After IV administration, peginesatide attains the C_{max} levels in approximately 15 minutes in both healthy subjects and subjects with CKD on dialysis. Plasma concentration of peginesatide increased slowly following SC administration and attained a broad peak with maximum concentration around 33 to 51 hours in healthy subjects, 48 to 168 hours in CKD subjects not on dialysis (AFX01-04), and 47 to 73 hours in CKD subjects on dialysis (AFX01-07).

Comparisons of the mean exposure from the SC dose relative to the IV dose were used to estimate bioavailability of the SC dose. Absolute bioavailability of peginesatide between the SC and IV administrations is approximately 40% when data obtained after both routes of administration in the same study (AFX01-07) and across two different studies were compared (AFX01-102 and AFX01-103).

Figure 12. Mean Plasma Concentration-Time Profiles of peginesatide Following a Single IV or SC Administration of AF37703 Injection in Subjects with CKD on Dialysis (Study AFX01-07)



2.3.5.4 What are the characteristics of drug distribution?

The decline in plasma concentrations of peginesatide after IV injection was monophasic or biphasic. The volume of distribution (V_d) values after IV administration of peginesatide were 25 mL/kg and 35 mL/kg in healthy subjects and in subjects with CKD on dialysis, respectively; these values suggest that

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peginesatide is mostly restricted to the plasma volume, which is expected for a large, hydrophilic molecule. The apparent volumes of distribution (V/F) values after SC administration of peginesatide were approximately 163 mL/kg and 74 mL/kg in healthy subjects and in subjects with CKD on dialysis. In rats there was no evidence that peginesatide distributes beyond the blood-brain barrier.

In vitro plasma protein binding

The in vitro binding of peginesatide to albumin and lipoproteins in human serum was assessed using a combination of gel exclusion chromatography and potassium bromide density-gradient ultracentrifugation analyses (AF09-010), because conventional protein binding methods (e.g., equilibrium dialysis and ultrafiltration) are not feasible due to the high molecular weight of peginesatide (45 KDa). The ultracentrifugation analyses allowed the detection of peginesatide binding to the lipoprotein species, including low, very low, and high density lipoproteins (LDL, VLDL, HDL, respectively).

Samples of [^{14}C]-peginesatide (4 µg/mL) in human serum were incubated for 15 minutes at 37°C prior to analysis by gel-exclusion column chromatography. Additional serum samples were incubated, diluted ([^{14}C]-peginesatide 1.33 µg/mL), and then subjected to potassium bromide density-gradient ultracentrifugation. Bulk flotation ultracentrifugation was also performed on serum samples at a [^{14}C]-peginesatide concentration of 5 µg/mL following incubation and density adjustment with potassium bromide to examine binding between lipoproteins and proteins.

The elution profile of peginesatide by size exclusion column chromatography was comparable for drug alone and drug in the presence of serum indicating that drug did not bind to albumin. The radioactivity in the analytical ultracentrifugation method was associated with fractions corresponding to LDL, which also corresponded to the site in the gradient where serum was initially placed. However, analytical ultracentrifugation demonstrated an absence of radioactivity in fractions corresponding to VLDL, HDL, and high molecular weight serum proteins. In the bulk flotation ultracentrifugation method, the radioactivity was not associated with the fraction corresponding to all lipoprotein species, confirming an absence of binding to VLDL and HDL and demonstrating that binding to LDL did not occur. The pattern of radioactivity distribution was comparable for drug alone or drug plus serum.

In conclusion, peginesatide does not bind to serum albumin or lipoproteins in human sera.

In vitro partitioning into blood cells

The in vitro red blood cell partitioning of [^{14}C]-peginesatide was examined in study AF37702-10401 using human heparinized whole blood. [^{14}C]-peginesatide was added to whole blood, samples were incubated at 37°C for 30 minutes, and aliquots were analyzed for radioactivity by liquid scintillation counting (LSC). Plasma aliquots were analyzed for radioactivity by LSC. The partitioning ratios of [^{14}C]-peginesatide into human blood cells at final concentrations of 0.1, 1, 10, and 100 µg/mL were 0.9%, 0.0, 0.0, and 0.0, respectively. These results suggest that peginesatide did not distribute into human blood cells.

2.3.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

A human ADME study was not conducted. The overall mean CL values (all dose groups) were 60.5 mL/h in patients with CKD not on dialysis (AFX01-02) and 41.7 mL/h in patients on dialysis (AFX01-03). In contrast, the mean clearance rates of peginesatide ranged from ~60 to 114 mL/hr in healthy subjects which is faster than in patients with CKD, suggesting elimination by the kidneys.

In vivo studies with radio-labeled peginesatide in rats and monkeys indicate that peginesatide is essentially not metabolized and that urinary excretion was the predominant route of elimination following either IV or SC dosing. The total recovery of radioactivity after 336 hours in the urine and feces of rats at 336 hours was 41.3% and 11.8%, respectively, of the administered dose with the remainder of the radioactivity primarily in the carcass. In monkeys, the total recovery of radioactivity in the urine and feces at 336 hours was 59.7% and 7.0%, respectively. The parent molecule was the predominant moiety

excreted in urine with less than 2% and 10% of the total radioactive dose associated with unidentified moieties in the urine and feces, respectively, of the rat and the monkey. Negligible metabolism of peginesatide was also observed following SC dosing in rats, in the plasma of pregnant and lactating rats and in the milk of rats.

2.3.5.6 What are the characteristics of drug metabolism?

In vitro metabolism studies in liver and kidney microsomes and S9 fractions from rats, monkeys, and human donors and in vivo metabolism studies with radio-labeled peginesatide in rats and monkeys indicate that peginesatide is essentially not metabolized.

2.3.5.7 What are the characteristics of drug excretion?

Route of Elimination

The exact mechanisms for elimination of peginesatide in humans are not known. In an experimentally-induced renal failure model with nephrectomized rats, renal clearance was an important component of the overall clearance of peginesatide. Peginesatide was eliminated intact in the urine in nonclinical ADME studies in rat and monkey. It is expected that the elimination of the peptide and PEG portions of peginesatide would undergo typical catabolic processes. The peptide dimer would undergo proteolysis resulting in the constituent amino acids that would be available for elimination via dialysis or incorporation into the amino acid pool.

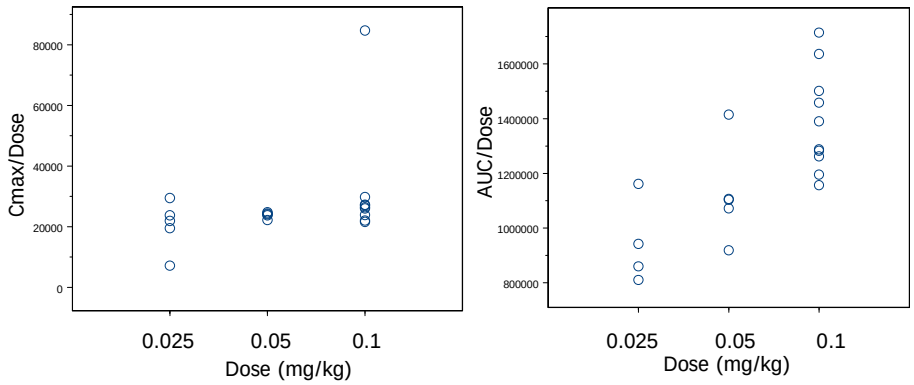
Clearance

Plasma clearance showed a small decrease with dose with geometric means of 78.0 mL/h (13.7 %CV), 70.7 mL/h (13.6 %CV), and 59.2 mL/h (14.4 %CV) in healthy volunteers (Study AFX01-0401) for the IV doses of 0.025, 0.05, and 0.1, respectively. In this study, first order kinetics were observed at lower drug concentrations only, suggesting saturation of metabolic/elimination processes at plasma concentrations in excess of ~400 ng/mL.

2.3.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Dose proportionality was assessed in a phase 1 healthy subject study (AFX01-0401) and two phase 2 studies in subjects with CKD on dialysis (AFX01-03 and AFX01-07). For the phase 1 study with IV administration, C_{max} appears to increase in a linear manner with dose (0.025, 0.05, and 0.1 mg/kg), but AUC_{inf} showed evidence of non-linearity (Figure 13), possibly associated with the small decrease in clearance at higher doses.

Figure 13. Correlation of Dose normalized C_{max} (left) and Dose normalized $AUC_{0-\infty}$ (right) with dose in healthy volunteers



For the phase 2 study with IV administration (AFX01-03), approximate dose proportional relationships

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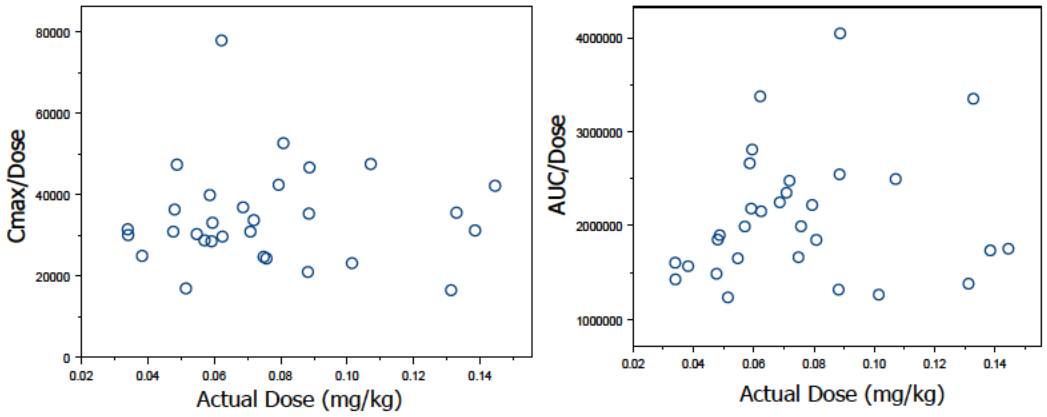
between C_{max} or $AUC_{0-\infty}$ and starting dose (0.03 to 0.14 mg/kg) in CKD dialysis patients were suggested (Figure 14).

Figure 14. Correlation of dose normalized C_{max} (left) and $AUC_{0-\infty}$ (right) with actual dose



The available data from another phase 2 study (AFX01-07) also suggested that the PK of peginesatide was linear following SC administration over the dose range of 0.040 and 0.10 mg/kg CKD dialysis patients.

2.3.5.9 How do the PK parameters change with time following chronic dosing?

After multiple Q4W dosing at doses up to 0.15 mg/kg in hemodialysis patients, no accumulation of peginesatide has been observed (Study AFX01-03). Please see Section 2.3.5.1 for more information on the pharmacokinetics of peginesatide following multiple doses.

2.3.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Variability of PK parameters was similar between patients and healthy volunteers as seen in Table 11.

Table 11. CV% of C_{max} and AUC in healthy volunteers (HV) and patients (P).

	IV (N)	SC (N)
Cmax in HV	36.6% (31)	44.7% (195)
Cmax in P	38.9% (30)	28.3% (13)
AUC in HV	19.2% (31)	38.3% (164)
AUC in P	35.2% (30)	26.9% (13)
N = number of subjects		

2.4 INTRINSIC FACTORS

2.4.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Population PK analysis

The pharmacokinetics of peginesatide in CKD patients on dialysis are not altered by age, gender or race based on population pharmacokinetic analyses.

Race – Japanese Study

A phase 1 dose escalation study in healthy male Japanese subjects conducted (CPH-001) in Japan was submitted as a supportive study. The doses were 0.0125 mg/kg, 0.025 mg/kg, 0.05 mg/kg, or 0.1 mg/kg

administered by IV or SC (80 subjects were dosed and completed the study). The PK data from this study was compared to the data from AFX01-0401 (Table 12). The PK parameters appear generally comparable between the two race groups.

Table 12. Single dose pharmacokinetic parameters of peginesatide in Japanese (CPH-001) and pharmacokinetics in Caucasian healthy subjects (AFX01-0401)

	Japanese	Caucasian
0.025 mg/kg	(n = 8)	(n = 5)
Tmax (hr)	1.39 ± 1.728	0.182 ± 0.093
AUCt (ng h/mL)	22891 ± 8572	18040 ± 10538
AUC (ng/mL)	23561± 7396	23589 ± 3878
Cmax (ng/mL)	572 ± 105	509 ± 206
$T_{1/2}$ (L/hr)	30.4 ± 21.7	19.3 ± 2.2
CL (L/hr)	66.1 ± 19.4	78.5 ± 10.7
Vd (mL)	2752 ± 1182	2174 ± 209
0.05 mg/kg	(n = 7)	(n = 5)[a]
Tmax (hr)	1.00 ± 1.369	2.618 ± 5.256
AUCt (ng h/mL)	58963 ± 13777	50717 ± 8786
AUC (ng/mL)	59986 ± 13441	56160 ± 9017
Cmax (ng/mL)	1409 ± 310	1192 ± 49
$T_{1/2}$ (L/hr)	21.7 ± 4.8	18.9 ± 3.7
CL (L/hr)	55.7 ± 9.9	72.1 ± 15.8
Vd (mL)	2129 ± 408	1915 ± 245
0.1 mg/kg	(n = 8)	(n = 10)[b]
Tmax (hr)	0.25 ± 0	0.456 ± 0.385
AUCt (ng h/mL)	132101 ± 17148	135960± 16626
AUC (ng/mL)	133136 ± 17350	138859 ± 18658
Cmax (ng/mL)	2571 ± 254	3147 ± 1888
$T_{1/2}$ (L/hr)	25.3 ± 6.9	24.0 ± 5.2
CL (L/hr)	48.5 ± 4.1	59.7 ± 8.6
Vd (mL)	2478 ± 312	2028 ± 287

[a]One Oriental (not an Asian) included
[b]One African American included

Gender

A gender analysis was conducted using data from AFX01-03 in subjects with CKD on dialysis. A one-way ANOVA was performed on log transformed AUC/Dose, C_{max}/Dose, Vd, mean residence time, and $t_{1/2}$ and CL.

Table 13. Means and Confidence Intervals for One-way ANOVA for Gender Comparison

Gender	Number	PK Parameters	Mean	Std Error	Lower 95%CI	Upper 95%CI
Female	12	Log AUC(0-∞)/Dose	6.326	0.03790	6.248	6.404
Male	18		6.282	0.03095	6.218	6.345
Female	12	Log Cmax/Dose	4.575	0.03896	4.495	4.655
Male	18		4.471	0.03181	4.406	4.536
Female	12	CL	0.4958	0.04554	0.3956	0.5960
Male	18		0.5419	0.03428	0.4696	0.6142
Female	12	Log Vz	1.490	0.04490	1.398	1.582
Male	18		1.534	0.03666	1.459	1.609
Female	12	Log MRT	1.810	0.03519	1.738	1.882
Male	18		1.831	0.02874	1.772	1.890
Female	11	Log T1/2 lz	1.649	0.04229	1.562	1.736
Male	17		1.670	0.03402	1.600	1.740

There were generally no statistically significant differences between male and female subjects in PK parameters (AUC, CL, Vd, and $t_{1/2}$), with the exception of a slight statistically significant difference

(p=0.048) for dose-normalized C_{max} (higher in female subjects) (Table 13). This borderline probably occurred by chance due to the small sample size of the comparison.

2.4.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.4.2.1 Pediatric patients

The PK of peginesatide has not been studied in pediatric subjects. The sponsor requested a waiver of pediatric studies for infants <12 months and a deferral of pediatric studies for children 12 months to <18 years. A summary of the proposed studies is included in the submission, and PerC meeting was held on 1/25/12.

2.4.2.2 Renal impairment

A dedicated renal impairment study was not conducted. This is acceptable because proposed population is patients with chronic kidney disease on dialysis. PK and PD in this population were characterized in phase 2 and 3 studies.

2.4.2.3 Hepatic impairment

A hepatic impairment study was not conducted. This is acceptable because of the lack of effect in metabolic pathways typically involved in drug metabolism (i.e., by CYP enzymes). The population PK and PK-PD analysis evaluated hepatic (ALP and TBILI) function markers and the magnitude of the effects of these covariates on C_{max} and AUC of peginesatide were not clinically meaningful. None of the hepatic function covariates were significant for the PK/PD analysis.

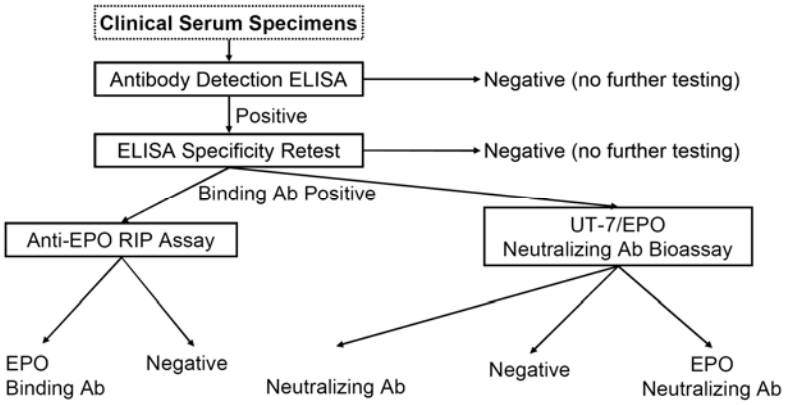
2.4.2.4 What pregnancy and lactation use information is there in the application?

The PK of peginesatide has not been studied in pregnant women. In addition, no clinical studies were performed to determine if peginesatide is excreted into human milk.

2.4.3 Immunogenicity

The sponsor's immunogenicity testing strategy is shown in Figure 15. Specimens were collected periodically during the studies and/or at the end of each study. The antibody detection direct ELISA was used to test for the presence of peginesatide-specific BAb (binding antibody) in serum samples. BAb+ serum samples were tested for peginesatide-NAb using the functional UT-7/EPO cell-based Nab (neutralizing Ab) assay. Serum samples positive for BAb also were tested for antibodies to EPO to enable assessment of immunological cross-reactivity between peginesatide and EPO.

Figure 15. Immunogenicity Testing Strategy for peginesatide Clinical Trials



2.4.3.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

Of the 2357 subjects in the overall safety population of phase 2 and phase 3 trials who received peginesatide IV or SC and had at least one antibody response assessment, 29 (1.2%) had detectable levels of peginesatide-specific binding antibodies (Table 14). The SC route of administration of peginesatide was associated with a higher observed rate of antibody development than the IV route: 1.9% (1.6 per 100 PEY [patient exposure years]) of SC dosed subjects became APA versus 0.7% (0.6 per 100 PEY) of IV dosed subjects.

Table 14. Peginesatide Binding Antibody Incidence by Subject Population and Dosing Route in the Overall Safety Population

Dosing Route	No. BAb+/Total Tested by Clinical Subject Population			Totals by Dosing Route	Adjusted Antibody Development Rate (per 100 PEY)
	CRF on Dialysis[a]	CRF Non-Dialysis[a]	CRF with PRCA (Study AFX01-06)[a]		
IV	9/1282 (0.7%)	0/28	NA	9/1310 (0.7%)	0.6
SC	6/211 (2.8%)	13/820 (1.6%)	1/16 (6.3%)	20/1047 (1.9%)	1.6
Totals by subject population	15/1493 (1.0%)	13/848 (1.5%)	1/16 (6.3%)	29/2357 (1.2%)	1.1

Note: BAb+ refers to AF37702-specific binding antibody positive sample.
[a] Subjects in Phase 2 and Phase 3 studies; Study AFX01-06 is discussed above.
NA = not applicable.

A validated direct enzyme-linked immunosorbent assay (ELISA) was used to detect antibodies to peginesatide. Antibody analysis schedules were designed to minimize the chance that residual peginesatide in the sample would interfere with the antibody detection direct ELISA or the NAb bioassay. Samples for antibody analysis in the single-dose clinical studies were taken pre-dose and 4 weeks after dosing. Samples in the multiple-dose clinical studies were generally taken prior to each dose, on a Q2W, Q3W, or Q4W schedule, including a pre-dose sample before the first dose. Several of the long-term studies, including the phase 3 studies, included sampling on an every 12 weeks schedule.

Six clinical studies (AFX01-0401, AFX01-101, AFX01-102, AFX01-103, AFX01-104, and AFX01-105) were conducted in healthy subjects. None of the subjects in this population who received peginesatide and who had at least one antibody response assessment (peginesatide IV: N=104; peginesatide SC: N=196) had detectable levels of peginesatide-specific BAb. There was no evidence of immunological cross-

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reactivity based on lack of formation of *de novo* antibodies to EPO following exposure to peginesatide.

2.4.3.2 Do the anti-product antibodies have neutralizing activity?

Yes. The incidences of peginesatide-NAb are shown in Table 15.

Table 15. Peginesatide-NAb Incidence by Subject Population and Dosing Route in the Overall Safety Population

Dosing Route	No. NAb+/Total Tested by Clinical Subject Population			Totals by Dosing Route	Adjusted Neutralizing Antibody Rate (per 100 PEY)
	CRF on Dialysis[a]	CRF Non-Dialysis[a]	CRF with PRCA (Study AFX01-06)[a]		
IV	5/1282 (0.4%)	0/28	NA	5/1310 (0.4%)	0.3
SC	5/211 (2.4%)	10/820 (1.2%)	1/16 (6.3%)	16/1047 (1.5%)	1.2
Totals by subject population	10/1493 (0.7%)	10/848 (1.2%)	1/16 (6.3%)	21/2357 (0.9%)	0.8

Note: NAb+ refers to AF37702- neutralizing antibody positive sample.
[a] Subjects in Phase 2 and Phase 3 studies; Study AFX01-06 is discussed below.
NA = not applicable.

2.4.3.3 What is the impact of anti-product antibodies on clinical efficacy?

Of the 29 subjects who developed BAb, 24 had a drop in Hgb by >2.0 g/dL, 12 had two or more Hgb <9 g/dL, and 9 had an increase in dose. Of the 21 subjects who developed NAb, 18 had a drop in Hgb by >2.0 g/dL, 11 had two or more Hgb <9 g/dL, and 7 had an increase in dose (all as defined above).

Of the 29 subjects who developed BAb, 7 received transfusions within the period of detectable antibodies ±90 days. Of the 21 subjects who developed NAb, 4 received transfusions within the period of detectable antibodies ±90 days. Of note, subject 12-1179-385, who had binding-only antibodies, had a blood transfusion for a treatment-emergent serious adverse event of gastrointestinal hemorrhage, which occurred approximately 70 days before first antibody detection date.

Table 16. Impact of anti-product antibodies on clinical efficacy

	↓ Hgb by >2.0g/dL	2 or more Hgb < 9g/dL	↑ Dose	*Transfusion
B-Ab (n)				
29	24	12	9	7
N-Ab (n)				
21	18	11	7	4
*Transfusions within the period of detectable antibodies ±90 days				

2.5 EXTRINSIC FACTORS

2.5.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed to evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the PK or PD of peginesatide.

The following frequently used concomitant medications were evaluated during the population PK and PK-PD analysis as covariates: β-blockers, calcium ion channel blockers, insulin, statins, diuretics, phosphate binders, and angiotensin-converting enzyme inhibitors. These were not significant covariates.

2.5.2 Drug-drug interactions

2.5.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

No. Results from in vitro studies demonstrate that peginesatide and its related compounds, including the [redacted] (b) (4), and potential degradants, are not inducers or inhibitors of CYP450 enzymes. Peginesatide is essentially not metabolized, the main route of elimination is via the urine (based on animal studies), and the predominant moiety excreted is the parent molecule. Thus, the potential of peginesatide or its metabolites (if generated in vivo) for CYP450 mediated drug-drug interactions is low. Peginesatide does not bind to serum albumin or lipoproteins, indicating that drug-drug interactions with highly protein bound drugs are not anticipated.

2.5.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

No. In vitro metabolism studies indicate that peginesatide is essentially not metabolized.

The in vitro metabolism of [^{14}C]-peginesatide was examined in Study AF37702-10425 using hepatic and renal microsomes and hepatic and renal S9 fractions from humans, male rats, and monkeys. Peginesatide is a peptide dimer conjugated to a branched 40 kDa PEG group [redacted] (b) (4). The [^{14}C]-peginesatide test article used contained approximately [redacted] (b) (4) [redacted] present at time zero. Incubation was carried out at an initial [^{14}C]-peginesatide concentration of 10 µg/mL in the presence of an NADPH-generating system. The ratio of [redacted] (b) (4) to the total radioactivity was slightly increased (the maximum increase observed was only 4% points from 9.1% to 13.1% over 2 hours) time-dependently by the incubation with hepatic microsomes from each species and human renal microsomes. No significant metabolite peak was observed.

2.5.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

No. Peginesatide as drug substance (DS) or drug product (DP) (stability sample containing degradants) was not a direct or time-dependent inhibitor of human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. There was no evidence of induction of enzyme activities associated with CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4. The peptide [redacted] (b) (4) and [redacted] (b) (4) were also determined to have no effect on the inhibition or induction of CYP enzymes.

Inhibition

The inhibitory effects of peginesatide, [redacted] (b) (4) and [redacted] (b) (4) on CYP activities were examined in Study AF-37702-00024. Mixtures were incubated at 37°C for 10 to 60 minutes with microsomes produced from baculovirus-infected insect cells expressing human CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). The initial concentrations of peginesatide in the incubation mixtures were 3, 10, 30, and 100 µg/mL. For [redacted] (b) (4) the initial concentrations were 0.3, 1, 3, and 10 µg/mL. Marker CYP enzyme activities, compared with control were ≥94.8% for peginesatide, ≥89.5% for [redacted] (b) (4) and ≥94.9% for [redacted] (b) (4) Peginesatide, [redacted] (b) (4) showed little inhibitory effects on any CYP activities.

In another study (AF08-013), the CYP in vitro inhibitory effect of two lots of peginesatide, an active pharmaceutical ingredient (API) batch (lot SF353/6AF1) and a 50 mg/mL drug product (lot PLI012-06), were determined with pooled human liver microsomes. Lot PLI012-06 was chosen to provide drug product that had been stored for 1 year at room temperature to provide a source of peginesatide that had evidence of some degradation. Pooled human liver microsomes were incubated with marker substrates, with and without peginesatide derived from both lots. The target concentrations ranged from 0.5 to 500 µg/mL (~10.6 to 10593 nM) peginesatide. In addition, each lot was evaluated for its ability to function as a time-dependent inhibitor by pre-incubation of peginesatide with human liver microsomes.

Peginesatide and its degradants caused no discernable direct or time-dependent inhibition of any of the CYP enzymes evaluated as the 50% inhibitory concentration values were greater than the highest concentration of peginesatide (500 µg/mL), regardless of the lot examined. Also, there was little or no increase in the inhibition observed after 30 minutes pre-incubation.

Induction

The potential for induction of CYP activity by peginesatide, [redacted] (b) (4) and [redacted] (b) (4) was determined using human hepatocytes (AF08-014). The lots of peginesatide were the same as used in Study AF08-13. One lot was an API batch, lot SF353/6AF1 and the other a [redacted] (b) (4) drug product lot PLI012-06 that had been stored for 1 year at room temperature. Lot PLI012-06 was chosen to provide drug product that had been stored outside of the long-term storage condition (2–8°C) and to provide a source of peginesatide that had evidence of some degradation. Human hepatocytes were treated once daily for 3 days with dimethyl sulfoxide (DMSO), test article vehicle control, DMSO + test article vehicle control, one of three concentrations of each peginesatide lot [redacted] (b) (4) or one of three known human CYP inducers (omeprazole [100 µM], phenobarbital [750 µM], and rifampin [10 µM]). After treatment, the cells were harvested to prepare microsomes for the analysis of phenacetin *O*-dealkylation (marker for human CYP1A2), bupropion hydroxylation (marker for human CYP2B6), diclofenac 4′-hydroxylation (marker for human CYP2C9), S-mephenytoin 4′-hydroxylation (marker for human CYP2C19), and testosterone 6β-hydroxylation (marker for human CYP3A4/5).

Results from the known CYP inducers were as expected and both peginesatide lots had little or no effect (less than 20% changes) on any of the CYP enzymes evaluated. These results suggested that peginesatide, [redacted] (b) (4) [redacted] (b) (4) were not inducers of human CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4.

2.5.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No studies have been conducted. This is acceptable because peginesatide is a large molecule; it is unlikely to interact with P-gp or other transporters.

2.5.2.5 Are there other metabolic/transporter pathways that may be important?

It is expected that the elimination of the peptide and PEG portions of peginesatide would undergo typical catabolic processes. The peptide dimmer would undergo proteolysis resulting in the constituent amino acids that would be available for elimination via dialysis or incorporation into the amino acid pool.

2.5.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No, the label does not specify co-administration of another drug.

2.5.2.7 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?

No *in vivo* drug-drug interaction studies were conducted.

2.6 GENERAL BIOPHARMACEUTICS

2.6.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Peginesatide is soluble in unbuffered water, buffer (20 mM acetate: pH 5.0; 20 mM phosphate: pH 6.0 and 7.0), acetonitrile, and 95% EtOH.

Table 17. Solubility Profile Results

Solution	Mean Area	Solubility [a] (%)	Solubility [b] (mg/mL)	Solubility [c] (mL solvent/g AF37702)
50:50 DMF:H_2O	25380639	100 [d]	50	20
Purified H_2O	25913362	103	50	20
Acetate Buffer, pH 5.0	25274306	100	50	20
Phosphate Buffer, pH 6.0	26462783[e]	99	50	20
Phosphate Buffer, pH 7.0	26058495[e]	97	50	20
Acetonitrile	25425690	101	50	20
95% Ethanol	21994663	87	43.5	23

a Calculated by mean peak area sample/ mean peak area DMF:water control.
b Calculated by percent solubility x 50 mg/mL; 100 ± 5 was considered to be 100%.
c Calculated by 1/(solubility in mg/mL) x 1000).
d DMF:water solution is defined as 100% soluble.
e DMF:water mean area control was 26595186 for these two runs.

A permeability study was not conducted. This is acceptable because peginesatide is a large, hydrophilic molecule, it is not expected to be permeable.

2.6.2 What is the composition of the to-be-marketed formulation?

For commercial distribution, Peginesatide Injection is proposed to be provided as three drug product types in multiple strengths:

- Single-dose vial (SDV): 2, 3, 4, 5, and 6 mg (0.5 mL fill),
- Prefilled syringe (PFS): 1, 2, 3, 4, 5, and 6 mg (0.5 mL fill)
- Multidose vial (MDV): 10 mg/1 mL and 20 mg/2 mL

The SDV and PFS drug products use the same phosphate-sorbitol formulation (SDV/PFS formulation), an aqueous, [redacted] (b) (4) isotonic solution (pH 6.0) containing sorbitol and polysorbate 20. The difference between the intended commercial SDV and PFS drug products and the formulation used in the majority of clinical studies, including phase 3 studies, is that the clinical studies used a drug strength of 10 mg/1 mL SDV while the proposed commercial presentations will be available in multiple strengths in a 0.5 mL fill. The MDV formulation is an aqueous, [redacted] (b) (4) isotonic solution (pH 5.4) containing phenol, sorbitol and methionine.

2.6.3 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

Clinical development of Peginesatide Injection has primarily utilized an SDV formulation at a drug concentration of 10 mg/mL. A range from 2 to 12 mg/mL of peginesatide concentrations are planned for marketing as discussed in Section 2.5.2. Two phase 1 cross-over studies evaluated the proposed MDV formulation by the IV or SC route of administration (Studies AFX01-102 and AFX01-103, respectively) and two phase 1 cross-over studies evaluated the 2 mg/mL and 16 mg/mL strengths of the SDV formulation by the SC route of administration (Studies AFX01-105 and AFX01-104, respectively). The comparator was the SDV 10 mg/mL formulation. All studies were conducted in healthy subjects. All four studies evaluated bioavailability (BA) by PK measures. Studies AFX01-105 and AFX01-104 also evaluated equivalence by PD measures.

Table 18. Ratios of Geometric means (test/reference) and 90% confidence intervals for primary PK parameters

SDV 10 mg/mL vs. MDV 10 mg/mL, IV (Study AFX01_102)	
Parameter	Ratio (90% CI)
Cmax	[redacted]
AUC	[redacted]

SDV 10 mg/mL vs. MDV 10 mg/mL, SC (Study AFX01_103)	
Parameter	Ratio (90% CI)
Cmax	[redacted]
AUC	[redacted]

SDV 10 vs 2 mg/mL, SC (Study AFX01_105)	
Parameter	Ratio (90% CI)
Cmax	[redacted]
AUC	[redacted]

SDV 10 vs 16 mg/mL, SC (Study AFX01_104)	
Parameter	Ratio (90% CI)
Cmax	[redacted]
AUC	[redacted]

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The Office of Scientific Investigations (OSI) was consulted for site inspection of the above four studies. The OSI reviewer inspected the study site [redacted] (b) (4) and concluded that the data generated from these studies are acceptable for review. See Appendix 4.2 for the attached OSI memo.

The results of study AFX01-102 and study AFX01-103 indicate that, when administered at the same dose of 0.05 mg/kg, the MDV and the SDV formulations were similar following IV and SC administration, respectively (Table 18). The 90% CIs for C_{max} and $AUC_{0-\infty}$ were within the bioequivalence limits of 0.80, 1.25.

Study AFX01-105 which evaluated the bioavailability and PD response (increase in reticulocyte count) of peginesatide following a 0.05 mg/kg single-dose SC administration from the proposed 2 mg/mL SDV formulation vs. the SDV 10 mg/mL formulation showed both concentrations to be bioequivalent for C_{max}. The lower bound of the 90% CI for the ratios of AUC_{0-inf} between the formulations (0.7809) was marginally below the bioequivalence limit of 0.80 (Table 18) and could due to the variability caused by large differences in injection volume. The total dose volume administered SC in the 2 mg/mL concentration regimen ranged from 1.28 mL to 2.56 mL, while the corresponding volumes for the 10 mg/mL concentration ranged from 0.26 mL to 0.52 mL. The PD measures of maximum change in baseline-corrected reticulocyte count (E_{max}) and area under the effect curve from Day 0–28 ($AUEC_{0-28}$) showed the 2 mg/mL formulation is equivalent to the 10 mg/mL formulation. Considering the comparable PK profiles and the similarity in reticulocyte counts following peginesatide SC administration, the 2 mg/mL and 10 mg/mL concentrations of the SDV formulation are considered to provide a comparable PD response.

Study AFX01-104 was of a similar cross-over design to Study AFX01-105 and established the bioequivalence of a 0.05 mg/kg single-dose SC administration from a 16 mg/mL SDV formulation and the SDV 10 mg/mL formulation by C_{max} and AUC measures. When the PD responses from the two formulations were evaluated, the 90% CIs for the ratio of reticulocyte E_{max} and $AUEC_{0-28}$ were equivalent.

In conclusion, equivalent effects are expected across the proposed range of commercial formulations.

2.7 ANALYTICAL SECTION

2.7.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

In vitro metabolism studies in liver and kidney microsomes and S9 fractions from rats, monkeys, and human donors and in vivo metabolism studies with radio-labeled peginesatide in rats and monkeys indicate that peginesatide is essentially not metabolized. Therefore, only peginesatide concentrations were measured in all CP studies.

2.7.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes. An enzyme-linked immunosorbent assay method for the quantification of peginesatide in human plasma was validated by (b) (4) (P06-17702). The calibration curve ranged from (b) (4). The lower limit of quantification was 25.00 ng/mL. The validation of stock solution stability was conducted (P08-17714), which extended stability of peginesatide stock solutions to 93 days at refrigerated temperatures. Additionally, the long-term frozen storage stability of peginesatide in plasma was conducted (P07-17704). Stability was determined to be acceptable for 369 days at –20°C.

The method P06-17702 was used to support studies AFX01-102, AFX01-103, AFX01-104, and AFX01-105. The quality control (QC) statistics for the original P06-17702 method are 90.5% to 102.9% of accuracy and 7.2 to 16.0% CV of precision. Individual validation runs were within acceptable specifications. Summaries of the bioanalytical methods used in clinical trials are presented in Table 19.

Table 19. Analytical methods for determination of peginesatide

Study	Analyte	Technique	Range (ng/mL)	Accuracy[a] (%)	Precision[b] (CV%)
AFX01-0401	peginesatide	ELISA	(b) (4)	-8.4 to 0.0	8.9 to 11.3
AFX01-02	peginesatide	ELISA	(b) (4)	-6.0 to 3.8	10.6 to 18.9
AFX01-03	peginesatide	ELISA	(b) (4)	-2.2 to 3.0	12.8 to 21.3
AFX01-04	peginesatide	ELISA	(b) (4)	0.6 to 2.5	12.6 to 18.0
AFX01-07	peginesatide	ELISA	(b) (4)	1.2 to 3.6	12.8 to 13.7
AFX01-14	peginesatide	ELISA	(b) (4)	3.8 to 12.0	9.6 to 86.5
CPH-001	peginesatide	ELISA	(b) (4)	-2.4 to 2.5	11.0 to 14.7
AFX01-101	peginesatide	ELISA	(b) (4)	93.9 to 102.2[a]	8.5 to 20.9
	Moxifloxacin	LC-MS/MS	(b) (4)	-1.48 to 0.335	2.08 to 3.79
AFX01-102	peginesatide	ELISA	(b) (4)	87.3 to 96.9[a]	7.7 to 9.3
AFX01-103	peginesatide	ELISA	(b) (4)	93.8 to 102.8[a]	7.7 to 14.1
AFX01-104	peginesatide	ELISA	(b) (4)	92.5 to 101.4[a]	9.2 to 12.9
AFX01-105	peginesatide	ELISA	(b) (4)	94.3 to 107.9[a]	8.4 to 12.5

[a]The accuracy is expressed as % difference from theoretical except where footnoted where the accuracy is expressed as percent of the theoretical concentration.
[b]Values outside acceptance criteria (so the corresponding runs were rejected) were also included in statistical calculations.

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4 APPENDIX

4.1 PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there a dose-response relationship for cardiovascular events in non-dialysis patients?

A dose-response relationship for cardiovascular (CV) events could not be identified because of the following limitations in the data:

- For an individual patient, the peginesatide (or darbepoetin) dose was titrated throughout the duration of the phase 3 trials to maintain hemoglobin in the range of 11 – 12 g/dL.
- The average dose of peginesatide (or darbepoetin) was inversely correlated with average hemoglobin levels.
- Patients who were not within the target hemoglobin by 3 months (*i.e.*, slow responders) were titrated to higher peginesatide (or darbepoetin) doses and had an increased risk of CV events.
- There was an imbalance of baseline CV risk factors between slow and normal responders.

To evaluate the dose-response relationship for CV events in trials AFX01-11 and AFX01-13, the average doses of darbepoetin and peginesatide were used instead of the randomized starting dose because patients' doses were titrated throughout the duration of the study to achieve target hemoglobin of 11 – 12 g/dL. For an individual patient, the average dose was defined as the mean of all doses administered between study enrollment and end of study or discontinuation.

Figure 1 shows an apparent trend for increased composite safety endpoint (CSE) events with increasing average dose quartile for both darbepoetin and peginesatide. However, as shown in Table 1 and Figure 2, hemoglobin is inversely correlated with dose. Therefore, it is difficult to tease out the contribution of dose or hemoglobin to CV risk.

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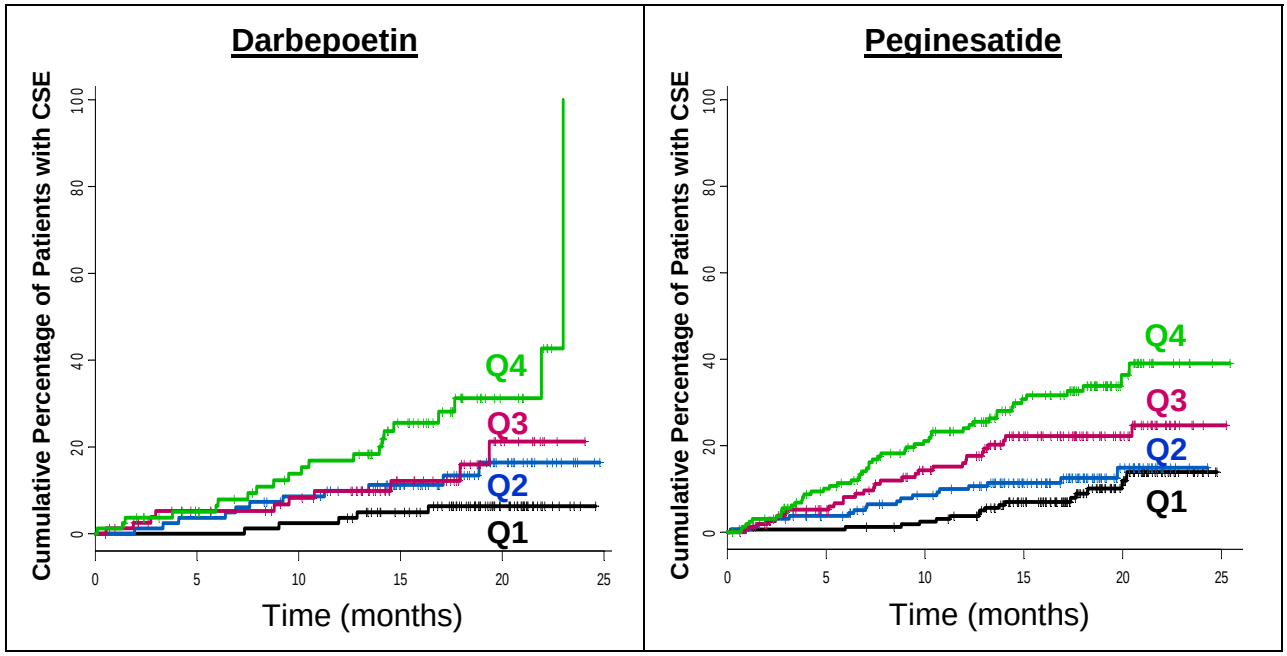
Figure 1. Cardiovascular risk appears to be correlated with average study dose for both darbepoetin and peginesatide. Curves for the cumulative percentage of patients with a primary CSE are shown for each average dose quartile.



Source: FDA pharmacometric analysis

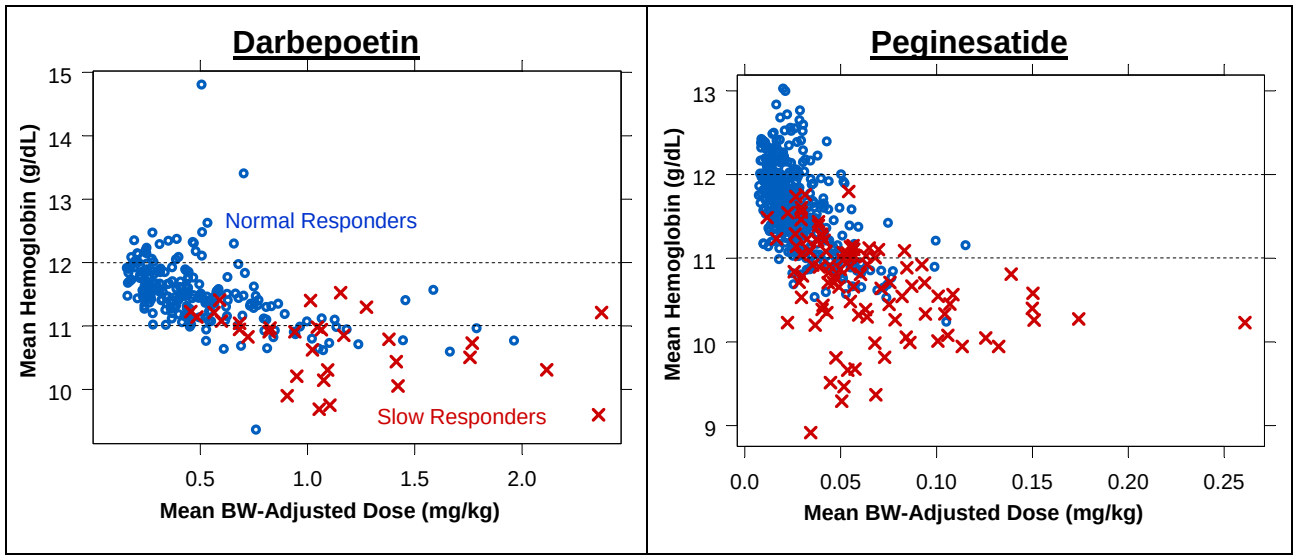
Table 1. Mean Hemoglobin is Inversely Correlated with Mean ESA Study Dose.

	Darbepoetin		Peginesatide	
Quartile	Mean Dose (mcg/kg)	Mean Hgb (g/dL)	Mean Dose (mcg/kg)	Mean Hgb (g/dL)
1	0.243	11.7	13.4	11.8
2	0.399	11.5	22.1	11.7
3	0.602	11.5	32.1	11.4
4	1.14	10.8	65.8	10.8

Source: FDA pharmacometric analysis

Reference ID: 3084101

Figure 2. Individual mean hemoglobin is inversely correlated with average dose of darbepoetin and peginesatide.



Source: FDA pharmacometric analysis

There is a subgroup of patients that the sponsor identified as "poor responders" who exhibited an increased CV event rate (see Section 3.3.1). In the sponsor's analysis, poor responders were defined as individuals with a change from baseline hemoglobin value at one month that was in the lowest quartile of response. FDA Pharmacometrics reached the same conclusion with an approach that defined the this subgroup as individuals who had hemoglobin values at 3 months that were less than the lower limit of their target hemoglobin range. FDA referred to this subgroup as "slow responders" to differentiate it from the sponsor's definition. Not achieving the target hemoglobin was an important criterion because the individual's dose would continually be increased until the target hemoglobin was met. This definition was based on the primary efficacy endpoint (target hemoglobin range of 11 – 12 mg/dL) and the current ARANESP (darbepoetin) label that states, "For patients who do not respond adequately over a 12-week escalation period, increasing the Aranesp dose further is unlikely to improve response and may increase risks."

In trials AFX01-11 and AFX01-13, slow responders comprised 18% of the peginesatide treated subjects and 13% of the darbepoetin alfa treated subjects. As shown in Figure 3, the subgroup of slow responders received higher average doses of study drug compared to normal responders. Slow responders had higher CV risk. The cumulative percent of patients with CV events over time for slow and normal responders are shown in Figure 4 for CSE and Figure 29 for MACE.

It is important to note that these results do not imply a causal relationship between hemoglobin, dose and CV risk. Slow responders were found to have a higher proportion of patients with underlying risk factors for CV events compared to normal responders as shown in Table 2.

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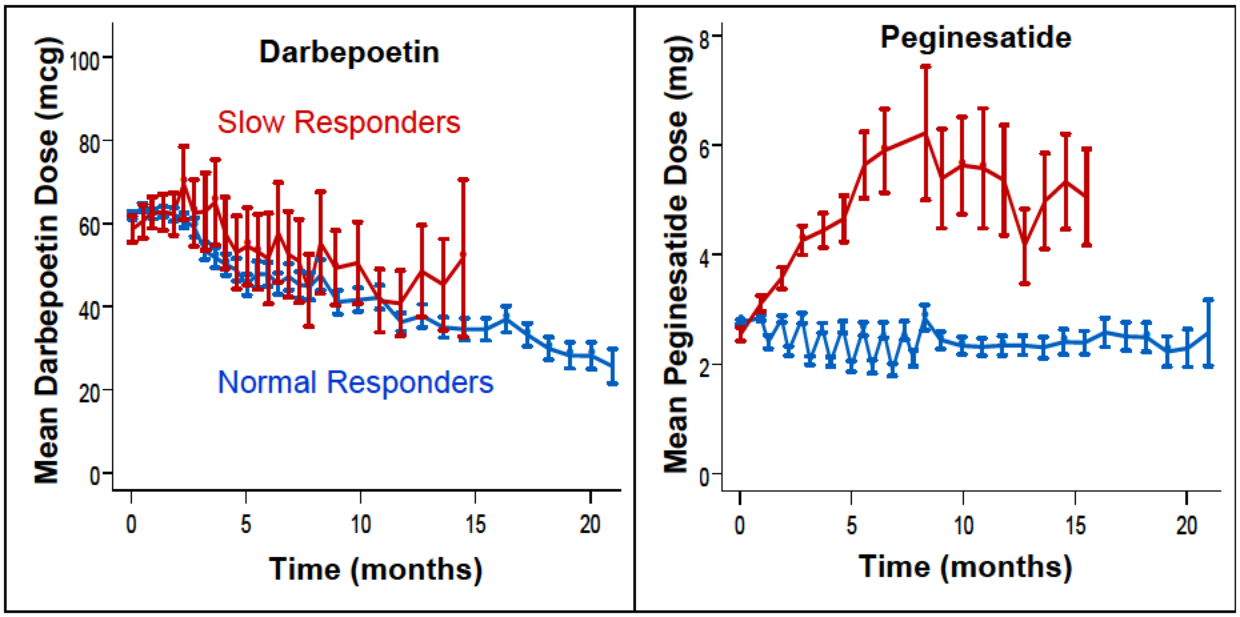
Table 2. Baseline demographics of slow versus normal responders contain imbalances.

	Darbepoetin		Peginesatide	
Baseline Demographic	**Normal Responder**	**Slow Responder**	**Normal Responder**	**Slow Responder**
N (% of Treatment Group)	286 (87)	41 (13)	536 (82)	120 (18)
% Female	58	69	55	61
% NYHA Class II	16	13	16	27
Base Hgb (g/dL)	10.1	9.7	10.1	9.7
C-Reactive Protein (mg/L)	7	11	6	12
% w. Peripheral Vascular Disease	19	21	26	32
% w. Coronary Artery Disease	38	46	39	44
% w. Cardiovascular Disease	17	18	18	20
% w. Cardiac Arrythmia	13	15	14	26

Figure 3. Slow responders were titrated to higher doses than normal responders in both the darbepoetin (left panel) and peginesatide (right panel) treatment groups. Red and blue lines indicate the mean dose at the corresponding time for slow and normal responders, respectively. Data are presented as mean ±SEM.



Source: FDA pharmacometric analysis

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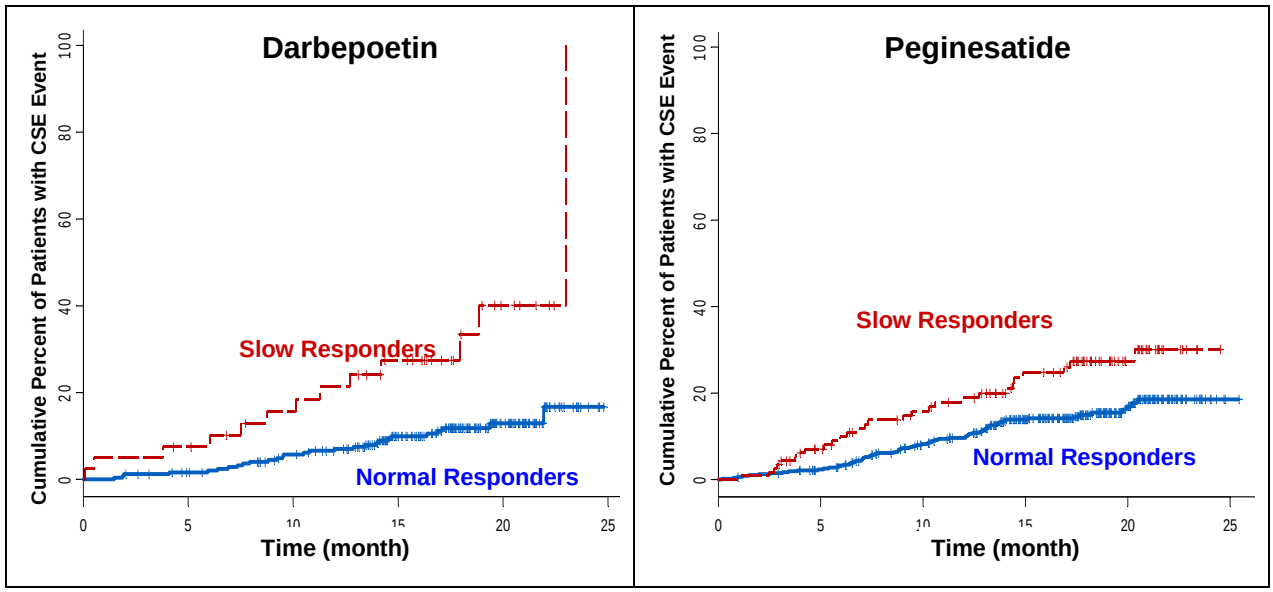
Figure 4. Slow responders appear to have increased CV risk in both the darbepoetin alfa (left panel) and peginesatide (right panel) treatment groups for the primary CSE. Red and blue lines depict the cumulative percent of patients with CSE events over time for slow and normal responders, respectively.



Source: FDA pharmacometric analysis

1.1.2 Is there a similar subgroup of dialysis patients who are at increased CV risk?

The phase 3 dialysis trials did not enroll this high-risk subgroup of slow-responders. The two phase 3 trials were conducted in dialysis patients who were previously receiving stable doses of epoetin and were randomized to either continue receiving their epoetin dose or convert to peginesatide. To be enrolled in the trials, dialysis patients were already on epoetin for > 8 weeks before randomization and baseline hemoglobin levels must have been in the target range of 10 – 12 g/dL for at least 4 weeks prior to study entry.

This is important because the sponsor is seeking an indication for all dialysis patients, not just those switching from a prior ESA. If a subgroup of slow responders exists for dialysis patients, it is in those individuals initiating treatment. However, the CV risk was not studied for dialysis patients initiating peginesatide treatment.

Figure 5 shows the percentage of slow responders in the peginesatide treated patients for both the dialysis and non-dialysis clinical trials. Trial AFX01-15 was a phase 2 trial conducted in subjects who were on dialysis and were initiating peginesatide treatment. From this small phase 2 study we expect that slow-responders are present in the dialysis population. However, the small number of peginesatide treated patients (n=69) and shorter trial duration (28 weeks) limited the ability to evaluate the cardiovascular safety in patients initiating treatment.

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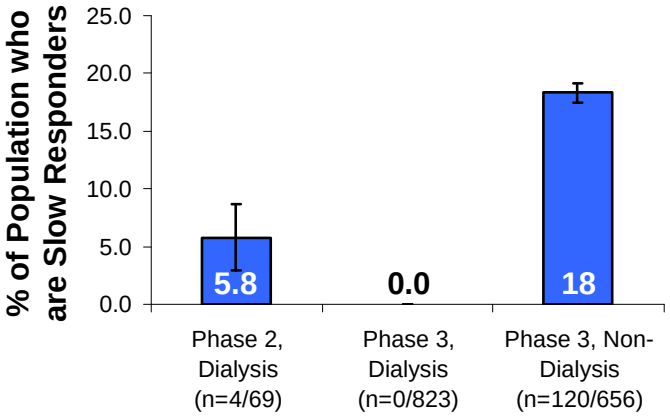
Figure 5. Slow responders are expected to be present in ESA treatment naive patients.



The CV risk for all dialysis patients has not been characterized. This includes both patients initiating treatment and those switching from a prior ESA. This is important because the sponsor is seeking the indication for all dialysis patients and the safety has only been characterized for those switching from another ESA.

1.1.3 Is the conversion of doses from either epoetin or darbepoetin to peginesatide appropriate?

Yes, the sponsor's approach to selecting doses of peginesatide is appropriate. The sponsor showed there is a log-linear correlation between the prior ESA dose and the mean observed peginesatide dose for both epoetin and darbepoetin (Figure 19, Figure 22) and used this correlation to identify the appropriate starting dose of peginesatide. Peginesatide starting doses are shown with their corresponding prior epoetin and darbepoetin doses in Table 3. See section 3.4 for details of the sponsor's analysis.

Table 3. Proposed nine-tier, epoetin-to-peginesatide and darbepoetin-to-peginesatide dose conversion chart.

Previous Total Weekly Epoetin Alfa Dose (U/week)	Previous Weekly Darbepoetin Alfa Dose (mcg/week)	Peginesatide Dose Once Monthly (mg/month)
<2,500	<12	2
2,500 to <4,300	12 to <18	3
4,300 to <6,500	18 to <25	4
6,500 to <8,900	25 to <35	5
8,900 to <13,000	35 to <45	6
13,000 to <19,000	45 to <60	8
19,000 to <33,000	60 to <95	10
33,000 to <68,000	95 to <175	15
≥68,000	≥175	20

(Source: Sponsor's Clinical Efficacy Summary, Table 31)

1.1.4 Is the starting dose range of 0.04 mg/kg to 0.08 mg/kg peginesatide for the correction of anemia in dialysis patients appropriate?

No, a lower starting dose of 0.04 mg/kg is recommended for initiating treatment in dialysis patients. Based on the phase 2 study AFX01-15, the sponsor proposed a starting dose range of 0.04 mg/kg to 0.08 mg/kg. In this study, the mean time course and mean hemoglobin for the 0.04 mg/kg and 0.08 mg/kg starting doses were similar (Figure 24). Furthermore, the average

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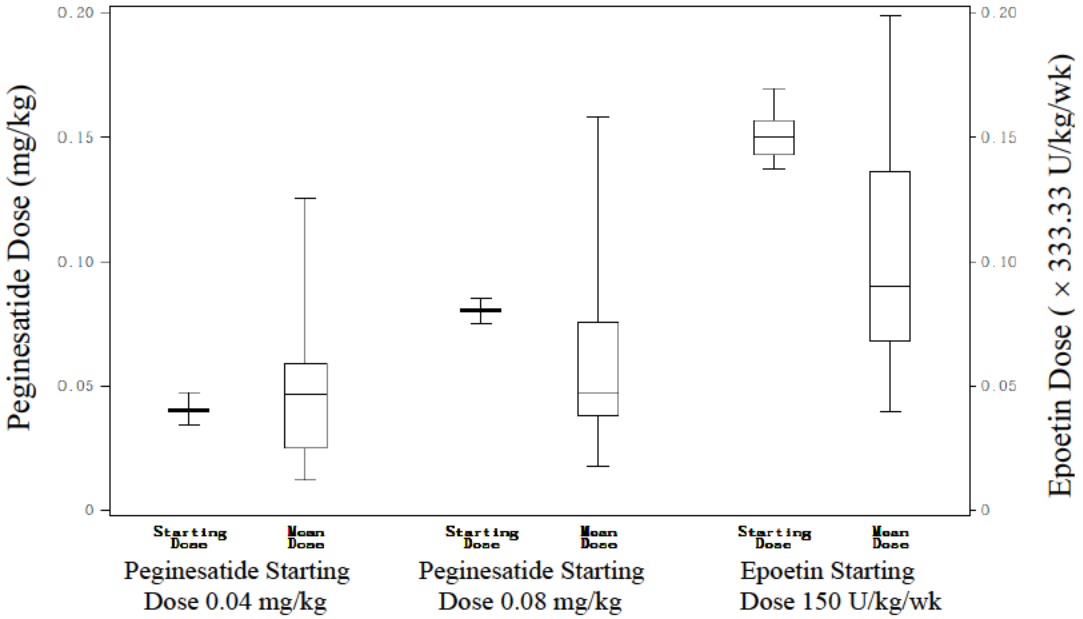
dose during the evaluation period was 0.05 for both dose groups (Figure 6). From an efficacy standpoint, the 0.04 mg/kg dose appears to be an appropriate starting dose.

Figure 6. Comparison of first dose and mean dose during evaluation period by starting dose.



(Source: Sponsor's Clinical Efficacy Summary, Figure 32)

Because the 0.04 mg/kg had an adequate hemoglobin response and CV safety was not evaluated in this phase 2 study, starting doses greater than 0.04 mg/kg are not justified.

1.2 Recommendations

- We recommend limiting the indication to those dialysis patients studied in the phase 3 clinical trials. The CV safety for dialysis patients initiating peginesatide treatment has not been evaluated.
- If the FDA Office of New Drugs approves peginesatide for all dialysis patients, we recommend a starting dose of 0.04 mg/kg instead of the proposed dose range (0.04 mg/kg to 0.08 mg/kg) for patients initiating treatment.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

"HIGHLIGHTS OF PRESCRIBING INFORMATION

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2 PERTINENT REGULATORY BACKGROUND

Peginesatide is a new molecular entity in the class of erythropoietin receptor stimulating agents (ESAs) that is being developed by Affymax, Inc. and Takeda Pharmaceutical Co. for the treatment of anemia in patients with chronic renal failure (CRF). The sponsor has submitted a new drug application seeking approval for CRF patients receiving hemodialysis. Currently approved ESAs in the United States include EPOGEN/PROCIT® (epoetin alfa) and ARANESP® (darbepoetin alfa).

To date ESA use has been controversial in how to manage hemoglobin levels. Results of the normal hematocrit study (NHS), Correction of Hemoglobin and Outcomes In Renal Insufficiency (CHOIR) trial, and Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT) trial have shown that individuals titrated to higher hemoglobin targets (>12 g/dL) have increased cardiovascular events [7]. However, it is not clear whether these events are associated with the higher hemoglobin targets or higher ESA doses required to attain these targets. Previous FDA analyses have suggested that hemoglobin values that are too low and rapid rates of hemoglobin change can also be indicative of increased risk for cardiovascular events [4]. Additionally, Solomon et al pointed to hemoglobin responsiveness to ESA treatment as another indicator of increased risk for CV events [1]. The FDA review of the TREAT study showed that slow responders at 1 month and at 12 weeks had increased cardiovascular risk [4,5].

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Clinical Trials

Efficacy and safety results were ultimately taken from studies AFX01-11, AFX01-12, AFX01-13, and AFX01-14. Please see the clinical review by Dr. Andrew Dmytrijuk (in DARRTS) for interpretation of the primary efficacy and safety results. Phase 2 studies AFX01-15 and AFX01-

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202 are presented because they are relevant for selection of the sponsor's proposed peginesatide doses.

3.1.1 Phase 3 Clinical Trials in Dialysis Patients, AFX01-12 & AFX01-14:

Clinical trials AFX01-12 and AFX01-14 were ≥52 week trials designed to evaluate the long-term efficacy and safety of peginesatide compared to epoetin, in dialysis patients. Data from these trials were used to select the dose of peginesatide when switching from epoetin alfa and compare the efficacy and safety (including cardiovascular outcomes) between peginesatide and epoetin alfa.

These were Phase 3, randomized, active-controlled, open-label, multicenter studies of the safety and efficacy of peginesatide for the maintenance treatment of anemia due to chronic renal failure in hemodialysis patients.

A total of approximately 750 eligible patients were to be enrolled for each study at approximately 120 sites. Eligible patients were randomized to the following two study treatment regimens in a 2:1 ratio:

1. IV or SC peginesatide every 4 weeks at a starting dose of 0.04 – 0.16 mg/kg based on the patient's prior epoetin alfa dose
2. Continued treatment with epoetin alfa 1 – 3 times per week

Randomization was stratified by the mean hemoglobin during screening (≤11.4 g/dL, ≥11.5 g/dL) and the New York Heart Association (NYHA) Heart Failure Class (class I, classes II–IV). Entry criteria include:

> "Eligible patients were consenting males or females ≥ 18 years of age with CRF on hemodialysis for ≥ 3 months before randomization, who had received continuous epoetin treatment for ≥ 8 weeks before randomization and maintained stable epoetin doses (≤ 50% change from the maximum weekly dose and no change in frequency) during the 4 weeks before randomization, who had not received a red blood cell (RBC) transfusion in the 12 weeks before randomization, and whose hemoglobin values met the following criteria: four consecutive hemoglobin values with a mean ≥ 10.0 g/dL and ≤ 12.0 g/dL during the Screening Period, with ≤ 1.0 g/dL difference between the mean of the first two consecutive values and the mean of the last two consecutive values, and ≥ 2 days between values, ≤ 2 values within 1 calendar week, and ≥ 9 days between the first and last of the four qualifying hemoglobin values. In addition, patients had to satisfy the following qualifying laboratory criteria within the 4 weeks before randomization: one transferrin saturation (TSAT) ≥ 20%, one ferritin level ≥ 100 ng/mL, one serum or red cell folate level ≥ the lower limit of normal (LLN), and one vitamin B12 level ≥ the LLN. Females of childbearing potential had to use a highly effective method of birth control prior to randomization, during the study, and for at least 4 weeks after the last dose of study treatment."

Theses studies each consisted of a screening period, enrollment, titration period (weeks 0 – 28), evaluation period (weeks 29 – 36), and long term safety and evaluation period (weeks 37 – 52+). Doses were titrated throughout the duration of the study to maintain hemoglobin concentrations within the target range of ≥10 g/dL – ≤12 g/dL. The primary efficacy endpoint was the mean change in hemoglobin between baseline and the evaluation period. A composite safety endpoint (CSE) was prospectively specified to assess cardiovascular risk following blinded adjudication by an independent Event Review Committee. The primary composite safety endpoint included all-cause mortality, myocardial infarction, stroke, congestive heart failure, unstable angina, and arrythmia. A secondary endpoint was also reported for major adverse cardiovascular events (MACE). These events included all-cause mortality, myocardial infarction, and stroke.

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3.1.2 Phase 3 Clinical Trials in Non-Dialysis Patients, AFX01-11 & AFX01-13:

Clinical trials AFX01-11 and AFX01-13 were ≥52 week trials designed to evaluate the long-term efficacy and safety of peginesatide compared to darbepoetin, in non-dialysis patients. Data from these trials were used to compare the efficacy and safety (including cardiovascular outcomes) between peginesatide and epoetin alfa.

These were Phase 3, randomized, active-controlled, open-label, multicenter studies of the safety and efficacy of peginesatide for the correction of anemia due to CRF in non-dialysis patients who had not received an ESA in the previous 12 weeks.

Approximately 450 eligible patients were to be enrolled in each study at approximately 100 sites. Eligible patients were randomized in equal proportions to one of three treatment regimens:

1. SC peginesatide at a starting dose of 0.025 mg/kg, once every 4 weeks
2. SC peginesatide at a starting dose of 0.04 mg/kg, once every 4 weeks
3. SC darbepoetin at a starting dose of 0.75 μg/kg, once every 2 weeks

Randomization was stratified by average hemoglobin during screening (≤10.4 g/dL, ≥10.5 g/dL), the New York Heart Association Heart Failure Class (class I or classes II–IV), and geographical regions (United States, Western Europe, and Central Europe). Entry criteria included:

> "Eligible patients were males or females ≥ 18 years of age having CRF (estimated glomerular filtration rate < 60 mL/min/1.73m2 within 4 weeks prior to randomization) who were not expected to begin dialysis for at least 12 weeks, who had not been treated with an ESA in the 12 weeks prior to randomization, who had not received an RBC or whole blood transfusion in the 12 weeks prior to randomization, and whose hemoglobin values met the qualifying criteria for anemia (two consecutive hemoglobin values within 4 weeks prior to randomization, no less than 5 days apart, with the last value within 10 days prior to randomization, with both values ≥ 8.0 g/dL and < 11.0 g/dL, and with the difference between the two values ≤ 1.3 g/dL). In addition, to be eligible to participate in the study, patients had to satisfy the following qualifying laboratory criteria within the 4 weeks prior to randomization: adequate iron stores (one transferrin saturation [TSAT] ≥ 20% or one ferritin level ≥ 100 ng/mL), one serum or red cell folate level ≥ the lower limit of normal, and one vitamin B12 level ≥ the lower limit of normal. Females of childbearing potential had to use a highly effective birth control method prior to randomization, during the study, and for at least 4 weeks after the last dose of study drug."

Theses studies each consisted of a screening period, enrollment, titration period (weeks 1 – 24), evaluation period (weeks 25 – 36), and long term safety and evaluation period (weeks 37 – 52+). Doses were titrated throughout the duration of the study to reach and maintain hemoglobin concentrations within the target range of ≥11 g/dL – ≤12 g/dL. The primary efficacy endpoint was the mean change in hemoglobin between baseline and the evaluation period. A composite safety endpoint (CSE) was prospectively specified to assess cardiovascular risk following blinded adjudication by an independent Event Review Committee. The primary composite safety endpoint included all-cause mortality, myocardial infarction, stroke, congestive heart failure, unstable angina, and arrythmia. A secondary endpoint was also reported for major adverse cardiovascular events (MACE). These events included all-cause mortality, myocardial infarction, and stroke.

3.1.3 Phase 2 Clinical Trial in Dialysis Patients, AFX01-15:

Trial AFX01-15 was a 28-week trial that evaluated the efficacy of different starting doses of peginesatide compared to darbepoetin in dialysis patients. The sponsor used data from this trial to select the starting dose of peginesatide for patients initiating ESA therapy(see Section 3.4).

This was a Phase 2, randomized, parallel design, active-controlled, open-label, multicenter study of the safety and efficacy of peginesatide for the correction of anemia in patients with chronic renal failure who were on dialysis and had not received an ESA in the previous 12 weeks. The study evaluated the dose response and safety of two starting doses of peginesatide. A total of 114 patients were enrolled at approximately 20 sites. Eligible patients were randomized in equal proportions to receive:

1. IV peginesatide at a starting dose of 0.04 mg/kg every 4 weeks
2. IV peginesatide at a starting dose of 0.08 mg/kg
3. IV epoetin alfa at a starting dose of 50 U/kg three times a week

The randomization was stratified by average hemoglobin during screening (≤ 10.4 g/dL or ≥ 10.5 g/dL) and the New York Heart Association Heart Failure Class (class I or classes II–IV).

The study consisted of a 4-week screening period, enrollment, titration period (weeks 1 – 20), and evaluation period (weeks 21 – 28). Doses were titrated to reach and maintain hemoglobin concentrations within the target range of ≥11 g/dL – ≤12 g/dL throughout both the titration and evaluation periods. Hemoglobin assessments during the evaluation period were used to determine the primary efficacy endpoint (mean change in hemoglobin between baseline and evaluation period).

3.1.4 Phase 2 Clinical Trial in Dialysis Patients, AFX01-202:

Trial AFX01-202 was a 24-week trial that evaluated the efficacy of peginesatide, once-every 4 weeks, at starting doses of 0.04, 0.08, 0.12, or 0.16 mg/kg according to the screening darbepoetin alfa dose. The sponsor used data from this trial to determine the dose of peginesatide when switching from darbepoetin (see Section 3.4).

This was a multi-center, open-label, Phase 2 study evaluating the conversion from darbepoetin alfa to peginesatide in both dialysis and non-dialysis chronic renal failure patients. The study consisted of a screening period, enrollment, titration period (weeks 0 – 18), and evaluation period (weeks 19 – 24). Doses were titrated to maintain hemoglobin concentrations within the target range of ≥10 g/dL – ≤12 g/dL

102 patients were enrolled. One person left the trial before beginning treatment. Entry criteria were similar to those individuals in the phase 3 dialysis trials with the exception that being on dialysis was not necessary.

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"Male and female CRF patients, aged 18 to 90 years, inclusive, with a stable mean hemoglobin ≥10.0 and ≤12.0 g/dL during the Screening Period (4 consecutive hemoglobin values, with the difference between the mean of the first 2 consecutive hemoglobin values and the mean of the last 2 consecutive hemoglobin values being ≤1.0 g/dL), who were on stable darbepoetin alfa maintenance therapy (administered intravenously [IV] or subcutaneously [SC]) and continuously prescribed for a minimum of 8 weeks prior to Enrollment with stable dose (defined as ≤50% change from the maximum prescribed dose and no change in prescribed frequency during the last 4 weeks prior to Enrollment). Other inclusion criteria included being either on dialysis for ≥6 months prior to Enrollment or not being on dialysis (hemodialysis or peritoneal dialysis) with no anticipation of needing dialysis during participation in the study and, within 4 weeks prior to Enrollment, having 1 ferritin level ≥100 ng/mL, 1 serum folate level ≥ lower limit of normal (LLN), and 1 vitamin B12 level ≥LLN."

The primary endpoint was mean change in hemoglobin between baseline and the evaluation period (mean hemoglobin from weeks 19 – 24).

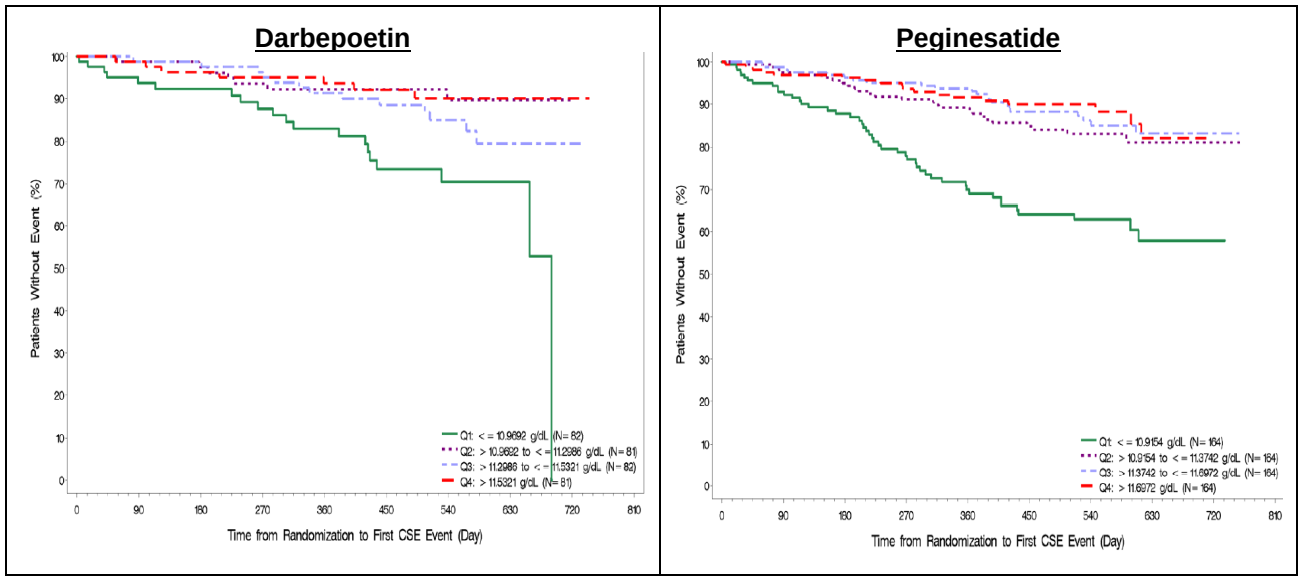
Results of this study were used to select the dose when switching from darbepoetin alfa to peginesatide (see Section 3.4).

3.2 Effect of Mean Hemoglobin and Dose on Cardiovascular Events

The sponsor concludes for the non-dialysis population that subjects at most risk for CSE events were those who required higher ESA dose (either peginesatide or darbepoetin) and achieved lower hemoglobin levels.

Figure 7 displays the CSE event-free rate over time by mean Hemoglobin quartile for the peginesatide group and for the darbepoetin group. In both treatment groups, greater CSE rates were generally associated with lower mean hemoglobin levels. In both the peginesatide and the darbepoetin groups, greater mortality was observed in the lowest hemoglobin quartile over time while lower rates were seen in the other three hemoglobin quartiles with little distinction between these quartiles.

Figure 7. Time to first CSE event by hemoglobin quartile in the phase 3 non-dialysis population for darbepoetin and peginesatide.



(Source: Sponsor's Integrated Summary of Safety, Figure 12.8.1)

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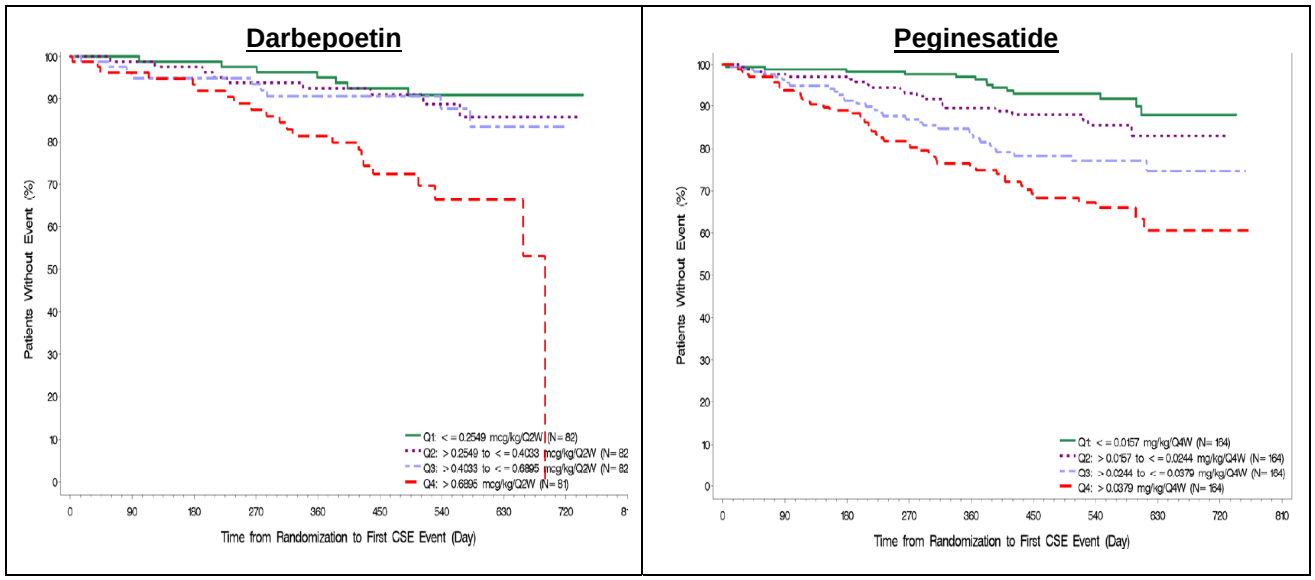
Figure 8 displays the CSE event-free rate over time by mean weight-adjusted dose quartile for the peginesatide group and for the darbepoetin group. In both treatment groups, greater CSE rates over time occurred in the higher mean dose quartiles.

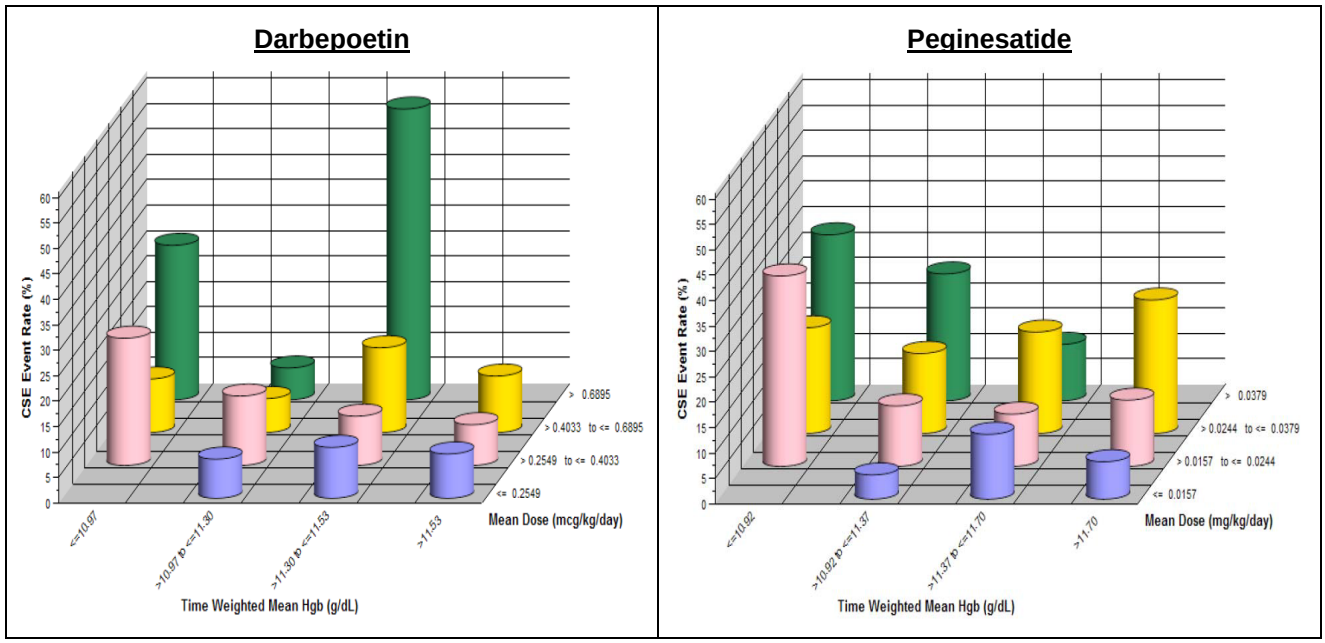
Figure 8. Time to first CSE event by mean dose quartile in the phase 3 non-dialysis population for darbepoetin and peginesatide.



(Source: Sponsor's Integrated Summary of Safety, Figure 12.4.1)

The sponsor evaluated the CSE event rate for 16 combinations of mean weight-adjusted dose and mean hemoglobin quartile and concluded that trends were less evident (Figure 9). The sponsor's plot for peginesatide indicates higher CSE rates were associated with the combination of lower hemoglobin quartiles and higher dose quartiles. The sponsor's plot for darbepoetin also showed CSE rates were associated with low hemoglobin and higher doses.

Figure 9. CSE event rate by mean darbepoetin or peginesatide dose and mean hemoglobin quartiles, phase 3 non-dialysis population



(Source: Sponsor's Integrated Summary of Safety, Figure 12.10.1)

The sponsor concluded that: "the subjects at most risk for CSE events were those who required higher ESA dose (either peginesatide or darbepoetin) and achieved lower hemoglobin levels. Often these subjects have more underlying comorbidities, especially cardiovascular risk factors, and thus have a greater inherent risk of mortality and cardiovascular morbidity."

Reviewer's Comments: The sponsor has highlighted three important points: 1) dose appears to be related to increased cardiovascular events, 2) low hemoglobin also appears to be related to increased cardiovascular events, and 3) low hemoglobin and high doses are tightly correlated due to the hemoglobin-based dosing regimen. These findings are consistent with the reviewer's analysis and limit the ability to determine if dose, hemoglobin or both contribute to the increased cardiovascular events in this population. This analysis may be limited even further by imbalances in other CV risk factors such as cardiovascular disease.

3.3 Effect of Hemoglobin Responsiveness on Cardiovascular Events

3.3.1 Poor Responders

A recent analysis of the TREAT data by Solomon et al assessed the relationship between initial hemoglobin response to darbepoetin and subsequent hemoglobin levels, subsequent darbepoetin dose levels, and safety outcomes [1]. Solomon demonstrated that patients with a poor initial hemoglobin response to darbepoetin continued to have lower hemoglobin levels and were at a higher subsequent risk of death or cardiovascular events, compared with those who had a better response. Solomon also showed that those with a poor initial hemoglobin response tended to continue to receive higher doses of darbepoetin than those patients with better initial hemoglobin response. To explore the risks of initial hemoglobin responsiveness on safety outcomes, the sponsor applied the approach used in the analysis of the TREAT data as published by Solomon et al to the peginesatide Phase 3 non-dialysis data.

3.3.1.1 Brief Description of Methods and Samples Analyzed

These analyses were performed using the data from the phase 3 non-dialysis studies. Applying exclusion criteria analogous to those used in Solomon's analysis of TREAT [1], subjects meeting any of the following criteria were excluded from the analyses:

- Subjects who did not receive the first two doses of darbepoetin alfa or the first dose of peginesatide prior to the end of Week 4 (Day 32).
- Subjects who experienced a CSE event prior to the end of Week 4.
- Subjects for whom the change in hemoglobin level at the end of Week 4 was unknown.

Of the subjects in the phase 3 non-dialysis studies, 91% (897/983) were included in these analyses; 65% (585/897) of these subjects had diabetes at baseline.

Initial hemoglobin response was defined as the percent change from baseline in hemoglobin level at Week 4. Baseline hemoglobin was defined as in the primary study analyses and Week 4 hemoglobin was defined as the average of all available hemoglobin values between Days 19 and 32. To allow a direct comparison with the Solomon findings, the definitions of the quartiles for initial hemoglobin response obtained by Solomon were used to categorize the initial hemoglobin responses observed in the non-dialysis phase 3 data. The following were the quartile definitions and the total number of subjects in each quartile:

1. SQ1: percent increase in hemoglobin from baseline to Week 4 <2% (n=125)
2. SQ2: percent increase in hemoglobin from baseline to Week 4 ≥2% and <8% (n=233)
3. SQ3: percent increase in hemoglobin from baseline to Week 4 ≥8% and <15% (n=332)
4. SQ4: percent increase in hemoglobin from baseline to Week 4 ≥15% (n=207)

Overall, the median percent change in hemoglobin during the first month was -1.1% in the poor responding quartile (SQ1) and 11.2% in the better responding quartiles (SQ2-SQ4); median hemoglobin at baseline was 10.2 g/dL in both the poor responding (SQ1) and better responding (SQ2-SQ4) quartiles (Table 19.2.4).

3.3.1.2 Baseline Characteristics by Initial hemoglobin Response Category

The sponsor noted there were differences in baseline characteristics that may help explain the higher rate of CSE events in poor responders.

The baseline characteristics of the poor responders (SQ1) were compared with those of the better responders (SQ2-SQ4), both overall and by treatment group. A greater proportion of the poor responders were female, both overall (64.0% vs. 55.2%) and by treatment group (Table 4).

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Table 4. Selected baseline characteristics of those with poor initial hemoglobin response (<2% increase) and better initial hemoglobin response (≥2% increase), by treatment group (non-dialysis)

	AF37702 Injection, starting dose of 0.025 mg/kg		AF37702 Injection, starting dose of 0.04 mg/kg		darbepoetin	
	Initial Hgb Response (Percent Increase in Hgb from Baseline to Week 4):					
	Poor (<2%)	Better (≥2%)	Poor (<2%)	Better (≥2%)	Poor (<2%)	Better (≥2%)
Number of subjects in subgroup*	**62**	**239**	**31**	**265**	**32**	**268**
Median Age	67	67	70	69	74	69
N (%) Female	37 (59.7%)	126 (52.7%)	18 (58.1%)	143 (54.0%)	25 (78.1%)	157 (58.6%)
Median BMI (kg/m^2)	30.6	29.4	29.2	29.7	28.1	29.5
Median hsCRP (mg/L)	5.0	2.8	3.5	2.7	2.0	2.8
(Selected Medical History:)						
N (%) Diabetes	43 (69.4%)	155 (64.9%)	21 (67.7%)	185 (69.8%)	16 (50.0%)	165 (61.6%)
N (%) Peripheral Vascular Disease	20 (32.3%)	65 (27.2%)	8 (25.8%)	68 (25.7%)	11 (34.4%)	48 (17.9%)
N (%) Coronary Artery Disease	26 (41.9%)	88 (36.8%)	17 (54.8%)	109 (41.1%)	10 (31.3%)	105 (39.2%)
N (%) Congestive Heart Failure	19 (30.6%)	56 (23.4%)	13 (41.9%)	71 (26.8%)	7 (21.9%)	63 (23.5%)
N (%) Cerebrovascular Disease	10 (16.1%)	42 (17.6%)	11 (35.5%)	49 (18.5%)	7 (21.9%)	45 (16.8%)
N (%) Stroke	7 (11.3%)	21 (8.8%)	4 (12.9%)	31 (11.7%)	4 (12.5%)	23 (8.6%)
N (%) Myocardial Infarction	10 (16.1%)	31 (13.0%)	9 (29.0%)	35 (13.2%)	2 (6.3%)	25 (9.3%)
N (%) Arrhythmia	13 (21.0%)	34 (14.2%)	6 (19.4%)	40 (15.1%)	7 (21.9%)	32 (11.9%)
N (%) Hyperlipidemia	52 (83.9%)	189 (79.1%)	24 (77.4%)	204 (77.0%)	25 (78.1%)	199 (74.3%)

* Denominator for percentage calculations.

(Source: Sponsor's Integrated Summary of Safety, Table 51)

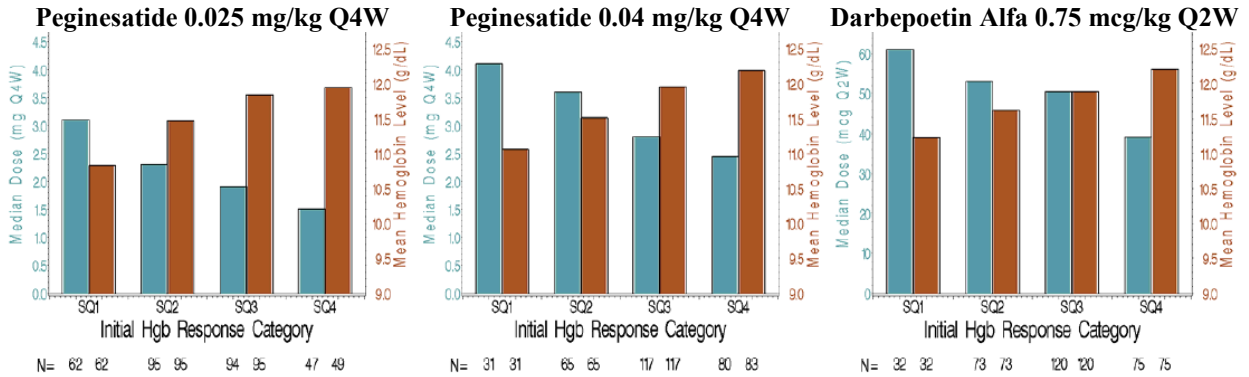
The sponsor's overall conclusions regarding the imbalances in baseline characteristics were:

- This is consistent with the Solomon analysis of TREAT, in which the poor responders were more likely to have cardiovascular disease and a marginally higher CRP [4].
- In the darbepoetin group these trends were not noted, however different trends were observed. Thus, the darbepoetin-treated subjects with a poor initial hemoglobin response appeared notably distinct, with a potentially lower burden of cardiovascular risk factors when compared with the poor responders who received peginesatide.
- The reasons for these differences are unknown, however this inconsistency potentially impacts the interpretation of the safety findings in the Non-Dialysis Population.

3.3.1.3 Association Between Achieved Hemoglobin and Dose by Initial Hemoglobin Response Category

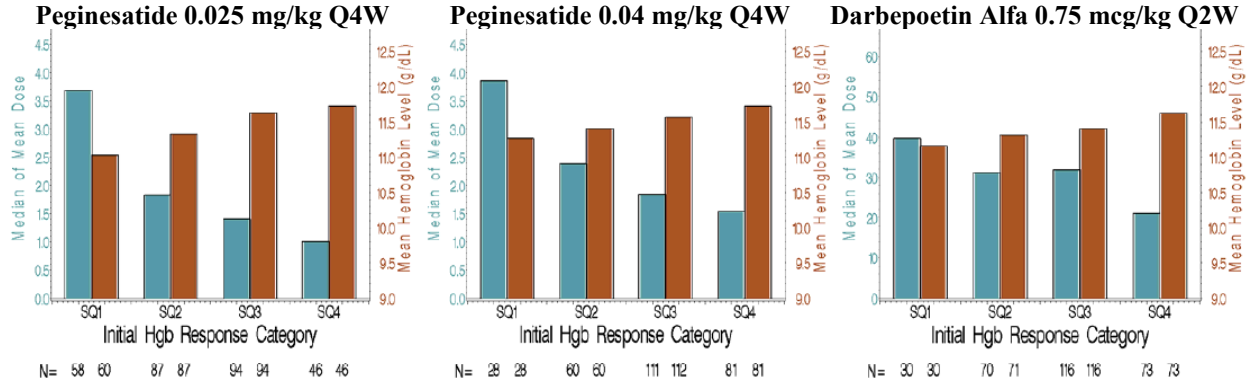
The sponsor noted that hemoglobin and dose were correlated through a responder category analysis. That is, those individuals with the best response generally had the lowest doses regardless of whether it was early in the study (Figure 10) or later (Figure 11).

Figure 10. Association between hemoglobin and dose by initial hemoglobin response category: Early phase (week 12)



(Source: Sponsor's Integrated Summary of Safety, Figure 13.1.1)

Figure 11. Association between hemoglobin and dose by initial hemoglobin response category: Late phase (weeks 13 to last dose + 28 days)



(Source: Sponsor's Integrated Summary of Safety, Figure 13.1.1)

3.3.1.4 Association Between Initial Hemoglobin Response Category and Primary Safety Outcomes

Subjects who had a poor initial hemoglobin response (<2% increase in hemoglobin from baseline to Week 4) were compared to subjects with better initial hemoglobin responses (≥2% increase in hemoglobin from baseline to Week 4) with respect to the safety outcomes of CSE event, MACE CSE event, and death. For each of these safety outcomes, the event-free rate over time (Kaplan-Meier survival analysis), annualized event rates, and hazard ratios (peginesatide vs. darbepoetin) were examined.

Plots of the event-free rates by treatment group over time (Kaplan-Meier survival analysis) are provided as follows:

- CSE – Figure 12
- MACE – Figure 13
- Death – Figure 14

Based on these three figures the sponsor concluded, for all three safety outcomes, differences between the treatment groups in the event-free rates over time were more evident in subjects

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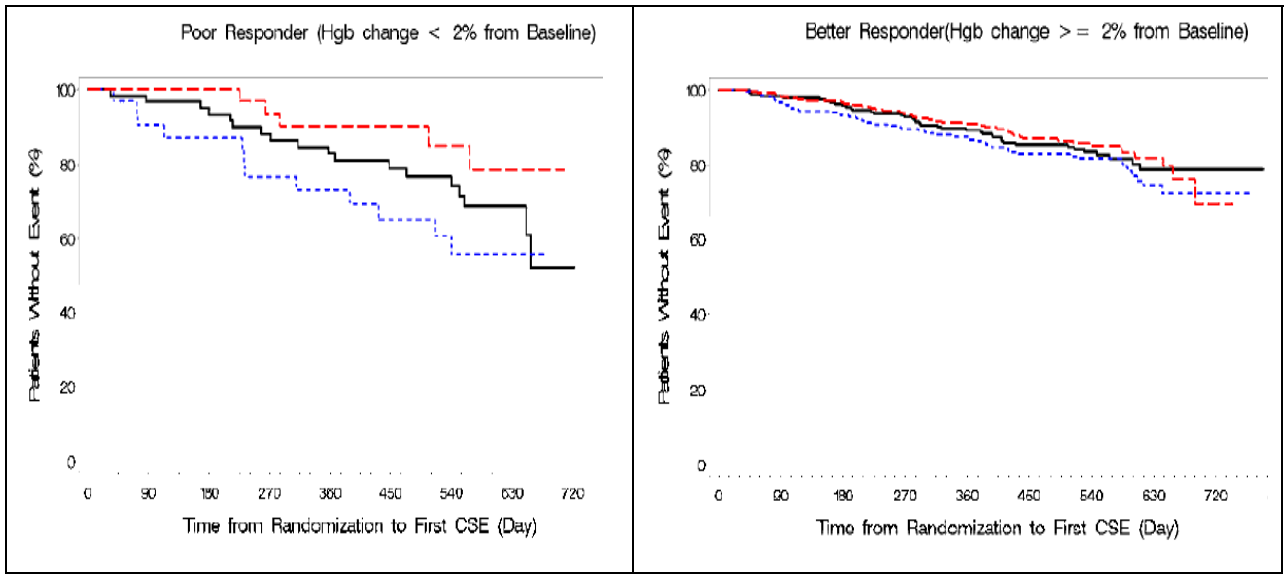
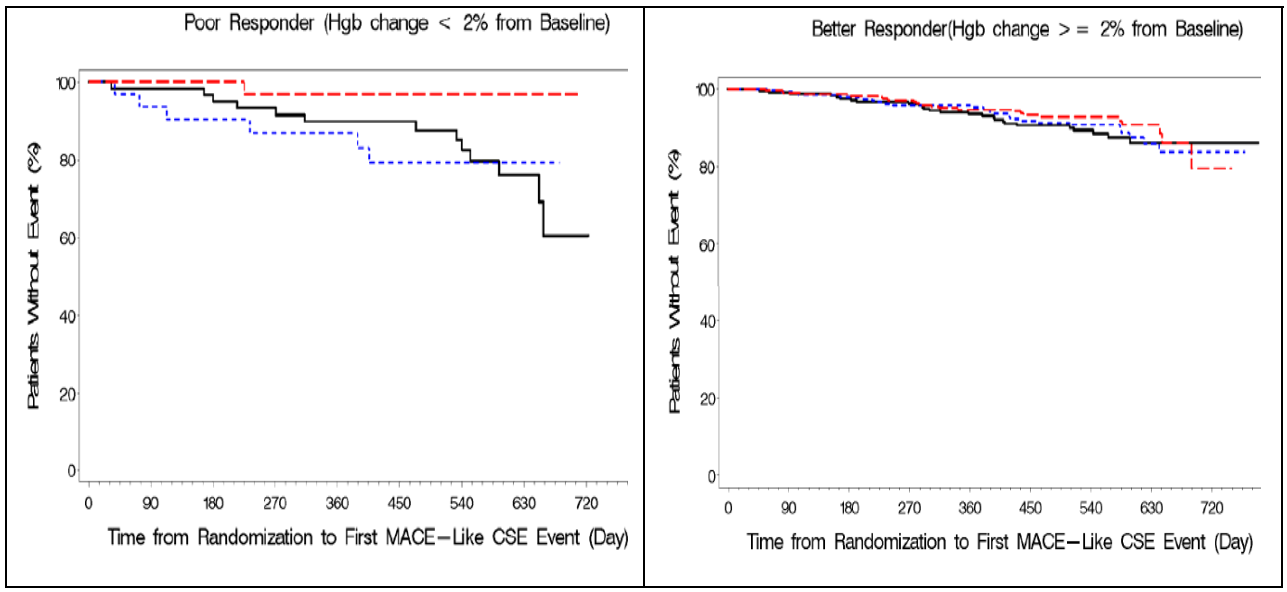
with a poor initial hemoglobin response and the treatment groups appeared more similar in the subjects who had better initial hemoglobin responses.

Figure 12. Time to first CSE event: event-free rate over time by initial hemoglobin response category (non-dialysis subjects). Red, black, and blue lines indicate the treatment groups darbepoetin alfa, peginesatide 0.025 mg/kg, and peginesatide 0.04 mg/kg respectively.



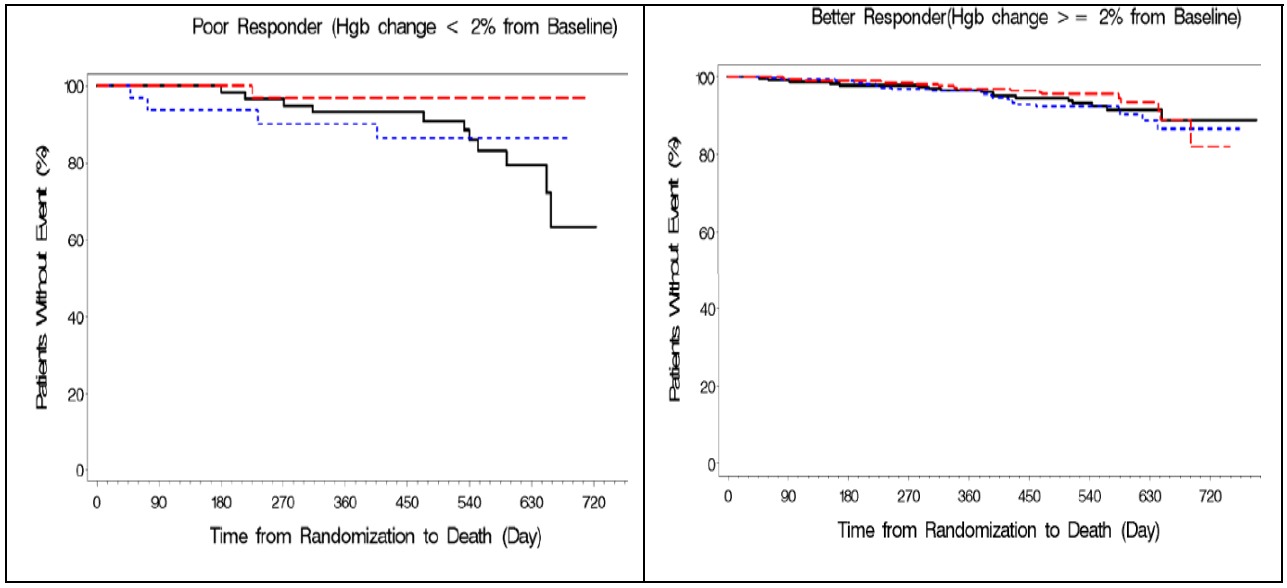
(Source: Sponsor's Integrated Summary of Safety, Figure 6)

Figure 13. Time to first MACE event: event-free rate over time by initial hemoglobin response category (non-dialysis subjects). Red, black, and blue lines indicate the treatment groups darbepoetin alfa, peginesatide 0.025 mg/kg, and peginesatide 0.04 mg/kg respectively.



(Source: Sponsor's Integrated Summary of Safety, Figure 13.4.1)

Figure 14. Time to death event: event-free rate over time by initial hemoglobin response category (non-dialysis subjects). Red, black, and blue lines indicate the treatment groups darbepoetin alfa, peginesatide 0.025 mg/kg, and peginesatide 0.04 mg/kg respectively.



(Source: Sponsor's Integrated Summary of Safety, Figure 13.3.1)

The sponsor's overall conclusions regarding their Solomon analysis are:

- "Consistent with the findings from the analysis of the TREAT data by Solomon, these analyses suggest that a poor initial hematopoietic response to ESA therapy in non-dialysis subjects not previously receiving ESAs may be an important indicator of a potential for increased subsequent risk of adverse safety outcomes.
- "Application of the Solomon approach to the peginesatide Phase 3 Non-Dialysis Population similarly showed that a poor initial hemoglobin response to ESA (in this case, either peginesatide or darbepoetin) was associated with poor subsequent hemoglobin response, higher overall dose requirements, and greater risk for subsequent CV events."

Reviewer's Comments: The sponsor's Solomon analysis is a reasonable look at whether the risk of cardiovascular events increases for individuals with a poor response to ESA therapy. The findings are consistent with that of the TREAT study as published by Salomon [1].

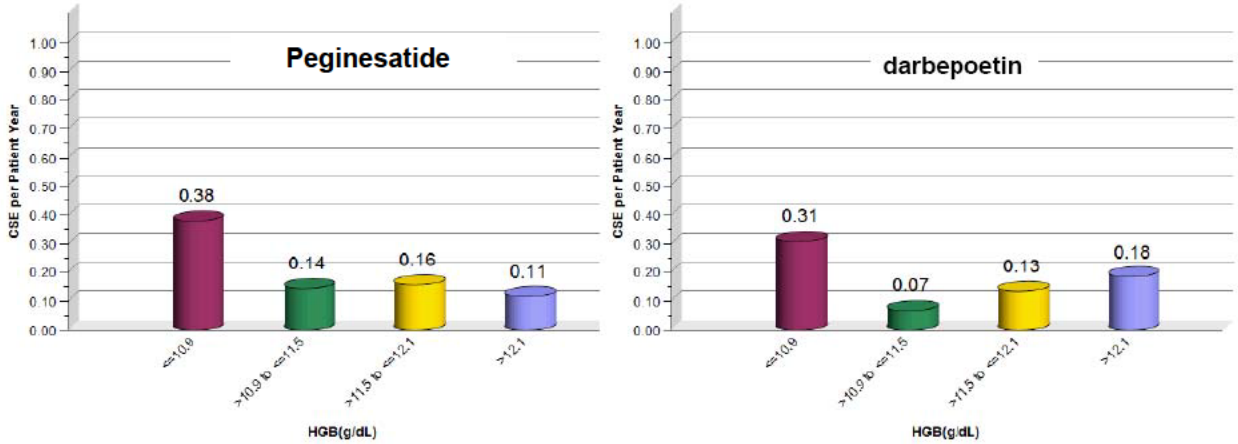
One point that is not apparent from the sponsor's figures is that when looking at a comparison between poor and normal responders within the same treatment group, the difference with poor responders is noticeable for peginesatide. Whereas for darbepoetin, if you superimposed the poor responders with the normal responders, there may not appear to be a difference between the two arms. The sponsor notes that the baseline characteristics for the darbepoetin arm are 'distinct' from the peginesatide treatment arms in that poor responders in the darbepoetin group did not appear to have the same burden of cardiovascular risk factors that the peginesatide arm.

It should also be noted that the Solomon analysis only looks at change from baseline at 1 month post treatment initiation. Using this short duration eliminates variability in classification as a poor responder introduced from dose titration.

3.3.2 Rate of Hemoglobin Change Analysis

The relationship between CSE events and temporally-associated hemoglobin in the Non-Dialysis Population is shown in Figure 15. In both the peginesatide and darbepoetin groups, the rate of CSE events was highest in the lowest hemoglobin quartile (hemoglobin ≤10.9 g/dL).

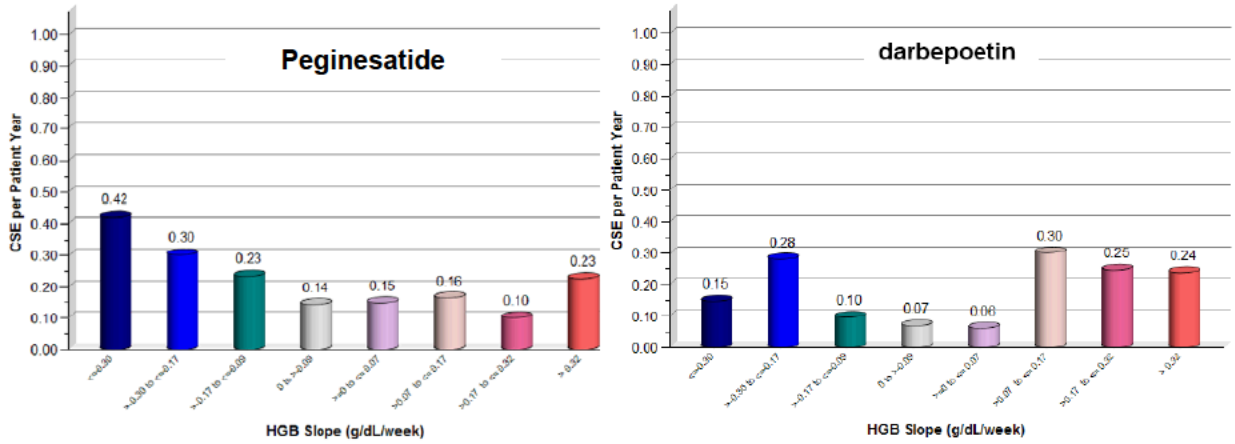
Figure 15. Unger-like approach: CSE events by temporally-associated hemoglobin, non-dialysis population.



(Source: Sponsor's Integrated Summary of Safety, Figure 9)

The relationship between CSE events and temporally-associated rate of change in hemoglobin is shown in Figure 16. Event rates were lower than in the comparable analysis of the dialysis population (Figure 17), and trends in the data were less evident. For both treatment groups, the four categories with the highest rates of CSE events corresponded to more rapidly decreasing or more rapidly increasing hemoglobin values (Figure 16). For the peginesatide group, the greatest rate of CSE events was in the hemoglobin rate-of-change category corresponding to the most rapidly decreasing hemoglobin levels (≤-0.30 g/dL/week).

Figure 16. Unger-like approach: CSE events by temporally-associated hemoglobin rate of change, non-dialysis population.



(Source: Sponsor's Integrated Summary of Safety, Figure 10)

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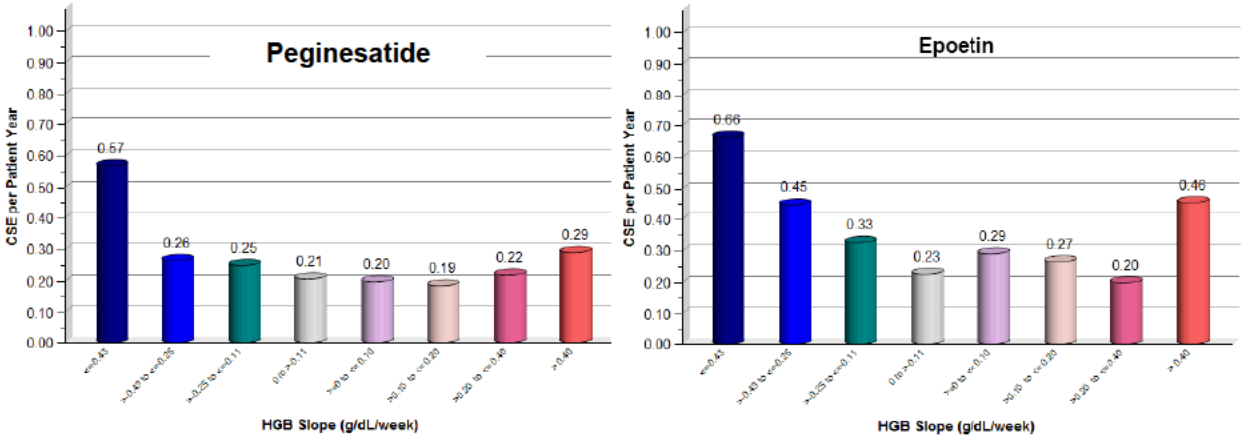
Figure 17. Unger-like approach: CSE events by temporally-associated hemoglobin rate of change, dialysis population.



(Source: Sponsor's Integrated Summary of Safety, Figure 8)

The sponsor concluded that: "the event rates were lower than observed in the dialysis population, and thus the trends in the data were less evident. Still, the data indicated an inverse relationship between hemoglobin level and CSE risk for both peginesatide and darbepoetin; low hemoglobin values were associated with greater risk of CSE events. Trends were less evident with respect to rate of change in hemoglobin, although rapidly decreasing and rapidly increasing hemoglobin levels appeared to be associated with greater risk of CSE events in peginesatide and darbepoetin groups. Associations of risk with low hemoglobin and with rapidly increasing and decreasing hemoglobin levels were also seen in Unger's analysis of the CHOIR Study data, which enrolled non-dialysis patients who were ESA-naive (see Figures 7, 8, and 9 in [4])."

*Reviewer's Comments: The sponsor's analysis for rate of hemoglobin change appears reasonable. The findings are consistent with those previously observed for the treat study and the reviewer's analysis. These results suggest that doses should not be administered to elicit rapid changes in hemoglobin levels. The sponsor makes note of this in the proposed label under section 2.2: "The dose of [TRADE NAME] should be reduced if the hemoglobin increases by more than 1 g/dL in the 2 weeks prior to the dose or more than 2 g/dL in 4 weeks [*see Dosage and Administration (2.3)*]." The value of 1 g/dL is a bit larger than the cut offs for the bins at either end of the plots in Figure 16 and Figure 17. These figures would suggest avoiding rates of change greater than 0.6 – 0.8 g/dL/2 weeks if possible.*

3.4 Selection of Dose

3.4.1 Route of Administration: IV or SC

The sponsor evaluated the doses necessary to maintain hemoglobin as either an IV or SC formulation because subcutaneous administration of Epoetin has been associated with lower dose requirements The possibility of a similar association was examined for peginesatide using the Phase 3 Dialysis Study AFX01-14. The sponsor used Figure 18 to show that both IV and SC formulations are able to maintain hemoglobin levels.

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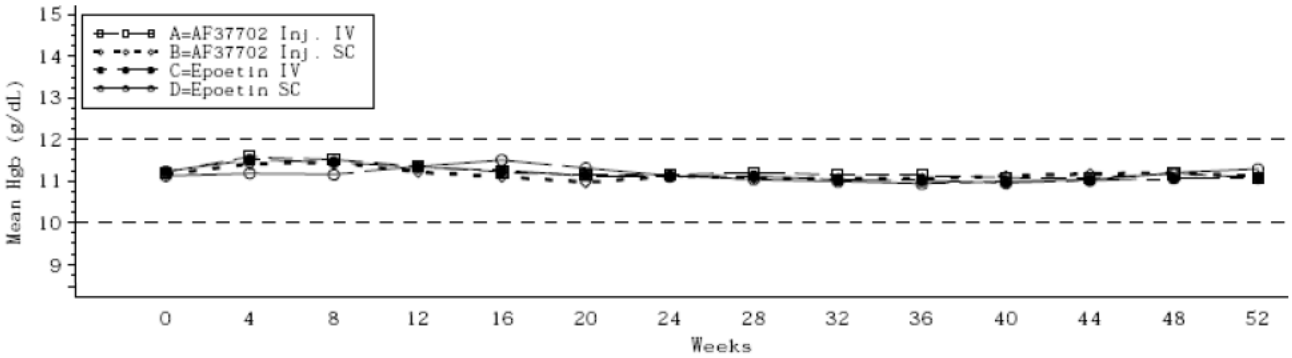
Figure 18. Mean hemoglobin during 4-week intervals through 52 weeks by treatment group and route of administration– Study AFX01-14



(Source: Sponsor's Clinical Efficacy Summary, Figure 20)

Table 5 was used to compare the within-subject doses at baseline and the evaluation period for treatment groups, region, and route of administration. Results indicate that the mean and median doses are similar between the SC and IV formulations when considering the overall population during the evaluation period.

Table 5. Mean within-subject dose at baseline and evaluation period by treatment group, geographic region, and route of administration – AFX01-14

			Subcutaneous		Intravenous	
			AF37702 Inj. Q4W (mg)	Epoetin 1-3 Times/Wk (U/week)	AF37702 Inj. Q4W (mg)	Epoetin 1-3 Times/Wk (U/week)
Non-US	Baseline	N	67	35	146	69
		Mean (SD)	3.7 (1.63)	5029 (1977.6)	3.8 (1.40)	5877 (3063.6)
		Median	3.1	5000	3.4	6000
	Evaluation Period	N	62	27	138	61
		Mean (SD)	5.2 (4.41)	4793 (3173.1)	4.8 (4.10)	5695 (3777.9)
		Median	3.9	4094	3.5	5000
US	Baseline	N	38	18	291	147
		Mean (SD)	7.1 (4.07)	12083 (8070.0)	6.8 (3.60)	14626 (15610.9)
		Median	6.3	12000	6.2	9900
	Evaluation Period	N	33	15	248	131
		Mean (SD)	11.3 (12.94)	9784 (7135.2)	8.2 (8.56)	13587 (14625.3)
		Median	6.8	7200	5.5	8350
Overall	Baseline	N	105	53	437	216
		Mean (SD)	4.9 (3.20)	7425 (5935.1)	5.8 (3.35)	11831 (13608.0)
		Median	3.8	6000	4.8	8000
	Evaluation Period	N	95	42	386	192
		Mean (SD)	7.3 (8.84)	6575 (5443.3)	6.9 (7.46)	11079 (12792.3)
		Median	4.8	4625	4.8	7100

(Source: Sponsor's Clinical Efficacy Summary, Table 24)

The sponsor concluded: "subjects in the overall population (US and non-US combined) who received peginesatide by the SC or IV route received similar doses and achieved similar hemoglobin levels, supporting that the same dosing recommendations are appropriate for both routes of administration."

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3.4.2 Dose Conversion from Epoetin

The studied conversion doses for trials AFX01-12 and AFX01-14 were derived from the phase 2 trial AFX01-03 and are shown in Table 6.

Table 6. Conversion Chart for Peginesatide Dosing in Trials AFX01-12 and AFX01-14.

Screening Epoetin Alfa Dose (U/kg/week)	AF37702 Injection (mg/kg)
<100	0.04
100 to 199	0.08
200 to 299	0.12
≥300	0.16

(Source: Sponsors Protocol for Studies AFX01-12 and AFX01-14)

Data from the phase 3 studies were used to select the proposed dose for the label. The sponsor took several steps to identify the proposed dose conversion from epoetin:

1. The sponsor reviewed the relevant data and rationale for the ESA-free transition period before administering study treatment, in studies AFX01-12 and AFX01-14.
2. The sponsor reviewed the adequacy of the dose conversion from epoetin to peganesatide used in the phase 3 dialysis studies with respect to hemoglobin levels over time and mean dose during the evaluation period (weeks 29-36).
3. **Figure 19:** The sponsor conducted a linear regression on the pre-randomization epoetin dose (log-transformed) and the mean peginesatide dose (log-transformed) during the evaluation period as a basis for relating the starting peginesatide dose to the prior epoetin dose.
4. **Figure 19:** Using the observed pre-randomization epoetin doses from the phase 3 dialysis data, a Classification and Regression Tree (CART) analysis was performed to obtain a statistically optimal set of partitions of the epoetin dose range.
5. **Table 7 & Figure 20:** Using the fitted linear relationship between (log-transformed) pre-randomization epoetin dose and (log-transformed) peginesatide dose, the proposed epoetin-to-peginesatide dose conversion table based on total dose was determined. The nine dose tiers in the conversion table were selected with consideration given to the range and distribution of epoetin doses observed in the phase 3 dialysis studies and in current US databases (USRDS, DaVita). Examining the data from the phase 3 dialysis Studies, mean evaluation period doses (reflecting the average peginesatide dosing requirement in mg after titration) were seen to be approximately centered around the first peginesatide dose when determined based on the conversion chart, supporting the appropriateness of the nine-tier conversion based on total dose as proposed.

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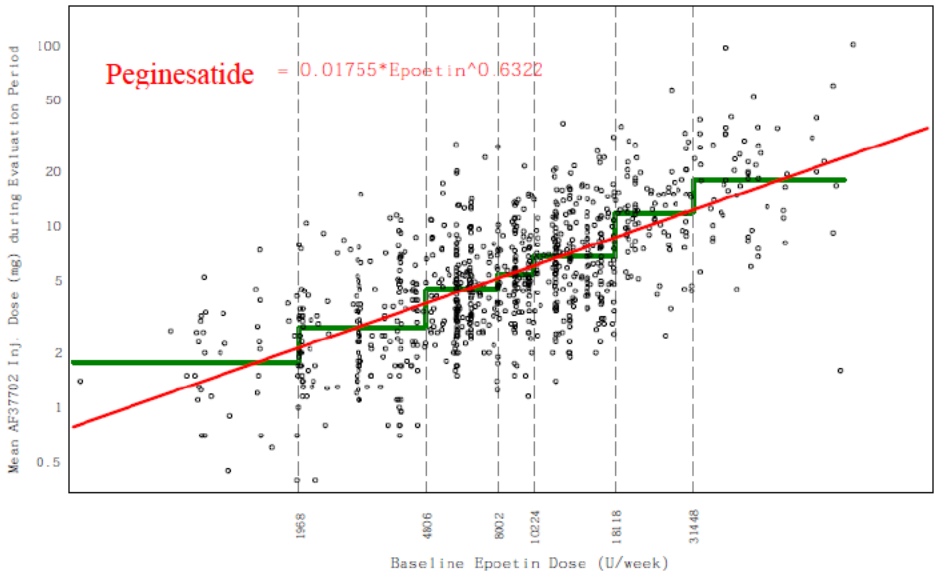
Figure 19. Comparison of CART analysis of phase 3 dialysis data and fitted epoetin-peginesatide (AF37702 Inj.) regression Line.



(Source: Sponsor's Clinical Efficacy Summary, Figure 26)

Table 7. Proposed nine-tier, epoetin-to-peginesatide dose conversion chart based on total dose, dose ratios (epoetin/peginesatide), and distribution of US subjects per tier in phase 3 studies.

Previous Weekly Epoetin alfa IV or SC Dose (U/week)	Monthly AF37702 Inj. IV or SC Dose (mg/month)	Dose Ratio (Epoetin/AF37702 Inj.) for Lower Limit, Upper Limit of Epoetin Dose Range	% of US Subjects in Phase 3 Dialysis Studies AFX01-12 and AFX01-14, 2007-2008 (N=1288)	Estimated % of Patients in USRDS Database, Nov 2007* (N=203803)	Estimated % of Patients in DaVita Database+		
					Jan/Feb 2008 (N=92397)	Jan/Feb 2009 (N=96727)	Jan/Feb 2010 (N=102423)
<2,500	2	NA, 1250	7%	8%	9%	10%	9%
2,500 to <4,300	3	833, 1433	9%	8%	9%	10%	8%
4,300 to <6,500	4	1075, 1625	13%	11%	11%	12%	10%
6,500 to <8,900	5	1300, 1780	10%	10%	11%	11%	10%
8,900 to <13,000	6	1483, 2167	19%	14%	15%	15%	14%
13,000 to <19,000	8	1625, 2375	17%	14%	15%	15%	15%
19,000 to <33,000	10	1900, 3300	15%	18%	18%	16%	18%
33,000 to <68,000	15	2200, 4533	7%	12%	11%	10%	12%
≥68,000	20	3400, NA	2%	4%	2%	2%	3%

* Based on USRDS Nov. 2007 summary statistics provided in 2500 Unit increments.[29] Linear interpolation used to derive percentage for given cut points.

+ Based on DaVita summary statistics in 2500 Unit increments.[30] Linear interpolation used to derive percentage for given cut points.

NA=not applicable.

(Source: Sponsor's Clinical Efficacy Summary, Table 28)

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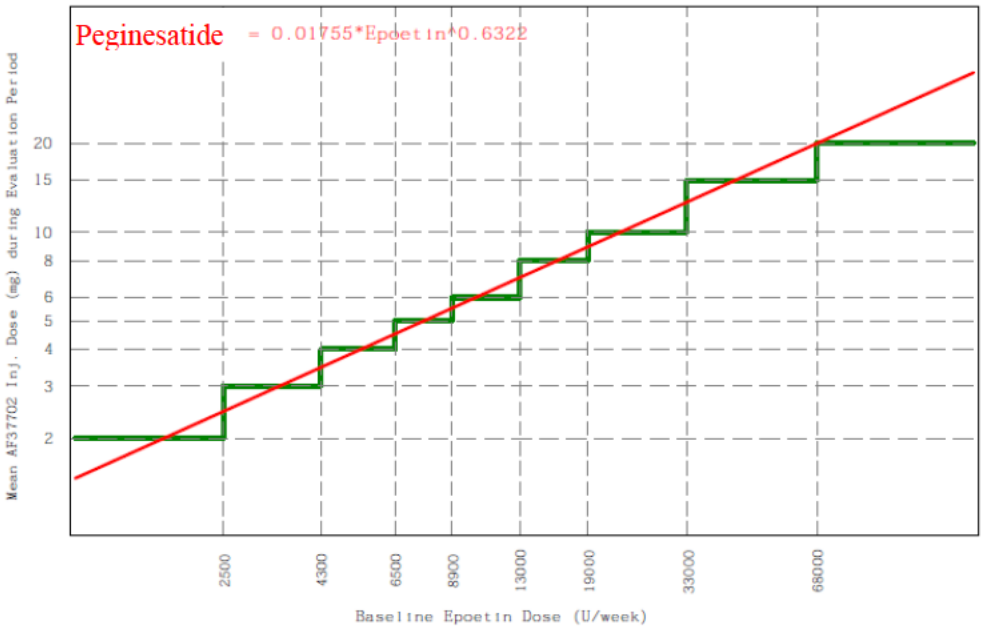
Figure 20. Nine dose tiers of proposed epoetin-to-peginesatide dose conversion in relation to the fitted regression line.



(Source: Sponsor's Clinical Efficacy Summary, Figure 27)

Reviewer's Comments: The sponsor's approach to dose selection using the linear regression and CART analysis on the Phase 3 data is acceptable. The peginesatide starting doses proposed in the label fall within the range of those studied in the phase 3 clinical trials (See Figure 19 and Figure 20).

3.4.3 Dose Conversion from Darbepoetin

The sponsor used a similar approach for the darbepoetin conversion, however this approach is reliant on the previously developed relationship between epoetin and darbepoetin [3]:

1. A darbepoetin-to-peginesatide dose conversion formula was derived by combining the epoetin-to-peginesatide conversion formula determined using the phase 3 dialysis study data as described in Section 3.4.2 with the epoetin-to-darbepoetin conversion formula as demonstrated by Scott [6], and mathematically solving for peginesatide dose as a function of darbepoetin dose (Figure 21).

2. **Figure 22:** Using the data from phase 2 dialysis study AFX01-202, a second darbepoetin-to-peginesatide dose conversion formula was determined by linear regression of the (log-transformed) evaluation period peginesatide dose on the pre-randomization (log-transformed) darbepoetin dose. This was seen to provide generally similar results to the formula derived in the first step, although the sample of dialysis subjects in Phase 2 Study AFX01-202 was relatively small (43 subjects during the evaluation period). The formula derived in the first step was used subsequently as it was based on a much greater number of subjects (the analysis by Scott [6] demonstrating the epoetin-darbepoetin relationship was based on over 500 subjects and the epoetin-peginesatide relationship was based on 916 subjects in the Phase 3 Dialysis Studies).

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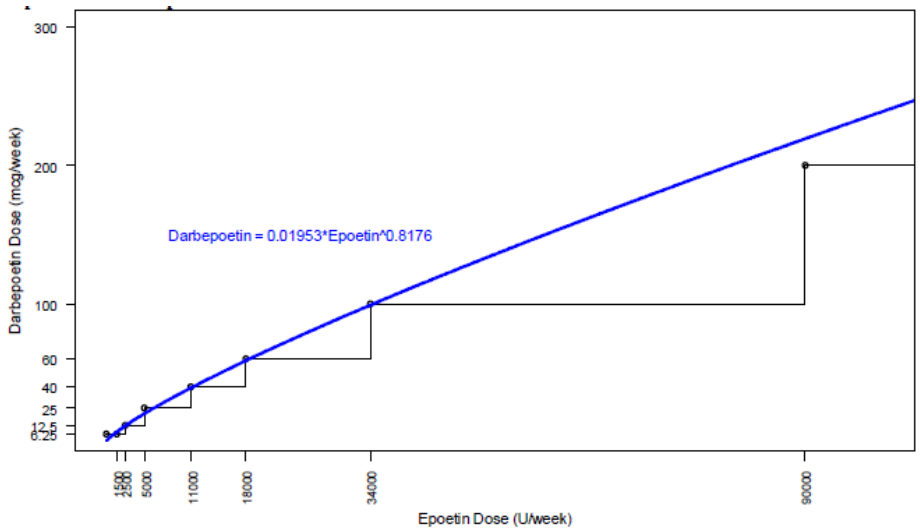
3. **Figure 23:** The derived relationship between (log-transformed) pre-randomization darbepoetin dose and (log-transformed) peginesatide dose was used to determine nine darbepoetin dosing tiers that corresponded to the nine peginesatide doses used in the proposed epoetin-to-peginesatide dose conversion. The nine tiers were examined with respect to the proportion of patients estimated per tier based on data regarding the distribution of darbepoetin doses obtained from USRDS.
4. **Table 3:** Ratios of median darbepoetin dose to median peginesatide dose from the evaluation period (Weeks 25-36) of the phase 3 non-dialysis studies AFX01-11 and AFX01-13 were compared with the range of dose conversion ratios in the proposed darbepoetin-to-AF37702 Injection dose conversion. This provided a general check on the reasonableness of the darbepoetin-to-peginesatide dose conversion.

Figure 21. Epoetin to darbepoetin dose conversion. The curve was determined by linear regression cut points for the dose tiers specified in the epoetin-to-darbepoetin conversion chart in the US package insert for darbepoetin alfa [3].



(Source: Sponsor's Clinical Efficacy Summary, Figure 29)

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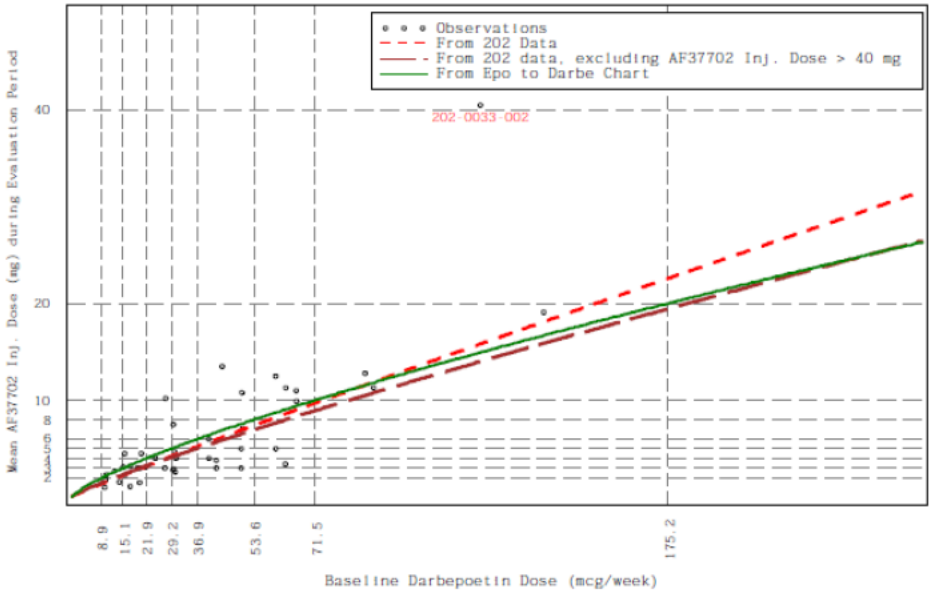
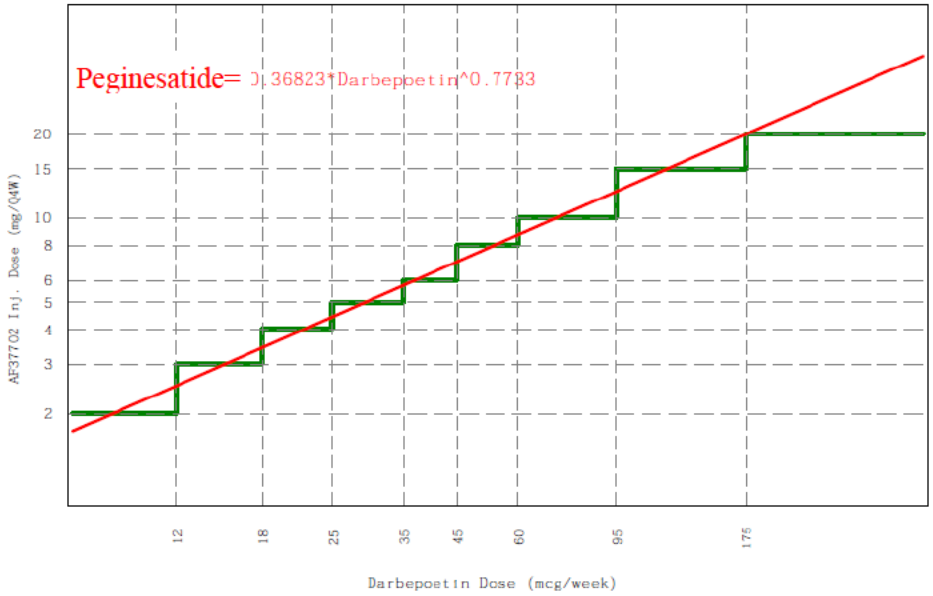
Figure 22. Mean evaluation period peginesatide (AF37702 Inj.) dose versus screening darbepoetin dose with fitted regression line and derived peginesatide-darbepoetin relationship.



(Source: Sponsor's Clinical Efficacy Summary, Figure 30)

Figure 23. Nine dose tiers of proposed darbepoetin-to-peginesatide dose conversion in relation to the derived relationship



(Source: Sponsor's Clinical Efficacy Summary, Figure 31)

Reviewer's Comments: The sponsor's approach to dose selection using the linear regression and CART analysis on the Phase 3 data are acceptable. The conversion from darbepoetin was not studied in the phase three trials. However the two assumptions that make this conversion possible (epoetin to darbepoetin dose correlation and the epoetin to peginesatide dose correlation) were derived from the approved Aranesp label and phase 3 data in dialysis patients. The results of this analysis are further supported by the phase 2 data from study AFX01-202.

Table 8. Proposed nine-tier, darbepoetin-to-peginesatide dose conversion chart with dose ratios (darbepoetin/peginesatide) and estimated percent of patients in USRDS database.

Previous Weekly Darbepoetin Alfa IV or SC Dose (µg/week)	Monthly AF37702 Inj. IV or SC Dose (mg/month)	Dose Ratio (Darbepoetin / AF37702 Inj.) for Lower Limit, Upper Limit of Darbepoetin Dose Range	Estimated % of Patients in USRDS Database, Nov 2007* (N=16379)
<12	2	NA, 6.0	11%
12 to <18	3	4.0, 6.0	10%
18 to <25	4	4.5, 6.3	13%
25 to <35	5	5.0, 7.0	10%
35 to <45	6	5.8, 7.5	10%
45 to <60	8	5.6, 7.5	11%
60 to <95	10	6.0, 9.5	16%
95 to <175	15	6.3, 11.7	12%
≥175	20	8.8, NA	6%

* Based on USRDS Nov. 2007 summary statistics provided in 25 µg increments and separately in 5 percentile increments.[29] Linear interpolation used to derive percentage for given cut points.

(Source: Sponsor's Clinical Efficacy Summary, Table 31)

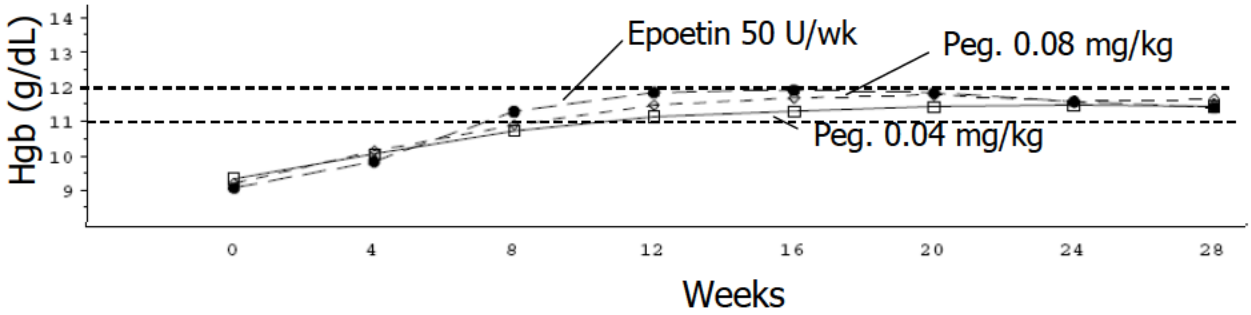
3.4.4 Determining the Starting Dose for ESA Treatment Initiation in CRF Patients

The starting doses for trial AFX01-15 were derived from the phase 2 trial AFX01-03 which suggested that the dose needed to maintain hemoglobin levels for dialysis patients is higher compared to the dose for non-dialysis patients (trial AFX01-04). Thus, trial AFX01-15 examined doses of 0.04 and 0.08 in dialysis patients compared to 0.025 and 0.5 previously studied in non-dialysis patients and 0.025 and 0.04 studied as starting doses in the phase 3 non-dialysis trials.

Data from Study AFX01-15 and the phase 3 dialysis trials were used to select the proposed starting dose for patients initiating ESA therapy. The sponsor used the following data and figures to justify the starting dose range for the correction of anemia:

- Study AFX01-15 (Section 3.1.3):
  - **Figure 24:** Hgb levels were examined over time by starting dose group (0.04 mg/kg Q4W, 0.08 mg/kg Q4W).
  - **Table 9:** The frequency and type (increase, decrease) of dose alterations following the initiation of dosing with peginesatide were examined by starting dose group.
  - **Figure 6:** The distribution of peginesatide doses after correction was examined by starting dose group.
- Studies AFX01-12 and AFX01-14 (Section 3.1.1):
  - **Table 10:** The distributions of the peginesatide and epoetin doses observed during the Evaluation Period were examined, both overall and by region (US, EU). Doses in Study AFX01-15 (conducted in Russia) appear more similar to the doses based on subjects from Europe in Study AFX01-14 than based on subjects from the US in Studies AFX01-12 and AFX01-14 (Table 10).
  - **Figure 25:** The distribution of AF37702 Injection dose during the Evaluation Period was examined relative to that of the pre-randomization Epoetin dose, both overall and by region (US, EU).

Figure 24. Mean hemoglobin value during 4-wk intervals of trial AFX01-15. The target hemoglobin range for this phase 2 study is indicated by the dashed lines. Dose amounts shown indicate the value of the first dose only. Subsequent doses were titrated based on hemoglobin response.



(Source: Sponsor's Clinical Efficacy Summary, Figure 12)

Table 9. Dose alterations at second and third dose by peginesatide starting dose.

	AF37702 Injection IV Starting Dose 0.04 mg/kg Q4W (N=39)	AF37702 Injection IV Starting Dose 0.08 mg/kg Q4W (N=37)
Number (%) Subjects with Dose Decreases:		
At Dose 2 (Week 5)	9/37 (24.3%)	12/37 (32.4%)
At Dose 3 (Week 9)	11/36 (30.6%)	13/37 (35.1%)
Number (%) Subjects with Dose Increases:		
At Dose 2 (Week 5)	16/37 (43.2%)	12/37 (32.4%)
At Dose 3 (Week 9)	18/36 (50.0%)	13/37 (35.1%)

A dose was classified as decreased (increased) if it was ≥20% lower (higher) than the starting dose.

(Source: Sponsor's Clinical Efficacy Summary, Table 32)

Table 10. Mean dose during evaluation period, study AFX01-15 compared to studies AFX01-12 and AFX01-14 by region

	AFX01-15	AFX01-12 +AFX01-14	
	(Conducted in Russia)	Subjects in US	Subjects in Europe
(Timing of Evaluation Period)	(Weeks 21-28)	(Weeks 29-36)	(Weeks 29-36)
Mean Dose During Evaluation Period:			
AF37702 Injection (mg/kg)			
N	73	716	200
Median (25th-75th)	0.05 (0.03-0.07)	0.07 (0.04-0.12)	0.05 (0.03-0.09)
Epoetin (U/kg/week)			
N	35	389	88
Median (25th-75th)	87 (68-144)	120 (66-217)	70 (38-99)

(Source: Sponsor's Clinical Efficacy Summary, Table 35)

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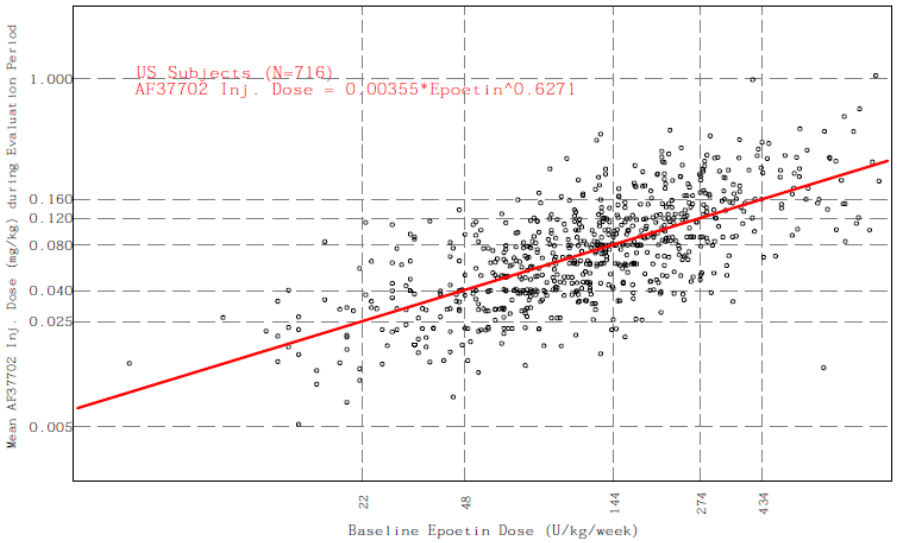
Figure 25. US subjects from studies AFX01-12 and AFX01-14: Mean peginesatide injection dose during evaluation period versus pre-randomization epoetin dose.



(Source: Sponsor's Clinical Efficacy Summary, Figure 34)

The sponsor's proposed dosing is 0.04 to 0.08 mg/kg for the correction of anemia. The sponsor based their decision on the following points:

- **Figure 24:** "Both the 0.04 and the 0.08 mg/kg Q4W starting dose of peginesatide resulted in similar increases in mean hemoglobin levels from baseline to the Evaluation Period (Weeks 21-28)."
- **Table 9:** "Comparing the two starting dose groups, the proportions of subjects with dose increases were somewhat greater in the 0.04 mg/kg Q4W starting dose group and the proportions of subjects with dose decreases were somewhat greater in the 0.08 mg/kg Q4W starting dose group."
- **Figure 6:** "In the 0.04 mg/kg Q4W starting dose group, the box plots indicate that the dose was increased over time in some subjects. In the 0.08 mg/kg Q4W starting dose group and in the Epoetin comparator group, the box plots indicate that the dose generally tended to be decreased over time.**"**
- **Figure 25:** "...starting doses of peginesatide at the upper end of the 0.04-0.08 range corresponded to doses that are at the low end of the Epoetin starting dose range, especially in the US population. Thus, the full range of doses examined in Study AFX01-15, from 0.04 mg/kg to 0.08 mg/kg, are included in the starting dose recommendations for peginesatide. An appreciable segment of the dialysis population (predominantly in the US) are anticipated to require starting doses at the upper end of this range to avoid a potentially long period below the target hemoglobin range and achieve optimal correction of anemia."
- "The proposal for a range of initial starting doses is intended to allow health care providers to individualize the peginesatide starting dose based on the hemoglobin level of the patient and the patient's overall clinical condition, so as to achieve a gradual increase in hemoglobin to the target range of 10 to 12 g/dL and avoid an excessively long period

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of time below target. Use of a starting dose range is consistent with prescribing information for epoetin alfa, which provides a two-fold starting dose range."

Reviewer's Comments: Figure 6 indicates that the difference between the starting dose and mean dose during the evaluation period was greater for the 0.08 mg/kg dose group compared to the 0.04 mg/kg dose group. The sponsor also shows that the 0.04 mg/kg dose can be adjusted to reach the target hemoglobin at a similar rate to the 0.08 mg/kg starting dose (Figure 24). From an efficacy standpoint, the 0.04 mg/kg dose should be sufficient as a starting dose.

From a safety standpoint, it is not possible to determine if dose is a cause of increased CV events. Thus a lower starting dose (0.04 mg/kg compared to 0.08 mg/kg) might be more appropriate.

3.5 Population PK Model

Pharmacokinetic data were obtained from 672 subjects from the studies shown in Table 11 and Table 12, contributing a total of 2665 peginesatide concentrations overall. Observations across all studies that were included in the population PK dataset and used in the analysis are summarized in Table 11. The total number of PK samples excluded in the analysis was less than 3.7%.

Table 11. Summary of the number of subjects and observed concentrations.

Study No	Total number of subjects	Total number of observed concentrations
AFX01-02	17	117
AFX01-03	30	468
AFX01-04	53	720
AFX01-07	23	329
AFX01-14	549	1031

Table includes all the samples that were collected in each studies and were analyzed.

(Source: Sponsor's Population PK Report, Table 4.a)

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Table 12. Sample collection for PK data used in population PK analysis.

AFX01-02	AFX01-03	AFX01-04	AFX01-07	AFX01-14
PK sampling on days 1 and 2: Samples drawn predose and at 5 minutes, 15 minutes, 1 hour, 4 hours, 8 hours, and 24 hours after start of study drug administration.	Prior to Dose 1 and at 5, 15, and 60 minutes, 4 and 24 hours, pre and post the next dialysis (approximately 44 and 48 hours), 96 hours (±24 hours) and 1 week after administration of Dose 1. PK sampling on Week 5 and 9 dosing days: Samples drawn predose and at 15 minutes after administration of study drug. PK sampling on Week 13, 17, and 21 dosing days: Samples drawn predose only.	Predose (prior to Dose 1) Samples collected postdose 2 hours (±10 minutes) 1 day (24±1 hours) 2 days (48±2 hours) 4 days (96±4 hours) 6 days (144±6 hours) 7 days (168±6 hours) 9 days (216±6 hours) PK sampling on Weeks 5, 9, 13, 17 and 21 dosing days: samples drawn predose only. Optional PK profile drawn from Dose 2 onwards. Samples will be drawn prior to dosing and at 2 hours (±10 minutes), 1 day (24±1 hours), 2 days (48±2 hours), 4 days (96±4 hours), 6 days (144±6 hours), 7 days (168±6 hours), and 9 days (216±6 hours) after that dose.	**IV patients** Post Day 1 Dose Predose, 5 minutes, 15 minutes, 1 hour, 4 hours ±10 minutes, 24±1 hours, 44 hours, 48 hours, 96±4 hours, 168±6 hours postdose. **SC patients** Post Day 1 Dose Predose, 2 hours ± 10 minutes, 24±1 hours, 48±2 hours, 96±4 hours, 144±6 hours, 168±6 hours, and 216±6 hours postdose. PK sampling for subsequent doses: Samples drawn predose only.	Blood samples for population PK analysis were collected at Week 1 prior to Dose 1 and approximately 48-72 hours post Dose 1 of AF37702 Injection.

(Source: Sponsor's Summary of Clinical Pharmacology)

After selection of an appropriate structural population PK model, covariates were screened using a generalized additive modeling (GAM) approach and confirmed graphically. In order to avoid possible multicollinearity issues, GAM analyses were performed for volume of central compartment (V2), concentration needed to reach 50% of Vmax (KM) and absorption rate constant (KA) of peginesatide using 6 different combinations of covariates, which were deemed to be highly correlated (r >0.6) based upon graphical analysis. Subsequently, the impact of GAM-selected subject covariates on the PK of peginesatide was assessed using stepwise forward selection (% = 0.05) and backward elimination (% = 0.005) procedures.

Baseline subject covariates (continuous and categorical) in the analysis dataset included age, gender, race, ethnicity (ETHN), weight, body mass index (BMI), aspartate aminotransferase (AST), total bilirubin (TBILI), albumin, alkaline phosphatase (ALP), serum creatinine (CR), hematocrit (HT), estimated glomerular filtration rate (GFR), and concomitant medications. Subject demographics and laboratory values measured just before they started treatment with peginesatide were considered as baseline values for the covariate analysis.

The final population PK model to characterize the changes in peginesatide concentrations over time was a two compartment model with first order absorption and MM elimination where intercompartmental clearance (Q) was fixed to improve model stability. ETHN, TBILI, AGE, BMI, CR and ALP were identified as significant covariates for the peginesatide PK model.

Inter-subject variability was estimated for Ka, KM and V2 with a covariance term between Ka and V2. The residual variability was described using a combined additive plus CCV residual

error model. The parameter estimates along with their associated precision (%SEM) and goodness-of-fit plots for the final model for peginesatide are presented in Table 13 and Figure 26.

Table 13. Peginesatide parameter estimates and their associated precision for the final population PK model and bootstrap evaluation

Parameter (Unit)	Final estimate (%SEM)	Bootstrap estimate (a)	Bootstrap 95% CI (b)
VMAX (ng/kg/hr)	45.3 (10.0)	44.7	32.0 – 69.0
KM (ng/mL)	1880 (14.6)	1860	1120- 3222.5
V2(mL/kg)	35.6 (2.7)	35.6	33.3 -38.0
Ka (1/hr)	0.00865 (15.6)	0.00869	0.00582-0.013
F1	0.498 (4.4)	0.499	0.430-0.577
Q (mL/kg/hr)	*5.23*	*5.23*	*FIXED*
V3 (mL/kg)	7.44 (10.3)	7.415	5.49-9.84
V2: BMI Power for V2	-0.491 (8.7)	-0.485	-0.684 - -0.280
V2: AGE Slope for V2	-0.125 (19.0)	-0.125	-0.238 - -0.0015
KM: ALP Power for KM	-0.194 (25.5)	-0.19	-0.307 - -0.0895
V2: TBIL slope for V2	0.477 (22.4)	0.4815	0.086 - 0.933
KA: CR slope on KA (only for NDs)	7.84E-04 (69.1)	6.9E-04	-0.0013 - 0.0023
KA: (1-ETHN) shift for Ka	0.00811 (20.3)	0.00815	0.0035 - 0.0117
IIV in KM	0.0589 (29.0)	0.0575	0.032 - 0.102
IIV in V2	0.101 (8.1)	0.0998	0.0646 - 0.1372
Cov (IIV in V2, IIV in Ka)	-0.0928 (25.4)	-0.0903	-0.136 - -0.0342
IIV in Ka	0.197 (32.0)	0.19	0.0964 - 0.3391
RV: ratio of proportional to additive RV	0.0218(19.5)	0.0223	0.0135 – 5.15
Residual Variability (Additive Component)	81.8 (36.8)	78.2	0.0017 – 166.7

Italics indicates parameters were fixed; NA=not applicable; RV=Residual variability; IIV=inter individual variability %SEM values are enclosed in brackets.
(a) Median estimate is used.
(b) Based on 870/1000 successfully converged bootstrap runs.

(Source: Sponsor's Population PK Report, Table 4.m)

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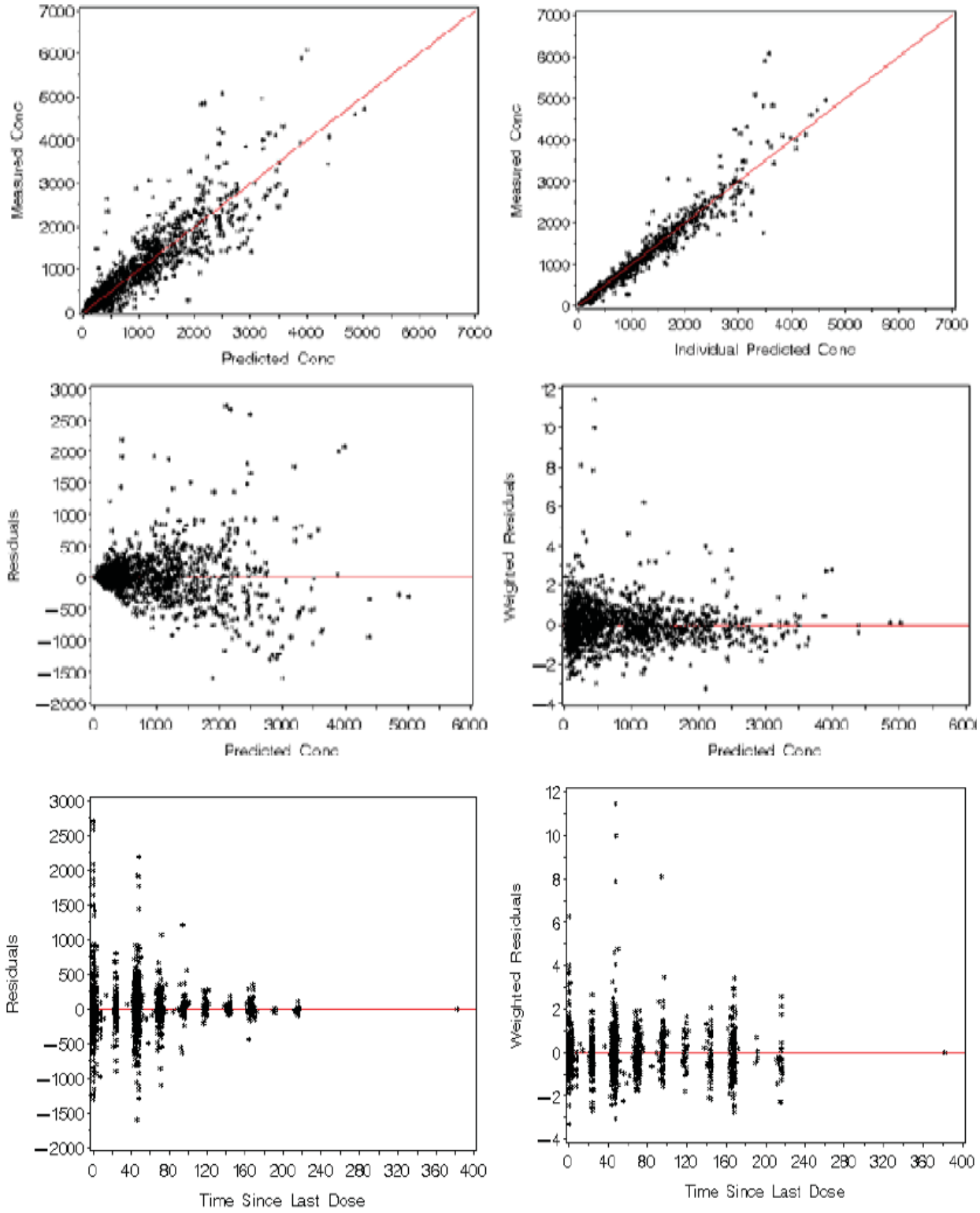
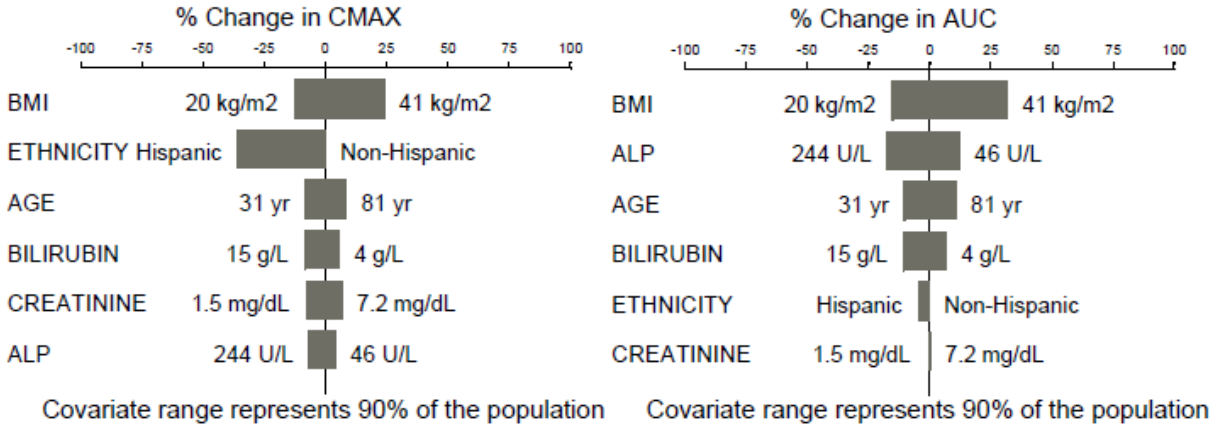
Figure 26. Goodness-of-fit plots for the final population PK model for peginesatide.



(Source: Sponsor's Population PK Report, Figure 4.c)

The covariates identified reduced the estimate of inter-individual variability for KM, V2, and KA in the final model by 13.4%, 1.5%, and 22.6%, respectively, compared with that of the same model without the covariate effects.

Figure 27. Tornado plot of covariate effects on C_{max} and AUC of peginesatide after IV or SC administration of peginesatide to subjects with CRF on dialysis and not on dialysis



(Source: Sponsor's Summary of Clinical Pharmacology, Figure 8)

Reviewer's Comments:

The sponsor's population PK model is acceptable.

In the proposed label, the sponsor indicates that the PK of peginesatide is not altered by age, gender or race. This is consistent with the data shown in Figure 27.

BMI was not included in the label. This is acceptable because dosing is based on a mg/kg basis and this fact should account for much of the variation due to BMI. This would be a concern if everyone were receiving the same dose amount.

The effects of PK covariates ethnicity and alkaline phosphatase were also not included in the label. This is acceptable because the effects of these covariates do not appear to be great enough that dose titration could not account for differences in exposure. Additionally, while Hispanic ethnicity appears to reduce peginesatide C_{max}, the effect on AUC is minimal. Because dosing is adjusted based on hemoglobin levels, the effects of these covariates do not govern dosing decisions.

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4 REVIEWER'S ANALYSIS

4.1 Introduction

The primary safety results of the non-dialysis trials AFX01-11 and AFX01-13 indicated that the peginesatide treatment group failed to meet non-inferiority compared to the darbepoetin treatment group for the primary composite safety event. See the clinical review by Dr. Andrew Dmytrijuk for further details.

Cardiovascular events are a major concern for peginesatide's development program and also existing ESA products, the aim of the reviewer's analysis was to ascertain whether a dose-response for cardiovascular events exists and if other factors could affect the dose-response relationship for CV events in the non-dialysis trials. As part of the dose-response for cardiovascular risk analyses it was necessary to identify if other factors such as hemoglobin response, rate of hemoglobin change, and baseline demographics were important predictors of cardiovascular risk. This review evaluates these aspects in an effort to understand if the proposed dosing in dialysis patients can be considered safe.

4.2 Objectives

Analysis objectives are:

1. Ascertain whether dose-response for cardiovascular risk exists and whether hemoglobin and baseline demographic data lend to determination of the effect of dose on cardiovascular risk.
2. Determine if individuals with poor response to peginesatide or darbepoetin are at greater risk for cardiovascular events.
3. Determine if greater rates of rise of hemoglobin indicate increased CV risk.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 14.

Table 14. Analysis Data Sets

Study Number	Name	Link to EDR
AFX01-11	dm.xpt, lb.xpt, ex.xpt	\\cdsesub1\EVSPROD\NDA202799\0000\m5\datasets\afx01-11\tabulations\sdtm
AFX01-13	dm.xpt, lb.xpt, ex.xpt	\\cdsesub1\EVSPROD\NDA202799\0000\m5\datasets\afx01-13\tabulations\sdtm
AFX01-12	dm.xpt, lb.xpt, ex.xpt	\\cdsesub1\EVSPROD\NDA202799\0000\m5\datasets\afx01-12\tabulations\sdtm
AFX01-14	dm.xpt, lb.xpt, ex.xpt	\\cdsesub1\EVSPROD\NDA202799\0000\m5\datasets\afx01-14\tabulations\sdtm
AFX01-15	dm.xpt, lb.xpt, ex.xpt	\\cdsesub1\EVSPROD\NDA202799\0000\m5\datasets\afx01-15\tabulations\sdtm
ISS	adhypo.xpt, adcse1.xpt, adcse2.xpt, adhgb.xpt, adsl.xpt	\\cdsesub1\EVSPROD\NDA202799\0000\m5\datasets\iss\analysis\datasets

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BLA 103951, TREAT study	attevent.xpt, ahbmonth.xpt, ahbwkly.xpt	\\cbsap58\m\eCTD_Submissions\STN103951\0334\m5\datasets\20010184\analysis

4.3.2 Software

SAS version 9.2 (Cary, NC) was used for Cox-proportional hazards models. All plots and were generated with S-plus software (Tibco, Palo Alto, CA).

4.4 Results

The reviewer's analysis consists of a set of exploratory analyses that aim to evaluate the risk of having a primary CSE event or MACE event as a function of ESA dose, hemoglobin response, and rate of hemoglobin change.

4.4.1 Evaluation of Dose-Response for Risk of CV Events in Non-Dialysis Patients

Refer to Section 1.1.1.

4.4.2 Evaluation of Dose-Response for Risk of CV Events in Dialysis Patients

To evaluate dose-response for cardiovascular risk, patients were grouped into four quartiles of average study dose by study drug and curves of cumulative CSE events were plotted over time for each quartile. Average study dose was defined as the mean of all doses administered to an individual between study enrollment and discontinuation or stopping drug because of a major safety event. Figure 28 shows an apparent dose-response relationship for the primary CSE for both darbepoetin and peginesatide in dialysis patients.

However, Table 15 shows it cannot be concluded that this is due to dose, because for peginesatide, average study dose is correlated with hemoglobin. This does not appear to be the case for epoetin. The mean hemoglobin by epoetin average study dose quartile does not appear to change. This finding potentially suggests either that epoetin dose could be associated with increased cardiovascular risk or that other potential cardiovascular risk factors may be imbalanced between the different exposure quartiles (Table 16).

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Figure 28. Cardiovascular risk appears to be correlated with ESA average study dose for both darbepoetin and peginesatide. Curves for the cumulative percentage of patients with a primary CSE are shown for each of four average study dose quartiles.

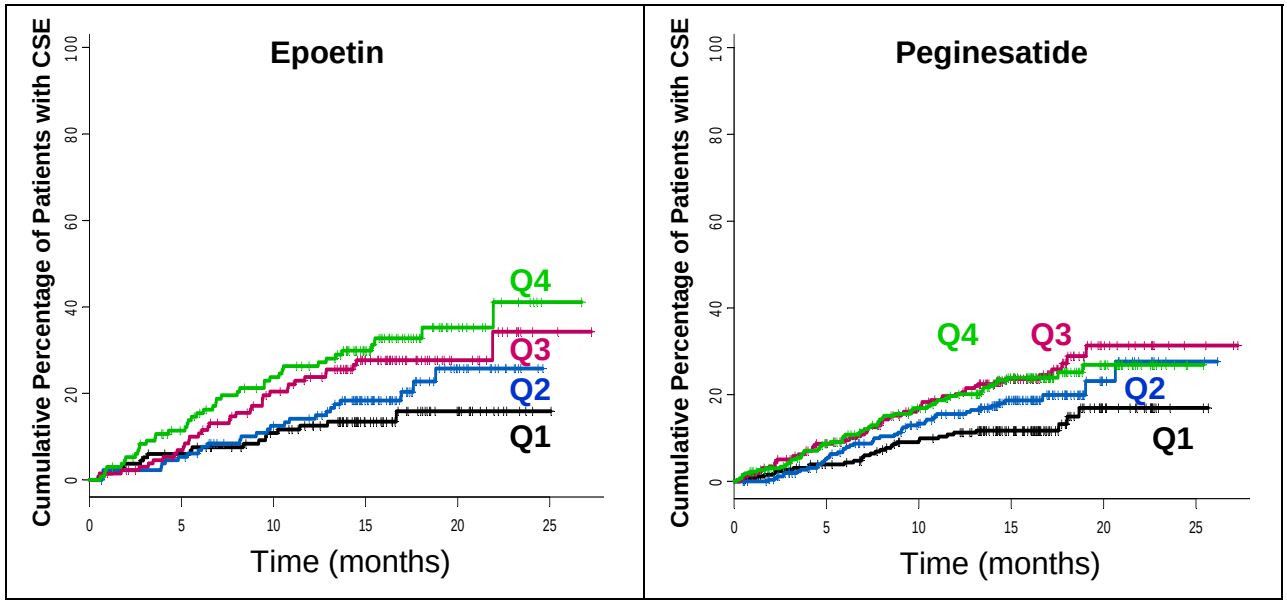

Table 15. Mean hemoglobin is inversely correlated with mean peginesatide dose but not with epoetin dose in dialysis patients.

	Epoetin		Peginesatide	
Quartile	Mean Dose Range (U/kg)	Mean Hgb (g/dL)	Mean Dose Range (mcg/kg)	Mean Hgb (g/dL)
1	4.4 - 63	11.4	11 - 41	11.7
2	63 - 113	11.1	41 - 69	11.1
3	113 - 201	11.1	69 - 110	11.1
4	201 - 1025	11.2	110 - 1069	10.8

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Table 16. Table of Potential Risk Factors for Cardiovascular Events.

Baseline Demographic	Quartile of Mean Peginesatide Study Dose				Quartile of Mean Epoetin Study Dose			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Age (yr)	59	59	59	54	58	60	57	56
Weight (kg)	86	81	82	81	86	80	80	79
% Female	36	34	49	44	41	46	48	46
% Black	37	37	41	42	33	39	47	48
% White	58	59	54	53	65	57	44	41
% Asian	1.6	2.9	2.5	3.7	0.8	3.3	5.6	6.5
% w. DiabD	53	48	49	50	43	52	48	54
% NYHA Class II	19	19	24	24	16	21	20	24
Base Hgb (g/dL)	11.4	11.2	11.3	11.2	11.3	11.2	11.3	11.4
C-Reactive Protein (mg/L)	9.1	9.6	10.6	10.9	9.6	8.4	10.7	13.4
% w. Peripheral Vascular Disease	23	24	27	22	14	20	23	28
% w. Coronary Artery Disease	40	38	47	43	30	36	37	41
% w. Cardiovascular Disease	18	19	19	16	16	20	15	17
% w. Cardiac Arrythmia	19	16	26	23	22	15	22	20

4.4.3 Cardiovascular Risk in Patients with Slow Response to ESA Products

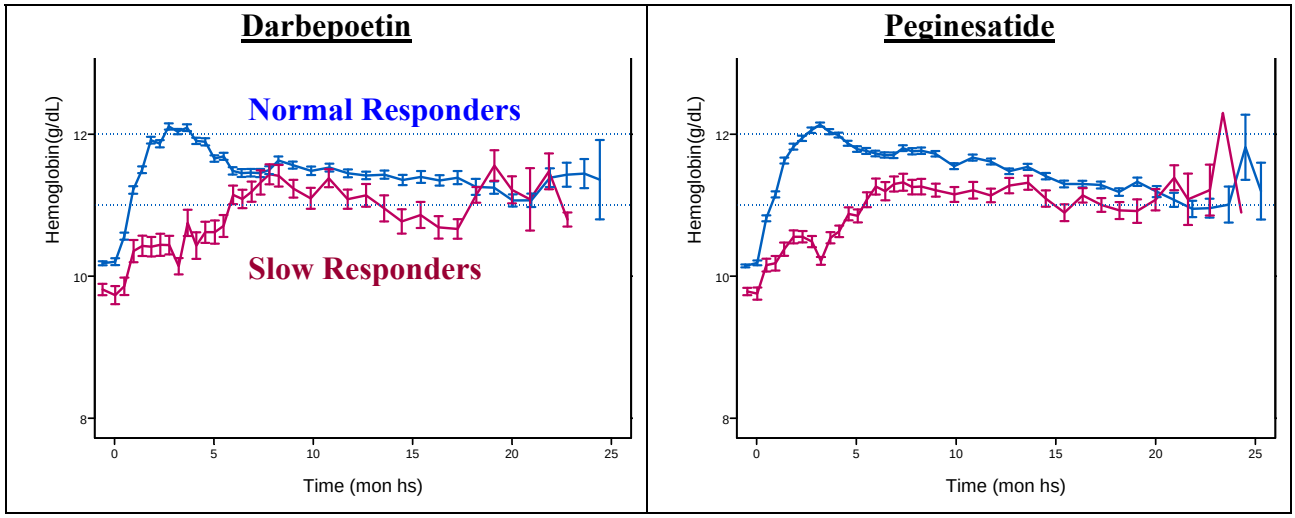
Exploratory analysis following the TREAT trial for Aranesp[1,2], and current ESA labeling [3] suggest that a population of poor responders to ESA therapy exists and that these individuals exhibit higher cardiovascular risk. Poor responders were first identified by Solomon et al as individuals in the lowest quartile of hemoglobin response (change from baseline) at 1 month after treatment initiation. Affymax conducted a Solomon-like analysis for both peginesatide and darbepoetin in the current NDA (see Section 3.3.1).

Our analysis defines slow responders as those individuals who did not achieve hemoglobin values within the target range (11 – 12 g/dL for non-dialysis patients) by 3 months (Figure 29). FDA referred to this subgroup as "slow responders" to differentiate it from the sponsor's definition. The revised definition was used over the Solomon definition for the following reasons:

- The slow responder criterion at 3 months is relevant to dosing decisions in the current ESA label for Aranesp. The current label (Section 2.2) reads, "For patients who do not respond adequately over a 12-week escalation period, increasing the Aranesp dose further is unlikely to improve response and may increase risks." The label under Section 5.1 reads, "Patients with chronic kidney disease and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients."
- The Division of Pharmacometrics review of the TREAT trial used both the Solomon approach and the 3-month criterion. The 3 month criterion appeared to be more sensitive than 1 month criterion for predicting increased risk of cardiovascular events. (See the clinical pharmacology review by Dr. Jiang Liu in DARRTS, March 2011)
- This metric is an overall measure of those individuals with the lowest hemoglobin values in the first 3 months.

Reference ID: 3084101

Figure 29. Slow responders exhibit poor initial hemoglobin response. Results are presented as the mean hemoglobin ± SEM for normal responders (blue) and slow responders (red) for Non-Dialysis Trials AFX01-11 and AFX01-13.



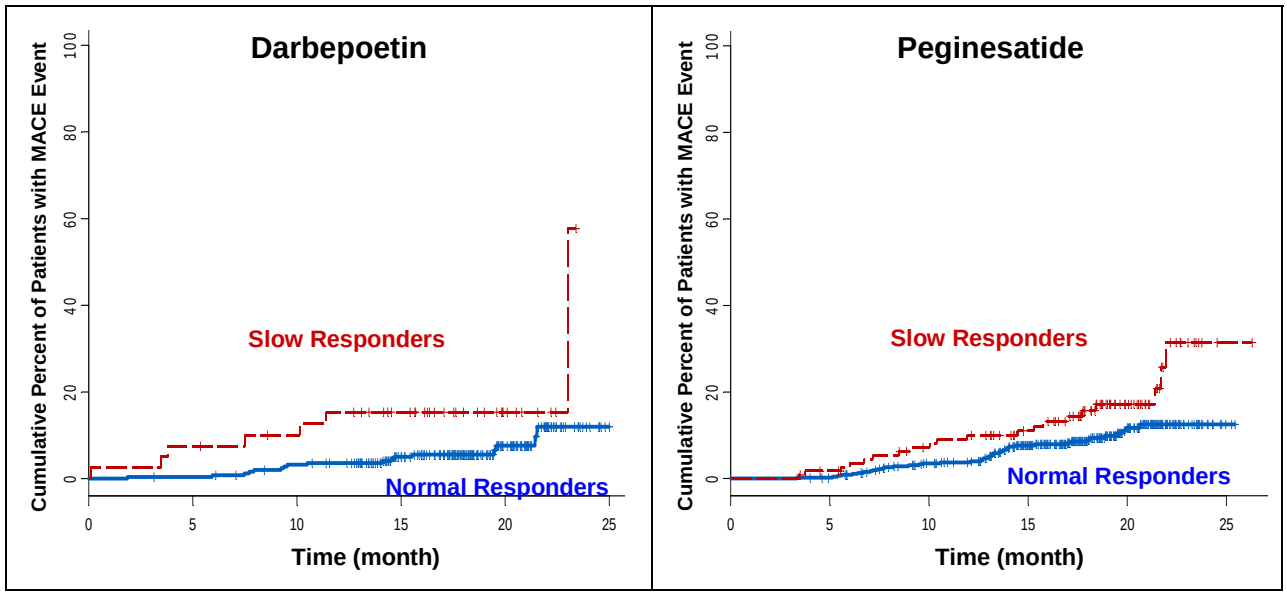
One additional difference between our analysis and the sponsor's is that if a patient left the trial prior to three months, but had achieved hemoglobin values within the target range, they were classified as normal responders. In contrast, the sponsor excluded these individuals from their analysis.

4.4.3.1 Non-Dialysis Population, Trials AFX01-11 and AFX01-13

Refer to Section 1.1.1. Additional analyses are presented below.

Figure 30 shows that slow responders also exhibited increased risk of having a MACE event in both the darbepoetin and peginesatide treated populations.

Figure 30. Slow responders appear to have increased CV risk in both the darbepoetin alfa (left panel) and peginesatide (right panel) treatment groups for the MACE composite safety endpoint*. Red and blue lines depict the cumulative percent of patients with CSE events over time for slow and normal responders, respectively.



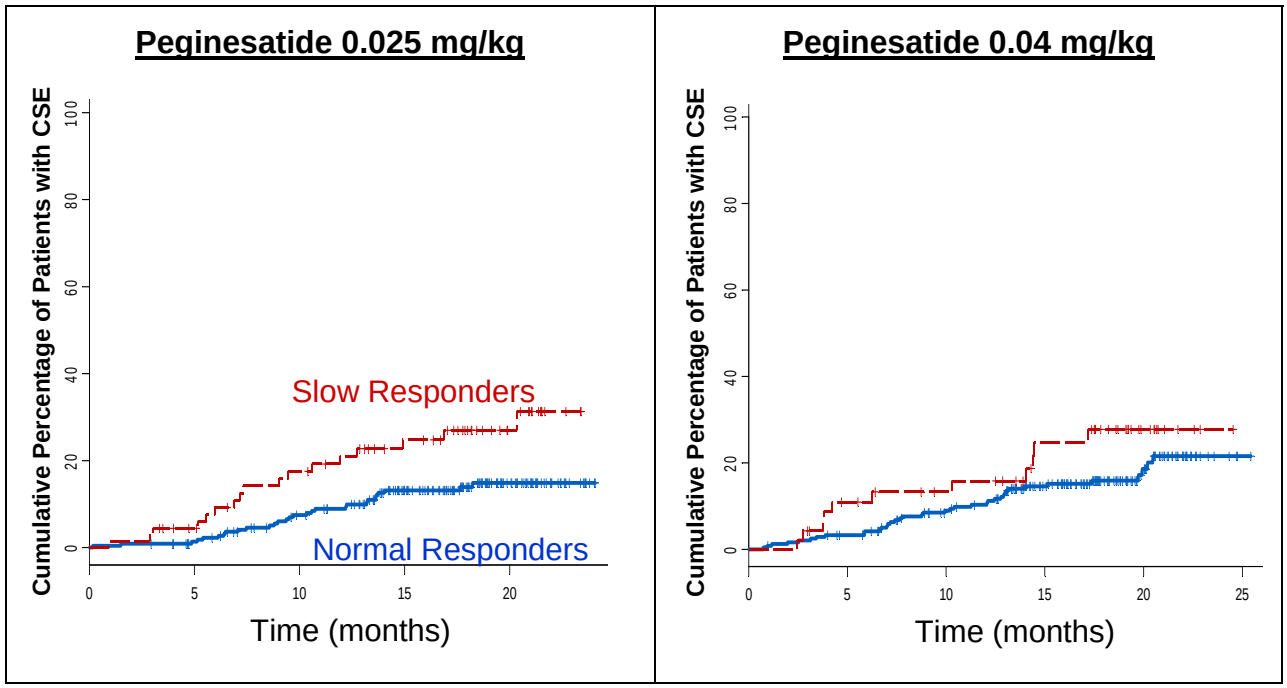
*Data are from non-dialysis patients in studies AFX01-11 and AFX01-13.

These results were found to be consistent with those of the TREAT study for darbepoetin in type 2 diabetes patients with chronic kidney disease (See the clinical pharmacology review by Dr. Jiang Liu in DARRTS, March 2011).

To evaluate whether starting dose played a role in the increased risk of CV events for slow responders the primary CSE profiles of the different peginesatide starting dose groups in non-dialysis patients were evaluated. Figure 31 shows that cardiovascular risk is similar between the 0.025 mg/kg and 0.04 mg/kg peginestide treatment arms.

Reference ID: 3084101

Figure 31. Similar risk of the primary CSE was observed between peginesatide treatment arms in the non-dialysis clinical trials AFX01-11 and AFX01-13.



4.4.3.2 Dialysis Patient Population, Trials AFX01-12 and AFX01-14

Refer to Section 1.1.2

4.4.4 Cardiovascular Risk by Rates of Hemoglobin Change

Previous FDA analyses have suggested that greater rates of hemoglobin change may be associated with increased cardiovascular events [4,5]. Division of Pharmacometrics conducted a similar analysis to determine if this trend was apparent for darbepoetin and peginesatide and for slow and normal responders in the non-dialysis trials AFX01-11 and AFX01-13.

The rate of hemoglobin rise analysis was performed by:

1) Identifying the slopes of hemoglobin change over 2 wk intervals when hemoglobin values were available and 4 weeks when values were missing.
2) Defining 8 separate bins of hemoglobin slopes. Bins were determined using all available data for both peginesatide and darbepoetin.
3) Determining the number of primary CSE events that occur within each hemoglobin slope category. CSE events were associated with the corresponding hemoglobin slope at the time the event occurred.
4) Determining the patient year for each hemoglobin slope category. Patient year was defined as the sum of the durations (in days) for which each slope in the category was calculated over, divided by 365.25 days (approximately14-28 days per slope value).
5) Rate is defined as number of CSE events divided by the patient year for that category.

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Figure 32 shows that peginesatide data in the non-dialysis trials are consistent with the previously observed trend for increased CV events with higher rates of hemoglobin. Whereas the darbepoetin data do not suggest this trend. The darbepoetin data need to viewed in light of the small number of patients being used to evaluate cardiovascular risk. The smaller number is due to the 2:1 randomization of subjects in trials AFX01-11 and AFX01-13.

Figure 32. Peginesatide data suggest that greater rates of change in hemoglobin indicate increased CV risk. The number of CSE events per patient year is shown for each of 8 bins of hemoglobin slope.

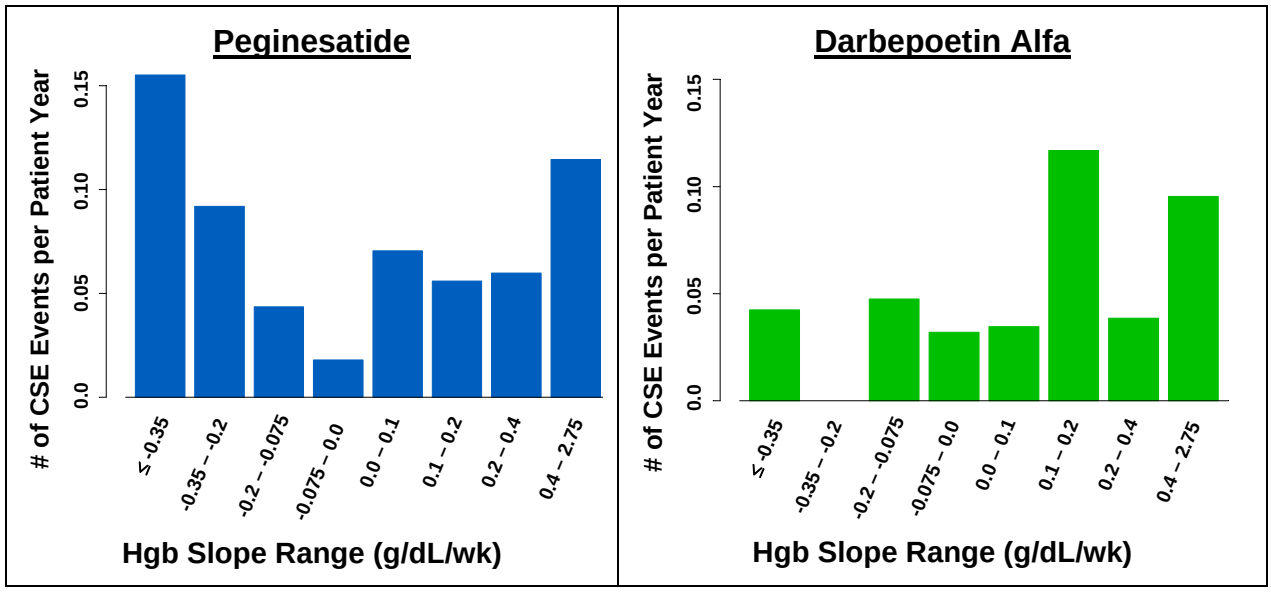


Table 17 and Table 18 show basic summary statistics of the hemoglobin slope categories, events, and patient year for darbepoetin and peginesatide. The number of events and overall patient year duration differs between darbepoetin and peginesatide because of the 2:1 randomization.

Table 17. Summary of rate of rise data for darbepoetin.

Quantile	lower slope limit (g/dL/wk)	upper slope limit (g/dL/wk)	# CSE Events	Patient Years	Events/ Patient Year
1	-2.15	-0.35	2	47.1	0.04
2	-0.35	-0.2	0	50.6	0.00
3	-0.2	-0.075	3	63.1	0.05
4	-0.075	0	2	62.5	0.03
5	0	0.1	2	57.8	0.03
6	0.1	0.2	7	59.9	0.12
7	0.2	0.4	2	51.8	0.04
8	0.4	2.75	4	41.9	0.10

Reference ID: 3084101

Table 18. Summary of rate of rise data for peginesatide.

Quantile	lower slope limit (g/dL/wk)	upper slope limit (g/dL/wk)	# CSE Events	Patient Years	Events/ Patient Year
1	-2.15	-0.35	15	96.7	0.16
2	-0.35	-0.2	9	97.9	0.09
3	-0.2	-0.075	5	114.9	0.04
4	-0.075	0	2	111.7	0.02
5	0	0.1	8	113.4	0.07
6	0.1	0.2	6	107.3	0.06
7	0.2	0.4	6	100.4	0.06
8	0.4	2.75	10	87.4	0.11

The limited number of patients and cardiovascular events also restricts our ability to determine if this trend exists for slow versus normal responders (Table 19) in the non-dialysis population.

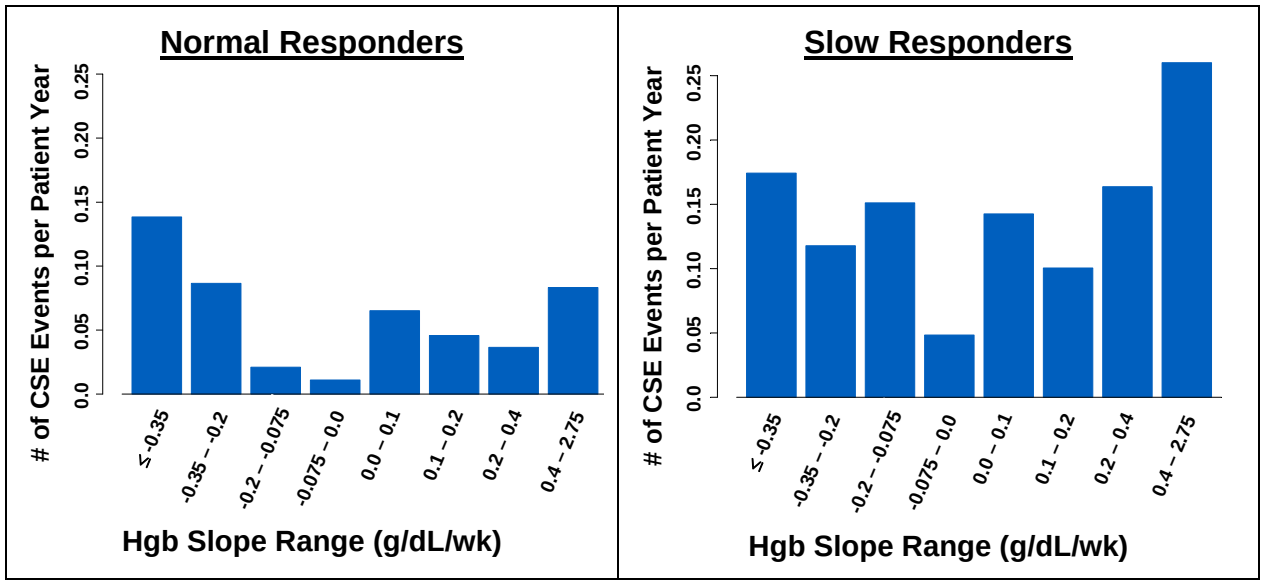
Table 19. Number of CSE events are few for slow responders.

			# CSE Events			
Quantile	lower slope limit (g/dL/wk)	upper slope limit (g/dL/wk)	Peginesatide, Normal Responders	Peginesatide, Slow Responders	Darbepoetin, Normal Responders	Darbepoetin, Slow Responders
1	-2.15	-0.35	11	3	2	0
2	-0.35	-0.2	7	2	0	0
3	-0.2	-0.075	2	3	2	1
4	-0.075	0	1	1	0	2
5	0	0.1	6	3	1	1
6	0.1	0.2	4	2	5	2
7	0.2	0.4	3	3	2	0
8	0.4	2.75	6	4	3	1

As indicated in Figure 32 and Table 19 the numbers of patients/events in the darbepoetin treated group are too few to conclude that a trend for CV events does not exist with great rates of hemoglobin change. Figure 34 shows the rate of rise analysis by normal and slow responders. Consistent with peginesatide slow responders had higher rates of CV events compared to normal responders.

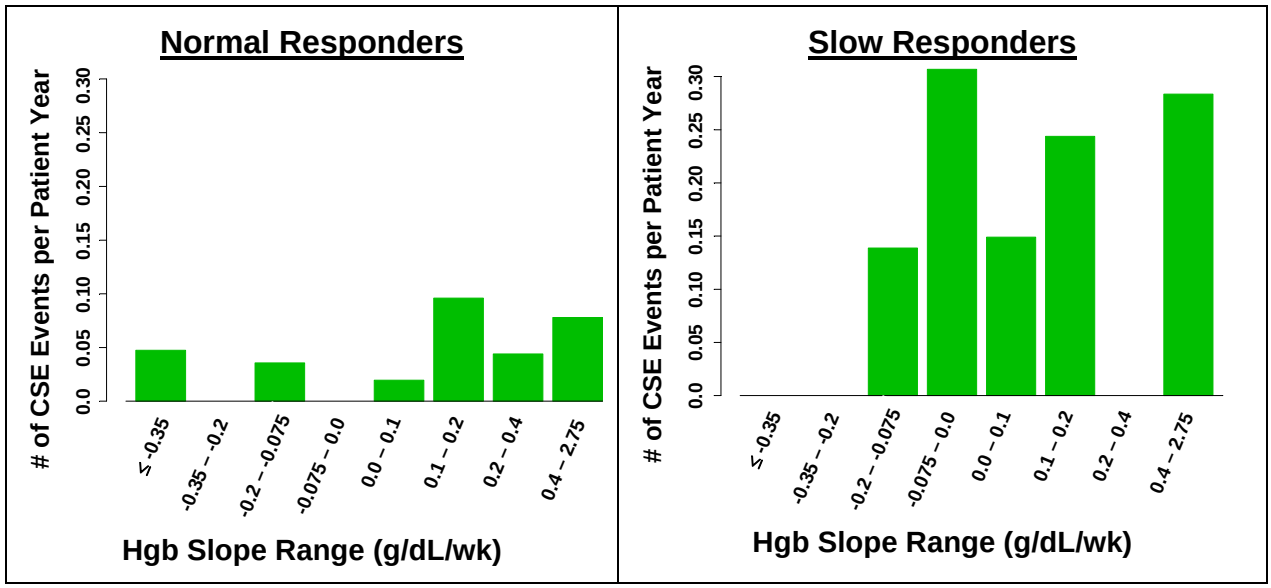
Figure 33 shows that the trend for increased risk of CV events exists for both normal and slow responders receiving peginesatide. This figure also indicates that slow responders overall had a greater occurrence of CV events compared with normal responders which is consistent with the results of Section 4.4.3.

Figure 33. Greater rates of change in hemoglobin are suggestive of greater risk of CV events for both normal and slow responders receiving peginesatide.



As indicated in Figure 32 and Table 19 the numbers of patients/events in the darbepoetin treated group are too few to conclude that a trend for CV events does not exist with great rates of hemoglobin change. Figure 34 shows the rate of rise analysis by normal and slow responders. Consistent with peginesatide slow responders had higher rates of CV events compared to normal responders.

Figure 34. For darbepoetin alfa no trend is observed for higher CV events with greater rates of hemoglobin change.



As the sponsor is seeking the indication for dialysis patients, the rate of hemoglobin change for a patient not receiving an ESA within 12 weeks prior to study enrollment was assessed using data from Trial AFX01-15. Table 20 shows that the distribution of slopes from the phase 2 study

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AFX01-15 is similar to that observed in the non-dialysis phase 3 trials. Cardiovascular outcomes were not evaluated in this trial.

Table 20. Distribution of hemoglobin rates of change for dialysis patients receiving treatment for the correction of anemia (Trial AFX01-15).

Bin	Slopes (g/dL/wk)
1	< -0.6
2	≥ -0.6 & < -0.3
3	≥ -0.3 & < -0.1
4	≥ -0.1 & < 0.1
5	≥ 0.1 & < 0.3
6	≥ 0.3 & < 0.5
7	≥ 0.5 & < 0.8
8	≥ -0.8

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in <\\cdsnas\pharmacometrics\Reviews\PM Review Archive\2012\Peginesatide_NDA202799_JCE\ >
Dose-Response.SSC	S+ Code for Figure 28 & Table 15	\ER Analyses\
Dose-Response2revisedplots.SSC	S+ Code for Figure 1, Figure 30 & Table 1	\ER Analyses\
Time to CV Events (Non Dialysis) at 3mo_Final.SSC	S+ Code for Figure 2, Figure 4, Figure 31, & Table 2	\ER Analyses\
Time to MACE Events (Non Dialysis) at 3mo_Final.SSC	S+ Code for Figure 30	\ER Analyses\
Rate of Rise Final.SSC	S+ Code for all plots and tables in Section 4.4.4	\ER Analyses\

6 REFERENCES:

1. Solomon SD, et. al. Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) Investigators. *N Engl J Med.* 2010 Sep 16;363(12):1146-55.
2. Advisory Committee Meeting for ARANESP, October 18, 2010
3. US package insert for ARANESP, June 2011.
4. Appendix 2 of the FDA Briefing Document for the ARANESP Advisory Committee Meeting, October 18, 2010
5. Jiang Liu. Clinical Pharmacology Review of Aranesp, DARRTS, March 2011.

Reference ID: 3084101

6. Scott SD. Dose conversion from recombinant human erythropoietin to darbepoetin alfa: recommendations from clinical studies. *Pharmacotherapy* 2002;22 (9 Pt 2):160S-5S.
7. Unger EF, Thompson AM, Blank MJ, Temple R. Erythropoiesis-stimulating agents--time for a reevaluation. *N Engl J Med*. 2010 Jan 21;362(3):189-92.

Reference ID: 3084101

4.2 OSI REVIEW

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 22, 2011

TO: Ann Farrell, M.D.
Director, Division of Hematology Products

FROM: Young Moon Choi, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 202-799, Peginesatide (AF37702 Injection) sponsored by Affimax, Inc.

At the request of the Division of Hematology Products (DHP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted an audit of the analytical portion of the following studies:

Study AFX01-102: "A Phase 1, Single-Center, Randomized, Open-Label, Single-Dose, 2-Period, Crossover Study Assessing the Pharmacokinetics of 2 AF37702 Injection Formulations (Single-Dose and Multidose Vials) Administered Intravenously in Healthy Adult Subjects"

Study AFX01-103: "A Phase 1, Single-Center, Randomized, Open-Label, Single-Dose, 2-Period, Crossover Bioequivalence Study Comparing 2 Formulations of AF37702 Injection (Single-Dose and Multidose Vials) Administered Subcutaneously in Healthy Adult Subjects"

Study AFX01-104: "A Phase 1, Randomized, Open-Label, Single-Dose, 2-Period Crossover, Bioavailability Study Comparing 2 Concentrations of AF37702 Injection Single-Dose Vial Formulation (10 mg/mL and

16 mg/mL Concentrations) Administered Subcutaneously in Healthy Adult Subjects"

Study AFX01-105: "A Phase 1, Randomized, Open-Label, Single- Dose, 2-Period Crossover, Bioavailability Study Comparing 2 Concentrations of AF37702 Injection Single-Dose Vial Formulation (2 mg/mL and 10 mg/mL Concentrations) Administered Subcutaneously in Healthy Adult Subjects"

Analytical Site: [redacted] (b) (4)

The inspection of [redacted] (b) (4) did not find any objectionable conditions and no Form FDA 483 was issued.

Conclusions:

DBGC recommends that the data generated from the above four studies be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Young Moon Choi, Ph.D.
Pharmacologist

Final Classification:
NAI - [redacted] (b) (4)

cc:
OSI/DBGC/Salewski/Moreno/Haidar/Choi/Skelly/Dejernett/CF
OCP/DCP5/Moon/Bullock
OND/DHP/Dmytrijuk/Robie-Suh/Scott/Farrell
ORA/Jason Abel
Draft: YMC 12/22/2011
Edit: MFS 12/22/11
DSI: 6268
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FACTS: 1343140

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

/s/

YOUNG M CHOI
12/22/2011

MICHAEL F SKELLY
12/22/2011
Skelly signing on behalf of Dr. Haidar

4.3 QT/IRT REVIEW

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	202799
Generic Name	AF37702 (peginesatide) injection
Sponsor	Affymax Pharmaceuticals, Inc.
Indication	Treatment of anemia associated with chronic renal failure in adult patients on dialysis
Dosage Form	Injection (intravenous or subcutaneous)
Drug Class	Erythropoiesis stimulating agent
Therapeutic Dosing Regimen	AF37702 injection (b) (4)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not defined
Submission Number and Date	SDN 001/ 27 May, 2011
Review Division	DHP / HFD 160

1 SUMMARY

1.1 Overall Summary of Findings

No significant QTc prolongation effect of AF37702 injection was detected in this TQT study. The largest upper bound of the 2-sided 90% CI for the mean differences between AF37702 injection and placebo of ΔΔQTcF was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

This was a Phase 1, single-dose, multi-center, randomized, double-blind, double-dummy, three-period crossover study, 65 healthy subjects received AF37702 injection, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for AF37702 Injection and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	ΔΔQTcF (ms)	90% CI (ms)
AF37702 Injection	0.75	0.2	(-1.6, 1.9)
Moxifloxacin 400 mg*	3	12.3	(10.3, 14.2)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 9.6 ms.

The dose tested was 0.1 mg/kg, however, the label indicates that doses up to approximately (b) (4) can be recommended as a starting dose. Therefore, the current dose proposed (b) (4) does not cover the highest therapeutic exposure. There have been no identified factors that can increase drug exposure and no accumulation

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anticipated since the half life is approximately 24 hours and the drug is given once per month.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

The sponsor proposed the following labeling language.

Section 12.2 Pharmacodynamics:

(b) (4)

2.2 QT-IRT PROPOSED LABEL

We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.

12.2 Pharmacodynamics

Effect on Cardiac Repolarization

The effect of peginesatide 0.1 mg/kg intravenously administered on QTc interval was evaluated in a randomized, double-blind, double-dummy, three-period crossover thorough QT study in 56 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 0.1 mg/kg is adequate to represent the median dose in the phase 3 trials, however is not sufficient to represent the maximum therapeutic dose in the intended patients.

3 BACKGROUND

3.1 PRODUCT INFORMATION

AF37702 Injection is an erythropoiesis stimulating agent (ESA) that is being developed for the treatment of anemia due to chronic kidney disease (b) (4) The drug substance in AF37702 is a synthetic, dimeric peptide that is covalently linked to polyethylene glycol (PEG). AF37702 has a molecular weight of (b) (4)

3.2 MARKET APPROVAL STATUS

AF37702 is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From eCTD 2.6.2

"An in vitro study evaluated the effects of AF37702 on hERG channel current conduction. AF37702 at 0, 1, and 5 μM was incubated with HEK293 cells transfected

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with the hERG potassium channel. Cells were held at -80 mV and AF37702-associated onset and steady state blockade were measured using a pulse pattern with fixed amplitudes (3 cells). The concentration-response curve relationship was characterized and IC50 values calculated. AF37702 minimally but significantly inhibited the hERG current by 6.5% at 1 µM and 7.1% at 5 µM vs. 0.5% in the vehicle control. The IC50 for the inhibitory effect of AF37702 on hERG potassium current could not be determined since inhibition was < 50% at the limit of solubility.

"The positive control (60 nM terfenadine) inhibited hERG potassium current by 77.6%. AF37702 did not cause appreciable inhibition of the hERG potassium current at a concentration (5 µM, 236 µg/mL) approximately 31-fold above the estimated human Cmax value (7.53 µg/mL [0.160 µM] in CRF patients [Section 2.6.6.9]. The latter assumes non-linear kinetics modeled from PK data from 500 subjects dosed between 0.02 to 0.21 mg/kg and an anticipated maximum human dose of 0.35 mg/kg (the maximum dose covering the majority [95%] of subjects in the Phase 3 dialysis clinical trials), suggesting a negligible potential for an in vivo inhibitory effect on cardiac potassium channel conduction.

"Cardiovascular (Hemodynamic) Evaluation of AF37702 in Anesthetized Dogs. This GLP study evaluated potential effects of AF37702 on selected CV parameters when administered to anesthetized, open chested Beagle dogs by IV injection. Pentothal®-anesthetized, male dogs (N = 4) were administered escalating doses of AF37702 at 0 (acetate in saline), 0.2, 2, and 20 mg/kg with a dosing interval of 30 minutes. Baseline values for heart rate; diastolic, systolic, and mean arterial blood pressure; left ventricular pressure (LVP); left ventricular end diastolic pressure (LVEDP); cardiac output (CO); rate of rise of left ventricular pressure (+dP/dt); and Lead II ECG were obtained over a 10 minute predose period and then data were collected for 30 minutes after each dose (5 seconds each minute).

"There were no apparent AF37702-related effects on blood pressure, heart rate, LVP, +dP/dt, CO, or LVEDP. The occasional significant changes observed in the CV parameters were not considered test article-related because of the sporadic nature of the effects, the absence of a dose-dependent effect, and/or comparable changes following administration of vehicle.

"In conclusion, the IV administration of AF37702 at doses up to 20 mg/kg was not associated with adverse changes in CV parameters in the anesthetized dog relative to the vehicle. However, treatment with AF37702 was not associated with any hematologic effects in dogs.

"Safety Pharmacology Studies of AF37702: Effects on the Cardiovascular System in Anesthetized Dogs. The study, conducted by Takeda Pharmaceutical Company to fulfill Japanese regulatory requirements, evaluated the potential effects of AF37702 on CV parameters in dogs. Anesthetized male Beagle dogs (N = 4) were administered ascending doses of AF37702 at 0 (vehicle control: 10 mM acetic acid in isotonic saline), 0.2, 2, and 20 mg/kg by slow IV bolus over 1 minute at 35-minute intervals. Endpoints included systolic, diastolic, and mean blood pressures; heart rate; Lead II ECG evaluation including measurement of PR interval, QRS duration, QT, and QTc intervals (Fridericia's formula). These parameters were determined 5 minutes before termination of dosing with

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the vehicle and immediately (0), 5, 15, and 30 minutes after termination of each dose of AF37702. The percent change from the baseline values (values at 5 minutes before administration) was calculated for all parameters at all time points in each animal, and the mean percent change at each dose level of AF37702 was compared to that of the vehicle.

"There were no statistically significant differences in any parameter at any time point following administration of AF37702 compared to the vehicle. The occasional significant changes observed in the CV parameters were not considered test article-related because of the sporadic nature of the effects, the absence of a dose-dependent effect, and/or comparable changes following administration of vehicle."

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

"In the Overall Safety Population, 2,383 subjects received AF37702 Injection for a total of 2,733 patient exposure years (PEY) with an average PEY per subject of 1.15, providing an adequate database to assess the safety and efficacy profile of AF37702 Injection. The overall exposure in dialysis subjects was consistent with ICH guidelines for the evaluation of safety and efficacy of a new drug. Within the Overall Safety Population, 1,519 Phase 2 and Phase 3 dialysis subjects received at least one dose of AF37702 Injection, and within the Phase 3 Dialysis Population alone, 1,066 subjects received AF37702 Injection for average PEY per subject of 1.16 and average patient follow-up years (PFY) per subject of 1.24.

"The overall incidence of TEAEs of Special Interest in the Phase 3 Dialysis and Non-Dialysis subpopulations is presented in Table 2.

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Table 2: Treatment-Emergent AEs of Special Interest, Phase 3 Dialysis and Non-Dialysis Populations

	Phase 3 Dialysis Population		Phase 3 Non-Dialysis Population	
TEAE Incidence	AF37702 Injection (N=1066)	Epoetin (N=542)	AF37702 Injection (N=656)	Darbepoetin (N=327)
Grouping of Cerebrovascular and Cardiovascular Events				
Cerebrovascular disorders	45 (4.2%)	40 (7.4%)	27 (4.1%)	12 (3.7%)
CNS Hemorrhages and Cerebrovascular Conditions	45 (4.2%)	40 (7.4%)	27 (4.1%)	12 (3.7%)
Hemorrhagic Cerebrovascular Conditions	24 (2.3%)	20 (3.7%)	7 (1.1%)	3 (0.9%)
Ischemic Cerebrovascular Conditions	36 (3.4%)	32 (5.9%)	25 (3.8%)	8 (2.4%)
Other CNS Hemorrhages and Cerebrovascular Accidents	10 (0.9%)	4 (0.7%)	4 (0.6%)	1 (0.3%)
Other Cerebrovascular Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac Failure	229 (21.5%)	116 (21.4%)	215 (32.8%)	92 (28.1%)
Cardiac Arrhythmias	210 (19.7%)	123 (22.7%)	104 (15.9%)	43 (13.1%)
Torsade de Pointes/QT Prolongation	87 (8.2%)	60 (11.1%)	39 (5.9%)	16 (4.9%)
Ischemic Heart Disease	118 (11.1%)	67 (12.4%)	70 (10.7%)	30 (9.2%)
Myocardial Infarction	57 (5.3%)	37(6.8%)	37 (5.6%)	13 (4.0%)
Other Ischemic Heart Disease	77 (7.2%)	43 (7.9%)	43 (6.6%)	22 (6.7%)
All Thromboembolic Events**				
Arterial Thromboembolic Events	71 (6.7%)	48 (8.9%)	39 (5.9%)	16 (4.9%)
Grouping of Potential Class Effects Described by Approved ESAs				
Hypertension***	208 (19.5%)	101(18.6%)	126 (19.2%)	65 (19.9%)
Malignant Hypertension Related AEs*	37 (3.5%)	22 (4.1%)	17 (2.6%)	6 (1.8%)
All Thromboembolic Events**				
Venous Thromboembolic Events	21 (2.0%)	9 (1.7%)	14 (2.1%)	6 (1.8%)
Other Thromboembolic Events	231 (21.7%)	135 (24.9%)	26 (4.0%)	8 (2.4%)
Vascular Access Complications*	193 (18.1%)	107 (19.7%)	11 (1.7%)	6 (1.8%)
Convulsions	23 (2.2%)	11 (2.0%)	8 (1.2%)	1 (0.3%)
Infusion/Injection Related Reactions*	32 (3.0%)	11(2.0%)	13 (2.0%)	4 (1.2%)
Gastrointestinal Hemorrhage	71 (6.7%)	47 (8.7%)	42 (6.4%)	18 (5.5%)
Malignancy***	41 (3.8%)	23 (4.2%)	31 (4.7%)	14 (4.3%)

* Sponsor-defined subgroup

** Note that the all thromboembolic events category is not summarized because arterial thomboembolic events is grouped separately from venous and other thromboembolic events.

*** Hypertension and malignancy SMQs are described in Sections 2.7.4.12.2 and 2.7.4.12.6, respectively.

Source: ISS Tables 4.12.2, 4.48.2, 4.49.2, 4.50.2

Source: ISS, Table 14

"In the Phase 3 studies, deaths that occurred through 28 days after termination from study (i.e., On-Study Deaths) were submitted to the ERC for adjudication of date and primary cause of death. ERC-adjudicated causes of death by study population are displayed in Table 25. The ERC criteria for sudden death were (1) non-traumatic, unexpected death either within one hour from the onset of symptoms or (2) unwitnessed death (ERC Charter). The ERC criteria for unknown primary cause of death was that the death did not meet ERC criteria for any of the following:

• Death due to a CSE component (other than the component of death itself)

• Sudden death

• Death due to other identifiable cause"

Table 3: Primary Cause of Death as Adjudicated by the ERC

ERC-Adjudicated Deaths and Primary Cause	Dialysis		Non-Dialysis	
	AF37702 Inj. (n=1066)	Epoetin (n=542)	AF37702 Inj. (n=656)	darbepoetin (n=327)
Deaths (On-Study)	115 (10.8%)	64 (11.8%)	58 (8.8%)	22 (6.7%)
Primary Cause of Death as Adjudicated by the ERC				
Cardiovascular and Unknown Causes	72 (6.8%)	40 (7.4%)	38 (5.8%)	10 (3.1%)
Sudden Death	26 (2.4%)	12 (2.2%)	14 (2.1%)	1 (0.3%)
Cardiovascular (CSE + Other CV Cause)	31 (2.9%)	14 (2.6%)	8 (1.2%)	5 (1.5%)
Unknown Primary Cause	15 (1.4%)	14 (2.6%)	16 (2.4%)	4 (1.2%)
Other Non-Cardiovascular Cause	43 (4.0%)	24 (4.4%)	20 (3.0%)	12 (3.7%)

The ERC adjudicated the primary cause of death for deaths that occurred through 28 days after termination from study (i.e., for On-Study Deaths).
Source: CSE Table 5.2.13

Source: ISS, Table 25

Reviewer's comments: In the Phase 3 Dialysis and non-Dialysis Population there was a similar frequency between AF37702 Injection and Epoetin for events of Torsade de Pointes/ QT prolongation, convulsions and cardiac arrhythmias.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of AF37702 injection's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 102846. The sponsor submitted the study report AF37702 injection-A001-013 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase 1, Multi-Center, Randomized, Double-Blind, Double-Dummy, Placebo and Positive Controlled Crossover Study to Evaluate the Effects of Intravenous AF37702 Injection on QTc Intervals in Healthy Adults

4.2.2 Protocol Number

AF37702 injection-A001-013

4.2.3 Study Dates

First subject enrolled: 28 April 2009
Last subject completed: 20 August 2009

Reference ID: 3084101

4.2.4 Objectives

Primary objective: to evaluate the effects of a single 0.1 mg/kg intravenous (IV) dose of AF37702 injection compared to AF37702 injection placebo (normal saline) on the QT interval in healthy male and female subjects.

Secondary objectives

- To evaluate the pharmacokinetics (PK) of AF37702 injection in healthy subjects when it is administered as a single IV dose in the fasted state, and correlate as indicated with corrected QT (QTc) interval assessments.
- To provide additional safety information on AF37702 injection.

4.2.5 Study Description

4.2.5.1 Design

This study was a Phase 1, single-dose, multi-center, randomized, double-blind, double-dummy, placebo and positive controlled (moxifloxacin), three-period crossover study. The study periods were as follows:

- Pretreatment Period, including the Screening Period (Day –21 through Check-in on Day –1 of Period 1);
- Treatment Period (three 3-day confinement periods that each included a single dose of study medication on Study Days 1, 17, and 33, with PK samples drawn at intervals for 22 hours after each dose), and
- Follow-up Period consisting of four follow-up visits after the last dose of study drug (Study Days 40, 47, 54, and 61).

Subjects were confined at the study site for 3 days in each of the three treatment periods from the day prior to each dose. There was a washout interval of 14 days between the dose in one period and the dose in the subsequent period.

Each subject received a single dose of each of the three regimens given on Study Day 1 (Period 1), Study Day 17 (Period 2), and Study Day 33 (Period 3). A washout interval of at least 14 days separated the dose in one period and the dose in the subsequent period.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

AF37702 injection and moxifloxacin treatments were double-blinded.

4.2.5.4 Treatment Arms

Subjects were randomized in a ratio of 1:1:1:1:1:1 to six regimen sequence groups (ABC, BCA, CAB, ACB, BAC, CBA) where each subject received one of the following regimens in each of the three treatment periods:

- Regimen A (placebo): AF37702 injection placebo and moxifloxacin placebo.
- Regimen B (AF37702 injection): AF37702 injection and moxifloxacin placebo.
- Regimen C (moxifloxacin): AF37702 injection placebo and moxifloxacin.

Reference ID: 3084101

4.2.5.5 Sponsor's Justification for Doses

"For safety reasons, a dose of 0.1 mg/kg was selected for the current study in healthy subjects. The median doses at 6 months of treatment used in subjects with CRF ranged from 0.03 mg/kg every 4 weeks in subjects not on dialysis (range: 0.02 to 0.1 mg/kg) to approximately 0.09 mg/kg every 4 weeks in subjects on hemodialysis (range: 0.02 to 0.5 mg/kg). The 0.1 mg/kg dose of AF37702 Injection was approximately three times the median dose used in subjects not on dialysis (CKD Stage 3 and 4) to maintain Hgb within target for correction of anemia and slightly above the median dose used in subjects on hemodialysis. Although a dose of 0.1 mg/kg in healthy subjects did not represent a significant multiple of the upper therapeutic dose of AF37702 Injection that was administered to anemic subjects with CRF, a study in normal healthy volunteers was thought to be more informative with respect to a controlled evaluation on the QTc interval because of the high prevalence of underlying cardiac disease and cardiac arrhythmia in subjects with CRF. In addition, a dose of 0.1 mg/kg was determined to be the highest dose that could be safely administered to nonanemic healthy subjects for which there was an acceptable risk profile.

"The PD effect of AF37702 Injection is similar to other drugs in the ESA class, and results in dose-dependent increases in Hgb levels. In a Phase 1 study, AFX01-0401, conducted in healthy subjects, the PK and PD data indicated a dose dependent response; the 0.1 mg/kg dose was associated with a clinically and statistically significant increase in Hgb from baseline, with a 1.14±0.6 g/dL increase in Hgb within 12 days and an average maximum increase from baseline of 1.36±0.39 g/dL (range 0.7–1.9, N=10). Additionally, in the AFX01-0401 study, several of the prespecified dose-escalation stopping criteria for Hgb levels were achieved in the two cohorts at the dose of 0.1 mg/kg of AF37702 Injection. These criteria were: any subject with an increase in Hgb of =1.5 g/dL above baseline; at least three treated subjects in a cohort with an increase in Hgb of =1.0 g/dL above baseline; and more than one subject in a cohort with a =1.0 g/dL increase of Hgb over any 2-week period after administration of study drug. The study was terminated after the two cohorts at this dose level were enrolled. Therefore, the rate of Hgb rise in healthy subjects at the 0.1 mg/kg dose level exceeds the typical threshold for withholding further ESA dosing in CRF patients, but does not pose an excessive safety risk as additional doses of AF37702 Injection were not given since this study was of a single-dose, crossover design.

"In summary, the selection of a 0.1 mg/kg dose was based on minimizing the risk to research subjects of either an excessive absolute Hgb level (>18 g/dL), or an excessive rate of rise of Hgb (>1 g/dL over 2 weeks), either of which could increase the potential for cardiovascular events such as hypertension and thrombotic events. Utilizing a dose higher than 0.1 mg/kg would have placed research subjects at a higher risk of these adverse effects and could have increased the need to phlebotomize in order to maintain Hgb at a safe level. A therapeutic phlebotomy would have been considered in the event that a subject's Hgb level was increased to >17 g/dL. Accordingly, the selected dose of

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0.1 mg/kg represented the highest dose that could be studied in healthy subjects consistent with a reasonable benefit-risk profile."

(Source: Clinical Study Report, P-52-54, Section 9.4.4)

Reviewer's Comment:
The dose tested was 0.1 mg/kg, however, the label indicates that doses up to approximately (b) (4) *can be recommended as a starting dose. Therefore, the current dose proposed* (b) (4) *does not cover the highest therapeutic exposure. There have been no identified factors that can increase drug exposure and no accumulation anticipated since the half life is approximately 24 hours and the drug is given once per month.*

4.2.5.6 Instructions with Regard to Meals

"On Day 1 of each period, a standard-fat light lunch was served at approximately 4.25 hours post- IV dosing. The 4-hour PK blood draw was to be completed within 5 minutes so that the meal started soon thereafter and had no effect on the QT interval. Lunch was to be completed within 30 minutes to allow 10 minutes before the next ECG measurement at 5 hours post-dose. A standard-fat light dinner was served at approximately 10.5 hours post-dose and was to be completed in 30 minutes to allow for 1 hour before the next ECG time point at 12 hours post-dose. An evening snack was served approximately 13 hours post-dose.

"On Day 1 of each period (Study Days 1, 17, and 33), identical meals (in content and portion), including snacks, were served. All meals for the study subject cohorts were identical. Foods high in fiber or those known to have a laxative effect were avoided. Total daily caloric content of meals were approximately 2000 kcal and were not allowed to exceed 2500 kcal.

"The study centers provided a study menu prior to the start of the study for Sponsor review and approval.

"No solid food was allowed after midnight prior to the dosing days. No breakfast was served on dosing days. All subjects could consume water ad libitum except for 1 hour prior to IV dosing and 2 hours thereafter."

(Source: Clinical Study Report, P-29, Section 9.1.3.3)

Reviewer's Comment: Not applicable. AF37702 *was administered intravenously in the study.*

4.2.5.7 ECG and PK Assessments

ECGs (baseline) extracted from Holter recordings in triplicate pre–AF37702 injection dose (–1 hour, –30 minutes, and –15 minutes) on the day of dosing for each treatment period. The continuous Holter ECG data from extraction windows were used by the core ECG laboratory to acquire ECGs for QT analysis. These critical observation periods preceded the nominal times of PK blood sample collections (i.e., 15 minutes pre-dose, and 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 10, and 22 hours post–AF37702 injection).

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On Study Days 1, 17, and 33, one 4 mL blood PK sample for determination of AF37702 concentration in plasma was collected at pre-dose (within –1 hour) and 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 10, and 22 hours post–AF37702 injection. For determination of moxifloxacin plasma concentrations, one 2 mL blood sample was taken immediately after the AF37702 sample collection at 1 (prior to moxifloxacin dose), 2, 3, 4, 5, 6,7, 10, and 22 hours post–AF37702 injection. The samples collected from the treatment period when subjects were administered placebo dose were collected to maintain the blind. However, the samples were not assayed. PK samples were collected following ECG collection.

Reviewer's Comment: The PK and ECG assessments are adequate to capture the QT at peak concentrations of AF37702 injection (T_{max} = 0.8 hours) and potential delayed effect up to 22 hours post-dose.

4.2.5.8 Baseline

The sponsor used the average of pre-dose at the -1, -0.5, and -0.25 h time points on Day 1 as the QTc baseline values.

4.2.6 ECG Collection

GE Medical Systems ApexPro Multi-Lead Frequency Hopping Telemetry System ([redacted] (b) (4) and Viridia Telemetry System (Model M2609A) [redacted] (b) (4) were used for (a) monitoring rhythm and other ECG characteristics from approximately 10 hours prior to dosing through to approximately 1.5 hours post–AF37702 Injection or placebo dose injection in each period, for enrollment qualification purposes and safety monitoring, and (b) monitoring of signal quality to allow active intervention to correct signal quality problems as they arose.

Holter recordings were obtained using a 12-lead Holter recorder (Mortara H12 Plus; Mortara Instruments, Milwaukee, Wisconsin, USA), provided by the ECG core laboratory. The recordings were done with a sampling frequency of 1000 Hz and stored on data flashcards. The flashcards were couriered to the central cardiac core laboratory at the end of each Holter session (i.e., Day 2 of each treatment period).

The central cardiac core laboratory provided the sites with identical H-12+ continuous 12-lead Holter recorders (Mortara Instruments, Milwaukee, Wisconsin, United States), flash memory cards (flashcards), and all supplies.

Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

A total of 66 subjects were planned to be enrolled. More subjects than expected failed to meet the study entry criteria at Day –1 of Period 1. As a result, 65 instead of 66 subjects were enrolled. Subjects had a mean age of 35.6 years (range 19–50 years) with 19 men (29.2%) and 46 women (70.8%) enrolled. A total of 61 subjects completed all 3 dosing regimens. Four subjects prematurely discontinued from the study drug. As a result, 62 subjects received Regimen A, 64 subjects received Regimen B, and 62 subjects received

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Regimen C in this crossover study. The study was conducted at two study centers. A summary of demographic and baseline characteristics is in Table 4.

Table 4: Summary of Demographic and Baseline Characteristics of Enrolled Subjects

Characteristic	Overall (N=65)
Gender, n (%)	
Male	19 (29.2)
Female	46 (70.8)
Mean age (min-max) (yr)	35.6 (19–50)
Ethnicity, n (%)	
Hispanic or Latino	29 (44.6)
Race, n (%)	
American Indian or Alaska Native	1 (1.5)
Asian	4 (6.2)
Black or African American	13 (20.0)
White	46 (70.8)
Multiracial[a]	1 (1.5)
Mean weight (SD) (kg)	70.0 (11.7)
Mean height (SD) (cm)	164.8 (9.1)
Mean BMI (SD) (kg/m^2)	25.7 (2.9)

[a] Subjects who belong to multiple racial categories; if a subject's case report form had more than one race checked, that subject was summarized only with multiracial.
N = number of subjects, n = number of subjects in subgroup.
Source: Table 14.1.6.

Source: CSR. Table 6

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary endpoint was the largest time-matched baseline-adjusted mean difference between AF37702 injection and placebo in QTcF. The sponsor used mixed model including treatment, time, and treatment-by-time interaction. The results are presented in Table 5. The upper limit of the 2-sided 90% CI for AF37702 injection was below 10 ms.

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Table 5: Sponsor's results for ΔΔQTcF for AF37702 Injection 0.1 kg/mg and Moxifloxacin 400 mg

	AFX37702 0.1 kg/mg vs. Placebo		Moxifloxacin 400 mg vs. Placebo		
Scheduled Time	Difference (msec)(a)	Upper Bound of 95% One-Sided C.I.(b)	Difference (msec)(a)	Lower Bound of 95% One-Sided C.I.(b)(c)	Upper Bound of 95% One-Sided C.I.(b)
ECG Parameter: QTcF (msec)					
0.25 Hr	0.63	2.06	0.34	-1.11	1.79
0.5 Hr	0.10	1.64	-0.35	-1.91	1.22
0.75 Hr	0.54	2.19 #	-0.27	-1.93	1.39
1 Hr	-1.15	0.51	-0.19	-1.88	1.49
2 Hr	-1.33	0.71	6.87	4.05	8.93
3 Hr	-1.20	0.60	12.32	9.85 $	14.13 #
4 Hr	-2.55	-0.47	12.03	9.16 $	14.13
5 Hr	-1.71	0.82	11.28	7.79 $	13.83
6 Hr	-1.07	1.48	10.10	7.54	12.67
7 Hr	-1.69	0.93	9.39	6.74	12.04
10 Hr	-1.71	0.51	11.00	8.75	13.25
22 Hr	-1.64	0.63	6.57	4.28	8.86

(a) Difference in the least-square means of the change from baseline, from the linear mixed effect model with repeated measurements.
(b) The 95% one-sided confidence interval is for the difference in the least-square means of the change from baseline. No upper bound was adjusted for multiple comparisons.
(c) For 2, 3, 4 and 5 hours postdose, Bonferroni adjusted lower bounds were presented. For other time points, unadjusted lower bounds were presented.
(#) The maximum of the upper bound of the 95% one-sided confidence interval over all the time points.
($) The lower bound of the 95% one-sided confidence interval are greater than 5 msec and within 2,3,4,5 hour postdose.

Source: Sponsor's CSR Table 14.2.1.2 on page 32/597

4.2.7.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze ΔQTcF effect for moxifloxacin. The results are presented in Table 5. The lower limit of the two-sided 90% CI for each placebo-corrected, change-from-baseline LS mean QTcF value was above 5 ms threshold, which demonstrate assay sensitivity.

Reviewer's Comments: We will provide our independent analysis result in Section 5.2.

4.2.7.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc>450 ms, >480 ms, and >500 ms, and changes from baseline QTc >30 ms and >60 ms. No subject's absolute QTc >480 ms and ΔQTc >60 ms.

4.2.7.3 Safety Analysis

The number of subjects experiencing at least 1 TEAE was comparable between Regimen A (placebo), 18 (29.0%) and Regimen B (AF37702 Injection), 20 (31.3%) (Table 14). All of these TEAEs were of Grade 1 or Grade 2 in intensity except for 1 subject after receiving Regimen A.

Subject 0002/416 experienced severe headache (Grade 3) after receiving placebo on Study Day 1. The event was considered related to the study drug and the subject recovered the next day.

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For Regimen A, the most common drug-related AE was headache, reported by 5 subjects (8.1%). All other drug-related AEs during this regimen were reported by no more than 1 subject. For Regimen B, TEAEs considered related to study drug were headache (8 subjects, 12.5%) and dizziness (2 subjects, 3.1%). There are no other drug-related AEs during this regimen.

All but two TEAEs resolved during the study for Regimen B. Subject 0002/439 experienced a left arm pain and a mild left arm paraesthesia after receiving Regimen B (AF37702 Injection) in Period 2, which did not resolve during the study and were considered not related to study drug.

Four subjects prematurely discontinued the study drug (Table 6)

Table 6: Summary of Discontinuations of Study Subjects

Subject Number	Age/Gender/ Race	Study Day of Final Visit	Study Day of Last Dose of Study Drug	Regimens Received	Reason for Discontinuation
0002/235	22/F/White	36	17	B and A	TEAE/(sinus arrhythmia telemetry)
0002/281	34/F/White	20	1	B	TEAE/(elevated serum CK)
0002/290	26/F/White	20	1	C	Voluntary withdrawal
0002/408	27/F/White	41	17	B and A	Positive alcohol test at Check-in for Period 3

Regimen A: AF37702 Injection Placebo and Moxifloxacin Placebo (placebo).
Regimen B: AF37702 Injection and Moxifloxacin Placebo (AF37702 Injection).
Regimen C: AF37702 Injection Placebo and Moxifloxacin (moxifloxacin).
Source: Table: 14.3.2.1, Appendices 16.2.1.2.1, 16.2.1.2.2, and 16.2.4.1.1.

Source: CSR, Table 5.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 7 (AF37702 injection) and Table 8 (moxifloxacin). The mean concentration-time profiles are illustrated in Figure 1 (AF37702 injection) and Figure 2 (moxifloxacin).

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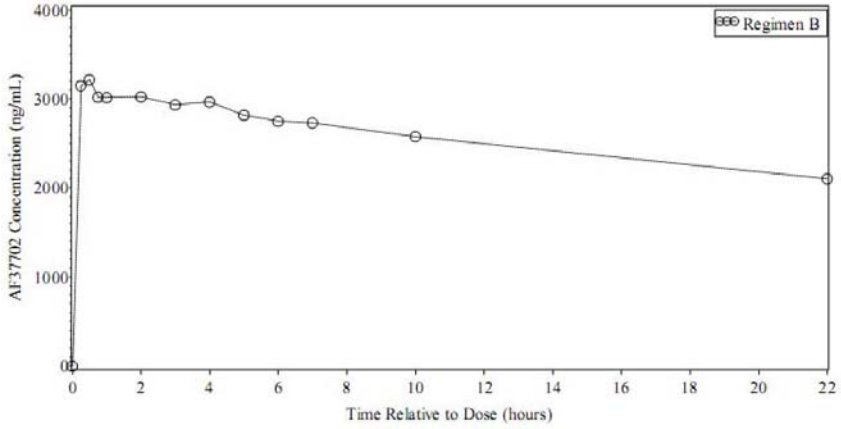
Table 7: Pharmacokinetic Parameters after Administration Regimen B (0.1 mg/kg AF37702 Injection; Pharmacokinetic Analysis Set, N=65)

	Tmax	Cmax	Cmax/Dose	AUC(0-tlqc)	AUC(0-tlqc)/Dose	T1/2
	(hr)	(ng/mL)	(g/mL)	(ng·hr/mL)	(g·hr/mL)	(hr)
n	64	64	64	64	64	57
Mean	0.8	3334	33.33	55619	556	41
SD	1.25	509.1	5.071	9373.3	93.7	10.0
Min	0.3	1998	20.11	33254	335	14
Median	0.5	3300	33.12	55097	550	40
Max	7.0	4835	48.41	79278	794	63
CV%	164	15	15	17	17	24

CV% = percent coefficient of variation, n = number of subjects.
Source: Table 14.2.12.1.

(Source: Clinical Study Report P-96, Table 12)

Figure 1: Mean AF37702 Concentration in Plasma Over Time (Pharmacokinetic Analysis Set, N=65)



Source: Figure 14.2.13.1.

(Source: Clinical Study Report P-95, Figure 6)

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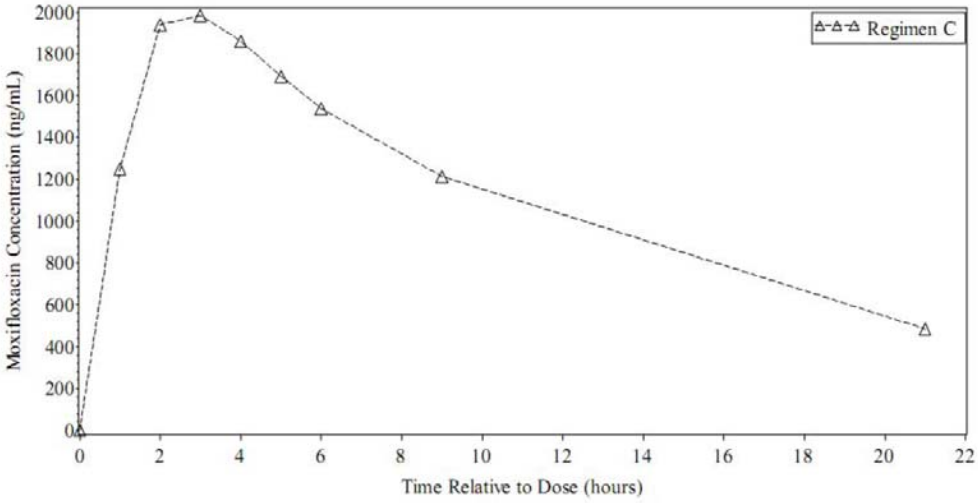
Table 8: PK Parameters after Administration of Regimen C (400 mg Moxifloxacin; Pharmacokinetic Analysis Set, N=65)

	Tmax	Cmax	AUC(0-tlqc)	AUC(0-inf)	T1/2
	(hr)	(ng/mL)	(ng·hr/mL)	(ng·hr/mL)	(hr)
n	61	61	61	21	61
Mean	2.4	2270	23465	29690	9.4
SD	0.98	500.43	4298.0	3697.6	1.78
Min	0.9	1280	12628	23310	5.4
Median	2.0	2280	23915	29450	9.2
Max	5.0	3280	32127	38167	13.0
CV%[a]	41	22	18	12	19

[a] CV(%)=(SD/Mean)×100.
CV% = percent coefficient of variation, n = number of subjects.
Source: Table 14.2.12.2.

(Source: Clinical Study Report P-98, Table 13)

Figure 2: Mean Moxifloxacin Concentrations in Plasma Over Time (Pharmacokinetic Analysis Set, N=65)



Source: Figure 14.2.14.1

(Source: Clinical Study Report P-97, Figure 7)

4.2.7.4.2 Exposure-Response Analysis

The sponsor states that no correlation between ΔQTcF vs. concentration of AF37702 injection was observed.

Reviewer's Comment: A plot of ΔΔQTc vs. drug concentrations is presented in Figure 5.

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5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 9, it appears that QTcF is better than QTcI. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is also consistent with the sponsor's choice of QTcF for their primary analysis.

Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
AF37702 Injection	64	0.0035	64	0.0024	64	0.0066
Moxifloxacin 400 mg	62	0.0105	62	0.0023	62	0.0037
Placebo	62	0.0046	62	0.0024	62	0.0063
All	65	0.0042	65	0.0012	65	0.0043

The QT-RR interval relationship is presented Figure 3 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

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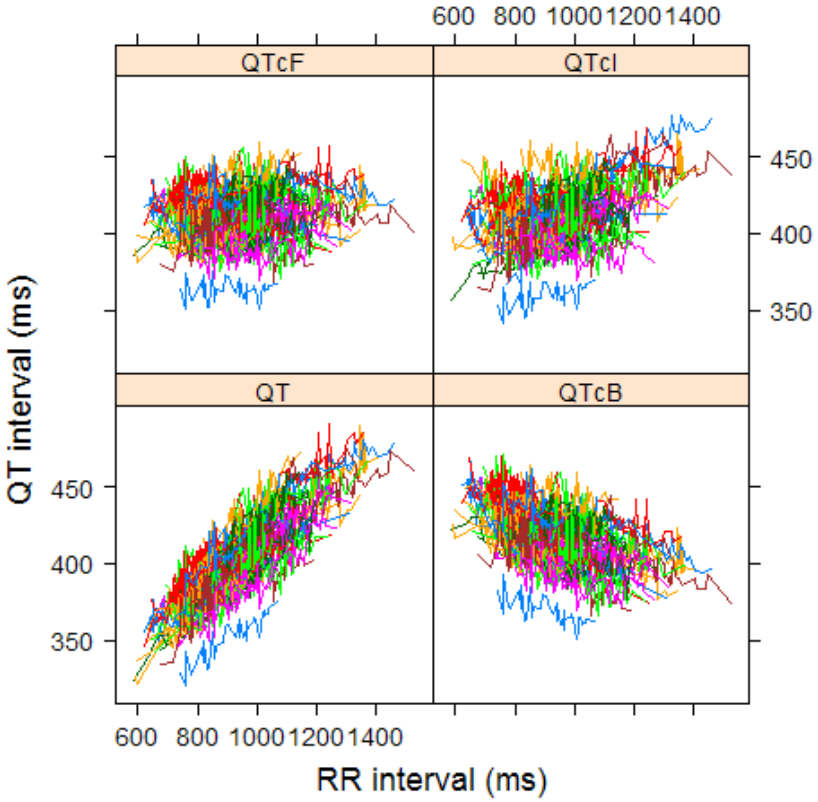
Figure 3: QT, QTcB, QTcI, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 10. The largest upper bound of the 2-sided 90% CI for the mean difference between AF37702 injection and placebo is 1.9 ms.

Reference ID: 3084101

Table 10: Analysis Results of ΔQTcF and ΔΔQTcF for AF37702 Injection and Moxifloxacin 400 mg

		Treatment Group								
		AF37702 Injection				Moxifloxacin 400 mg				
	Placebo	ΔQTc		ΔΔQTc		ΔQTc		ΔΔQTc		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj.* 90% CI
0.25	-1.6	64	-1.0	0.5	(-1.0, 2.1)	63	-1.3	0.2	(-1.3, 1.8)	(-1.9, 2.3)
0.5	-1.2	64	-1.4	-0.1	(-1.8, 1.5)	63	-1.7	-0.5	(-2.2, 1.2)	(-2.8, 1.8)
0.75	-2.8	63	-2.6	0.2	(-1.6, 1.9)	63	-3.2	-0.3	(-2.1, 1.4)	(-2.7, 2.0)
1	-1.7	64	-3.0	-1.3	(-3.1, 0.5)	62	-1.8	-0.2	(-1.9, 1.6)	(-2.6, 2.3)
2	-2.3	64	-3.7	-1.4	(-3.5, 0.7)	62	4.8	7.1	(5.0, 9.2)	(4.2, 10.0)
3	-3.8	64	-5.3	-1.5	(-3.4, 0.4)	63	8.4	12.3	(10.3, 14.2)	(9.6, 14.9)
4	-1.8	64	-4.3	-2.5	(-4.6, -0.3)	63	10.2	12.0	(9.9, 14.2)	(9.1, 15.0)
5	-5.8	64	-7.4	-1.6	(-4.0, 0.8)	63	5.6	11.4	(9.0, 13.8)	(8.1, 14.7)
6	-9.9	63	-10.9	-1.0	(-3.4, 1.4)	63	0.3	10.2	(7.8, 12.6)	(6.9, 13.5)
7	-11.3	64	-12.9	-1.6	(-4.1, 0.9)	63	-1.7	9.6	(7.0, 12.1)	(6.1, 13.0)
10	-7.4	64	-9.2	-1.8	(-4.0, 0.4)	63	3.7	11.0	(8.8, 13.2)	(8.0, 14.0)
22	-3.4	64	-5.0	-1.6	(-3.9, 0.7)	63	3.3	6.7	(4.4, 9.0)	(3.6, 9.9)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

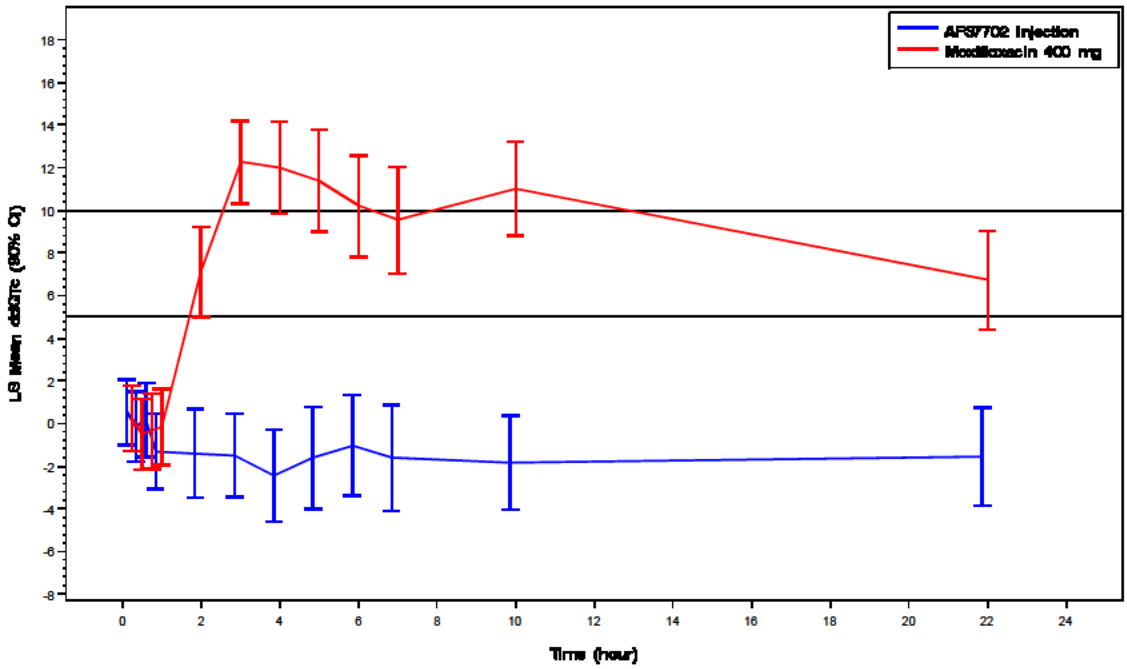
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 10. The largest unadjusted 90% lower confidence interval is 10.3 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 9.6 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of ΔΔQTcF Over Time

Figure 4 displays the time profile of ΔΔQTcF for AF37702 injection and moxifloxacin 400 mg.

Figure 4: Mean and 90% CI ΔΔQTcF Time Course for AF37702 Injection and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcF values are ≤450 ms and between 450 ms and 480 ms. No subject's QTcF is above 480 ms. No subject's change from baseline is above 30 ms.

Table 11: Categorical Analysis for QTcF

	Total N	Value<=450 ms	450 ms<Value<=480 ms
AF37702 Injection	64	64 (100%)	0 (0.0%)
Moxifloxacin 400 mg	62	57 (91.9%)	5 (8.1%)
Placebo	62	61 (98.4%)	1 (1.6%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR interval. The point estimates and the 90% CI are presented in Table 12. The largest upper bound of the 2-sided 90% CI for the mean differences between AF37702 injection and placebo is 4.7 bpm. Table 13 presents the categorical analysis of HR. No subject who experienced HR interval greater than 100 bpm was in AF37702 treatment group.

Reference ID: 3084101

Table 12: Analysis Results of ΔHR and ΔΔHR for AF37702 Injection and Moxifloxacin 400 mg

		Treatment Group							
		AF37702 Injection				Moxifloxacin 400 mg			
	Placebo	ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.25	1.0	64	1.2	0.2	(-0.9, 1.4)	63	1.5	0.5	(-0.7, 1.6)
0.5	1.2	64	1.3	0.1	(-1.1, 1.2)	63	1.2	0.0	(-1.2, 1.2)
0.75	1.3	63	1.3	-0.0	(-1.2, 1.2)	63	2.5	1.2	(-0.0, 2.4)
1	2.5	64	2.1	-0.4	(-1.6, 0.7)	62	2.6	0.1	(-1.1, 1.2)
2	0.8	64	3.2	2.4	(1.0, 3.8)	62	3.2	2.5	(1.0, 3.9)
3	0.8	64	2.6	1.8	(0.4, 3.3)	63	3.0	2.2	(0.7, 3.6)
4	1.8	64	3.8	2.1	(0.7, 3.5)	63	3.6	1.9	(0.4, 3.3)
5	8.3	64	10.6	2.3	(0.3, 4.2)	63	9.5	1.1	(-0.8, 3.1)
6	9.3	63	10.9	1.6	(-0.3, 3.6)	63	11.3	2.0	(0.1, 3.9)
7	7.8	64	10.8	2.9	(1.1, 4.7)	63	10.2	2.4	(0.6, 4.2)
10	4.5	64	7.5	3.0	(1.4, 4.7)	63	6.3	1.9	(0.3, 3.5)
22	2.0	64	4.6	2.6	(1.2, 4.0)	63	3.4	1.4	(-0.0, 2.8)

Table 13: Categorical Analysis of HR

	Total N	HR < 100 bpm	HR >=100 bpm
AF37702 Injection	64	64 (100%)	0 (0.0%)
Moxifloxacin 400 mg	62	60 (96.8%)	2 (3.2%)
Placebo	62	61 (98.4%)	1 (1.6%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% CI are presented in the following table. The largest upper bound of the 2-sided 90% CI for the mean difference between AF37702 injection and placebo is 3.2 ms. No subject who experienced PR interval greater than 200 ms was in AF37702 injection group.

Table 14: Analysis Results of ΔPR and ΔΔPR for AF37702 Injection and Moxifloxacin 400 mg

		Treatment Group							
		AF37702 Injection				Moxifloxacin 400 mg			
	Placebo	ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.25	-0.8	64	0.7	1.5	(-0.1, 3.1)	63	-0.5	0.4	(-1.3, 2.0)
0.5	0.5	64	0.2	-0.3	(-2.1, 1.4)	63	-0.5	-1.0	(-2.7, 0.7)
0.75	-0.0	63	0.2	0.2	(-1.7, 2.1)	63	0.6	0.7	(-1.2, 2.6)
1	0.2	64	-0.4	-0.6	(-2.4, 1.2)	62	-0.9	-1.0	(-2.8, 0.7)
2	-0.8	64	0.4	1.2	(-0.8, 3.2)	62	-1.7	-0.9	(-2.9, 1.2)
3	-1.0	64	-0.7	0.3	(-1.7, 2.3)	63	-1.4	-0.4	(-2.4, 1.6)
4	-1.9	64	-1.5	0.3	(-1.5, 2.2)	63	-3.6	-1.7	(-3.6, 0.1)
5	-1.4	64	-2.1	-0.7	(-3.0, 1.5)	63	-5.6	-4.2	(-6.4, -1.9)
6	-3.5	63	-4.0	-0.6	(-2.7, 1.6)	63	-7.3	-3.9	(-6.0, -1.7)
7	-5.6	64	-6.5	-1.0	(-3.2, 1.3)	63	-8.6	-3.1	(-5.4, -0.8)
10	-3.0	64	-5.5	-2.5	(-4.5, -0.6)	63	-6.0	-3.0	(-5.0, -1.1)
22	0.3	64	-0.9	-1.2	(-3.1, 0.7)	63	-0.6	-0.9	(-2.8, 1.0)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% CIs are presented in Table 15. The largest upper bound of the 2-sided 90% CI for the mean differences between AF37702 injection placebo is 0.7 ms. No subject who experienced QRS interval greater than 200 ms was in AF37702 injection group.

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Table 15: Analysis Results of ΔQRS and ΔΔQRS for AF37702 Injection and Moxifloxacin 400 mg

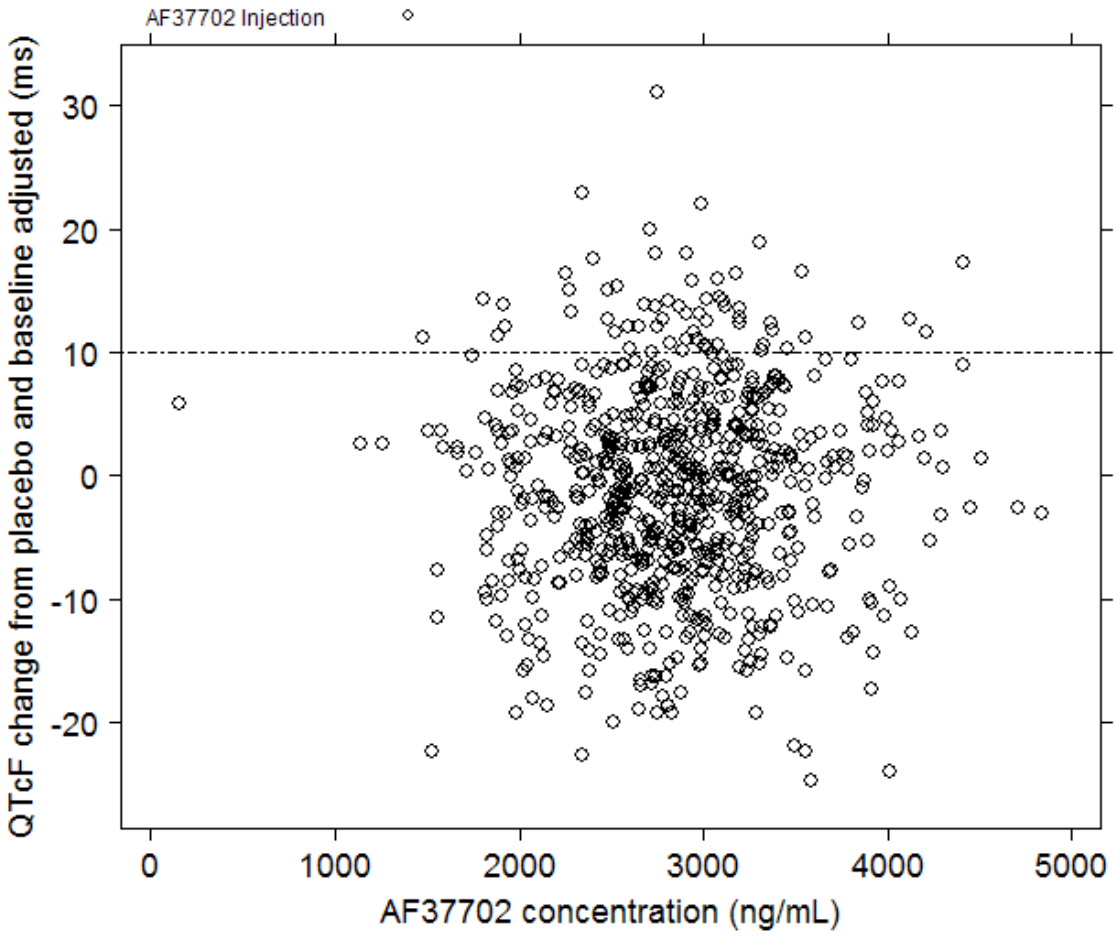
		Treatment Group							
		AF37702 Injection				Moxifloxacin 400 mg			
	Placebo	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.25	-0.2	64	-0.3	-0.1	(-0.6, 0.3)	63	-0.2	-0.0	(-0.4, 0.4)
0.5	-0.7	64	-0.4	0.2	(-0.3, 0.7)	63	0.3	1.0	(0.5, 1.5)
0.75	-0.5	63	-0.7	-0.2	(-0.7, 0.3)	63	-0.2	0.3	(-0.2, 0.8)
1	-0.3	64	-0.3	0.1	(-0.5, 0.7)	62	-0.3	0.0	(-0.6, 0.6)
2	0.2	64	-0.3	-0.5	(-1.1, 0.1)	62	0.2	0.0	(-0.6, 0.6)
3	-0.1	64	-0.3	-0.2	(-0.7, 0.4)	63	0.5	0.7	(0.1, 1.2)
4	-0.3	64	-0.4	-0.1	(-0.8, 0.5)	63	-0.0	0.2	(-0.4, 0.9)
5	1.6	64	1.1	-0.5	(-1.3, 0.4)	63	1.1	-0.5	(-1.3, 0.4)
6	0.5	63	0.1	-0.4	(-1.2, 0.4)	63	-0.3	-0.8	(-1.6, 0.0)
7	-0.0	64	-0.6	-0.6	(-1.4, 0.2)	63	-0.2	-0.1	(-0.9, 0.7)
10	-1.0	64	-1.4	-0.4	(-1.1, 0.3)	63	-0.8	0.2	(-0.6, 0.9)
22	-0.6	64	-0.6	0.0	(-0.5, 0.6)	63	-0.3	0.3	(-0.3, 0.8)

5.3 Clinical Pharmacology Assessments

The mean drug concentration-time profile is illustrated in Figure 1.

The relationship between ΔΔQTcF and AF37702 concentrations is visualized in Figure 5, with no evident exposure-response relationships for ΔΔQTcF.

Figure 5: ΔΔ QTcF vs. AF37702 Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 96% of the ECGs were annotated in the primary lead II, with less than 0.08% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no PR and QRS outliers during this study.

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6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	-Phase 2 studies in patients with Chronic Renal Failure (CRF): the median doses at 6 months of treatment with AF37702 Injection range from 0.03 mg/kg Q4W in patients not on dialysis (range: 0.02-0.1 mg/kg) to approximately 0.09 mg/kg Q4W in patients on hemodialysis (range: 0.02-0.5 mg/kg). Planned Phase 3 studies in patients with CRF: the median doses for the first dose of AF37702 Injection (i.e. starting dose) range from 0.03 mg/kg Q4W in patients not on dialysis (range: 0.025-0.04 mg/kg) to approximately 0.09 mg/kg Q4W in patients on hemodialysis (range: 0.04-0.2 mg/kg). Doses of AF37702 Injection are adjusted over time to maintain patients Hgb values within target range. This explains that the range of therapeutic doses at 6 months is broader than that observed for the starting dose (first injection). - Phase 2 study in oncology: the therapeutic dose is still being explored. Dose of 0.1, 0.15 and 0.2 mg/kg SC have all been found to be effective in a preliminary study.
Maximum tolerated dose	In patients, the MTD has not been defined, as to date no dose limiting adverse events have been identified. However, the dose of AF37702 Injection has been limited by the pharmacologic effect of the product which includes elevated Hgb levels and rapid rate of rise of Hgb. The dose of AF37702 Injection that yields excessive absolute Hgb levels or excessive rate of rise of Hgb varies across the spectrum of patients with CRF.

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Principal adverse events	Safety data in patients with CRF are presented from all 304 patients enrolled in both AFX01-03 (patients on dialysis) and AFX01-04 (patients not on dialysis) Phase 2 studies. **Adverse Events:** 18 (6%) patients reported 39 possible/probable drug-related adverse events; of these, events that were reported in two or more patients were: anaemia/low Hb (4 patients), fatigue (3), weakness (2), rash (2), hypertension (2), and headache (2) **Serious Adverse Events (SAEs):** 74 (24%) patients reported SAEs; two of these patients reported possible/probable drug-related SAEs (one case of transient ischemic attack in a patient with history of atrial fibrillation and one infusion reaction, Grade 2, responding to outpatient intervention) Seven deaths were reported, resulting from: cardiac arrest, cardiogenic shock, myocardial infarction, sepsis, pneumonia, respiratory failure, and end-stage renal failure. All the deaths were reported as not/probably not drug-related. Safety data in oncology patients are still being collected. No safety concern has been identified at this point. In the data available at this time for all studies in patients with CRF, hypertension has been the most frequently reported AE overall. The frequency of reported hypertension is not higher than would be expected in patients with CKD either treated with ESAs or not treated with ESAs. Dose Limiting Events: The dose of Hematide has not been limited by adverse events but has been limited by the predictable efficacy response which causes elevated Hgb and rapid rise of Hgb. In the Affymax Phase 1 Study AFX01-0401 conducted in healthy volunteers, the pharmacokinetic and pharmacodynamic data indicated a dose dependent response; the 0.1 mg/kg dose was associated with a clinically and statistically significant increase in Hgb from baseline, with a 1.14 +/- 0.6 g/dL increase in Hgb within 12 days and an average maximum increase from baseline of 1.36 ± 0.39 g/dL (range 0.7–1.9, n=10). Several of the pre-specified dose-escalation stopping criteria for Hgb levels were achieved in the 2 cohorts at the dose of 0.1 mg/kg of AF37702 Injection. These criteria were: any subject with an increase in Hgb of ≥ 1.5 g/dL above baseline; at least three treated subjects in a cohort with an increase in Hgb of ≥ 1.0 g/dL above baseline; and more than one subject in a cohort with a ≥ 1.0 g/dL increase of Hgb over any 2 week period after administration of study drug). The study was terminated after the two cohorts at this dose level were enrolled.	
Maximum dose tested	Single Dose	- IV 0.1 mg/kg in NHV (Study AFX01-0401); - IV 0.1 mg/kg in pre-dialysis, ESA naïve patients with CKD (Study AFX01-02)

	Multiple Dose	The maximum dose tested in patients with CRF is 0.5 mg/kg. This dose was administered in a single patient on dialysis for 1 injection only (the sixth and last dose) after the AF37702 Injection dose had been increased subsequent to a bleeding episode. Three patients with CRF on dialysis received doses in the range of 0.3 to 0.4 mg/kg IV Q4W (for 1 to 3 injections). In oncology patients, the maximum dose tested has been 0.2 mg/kg SC Q3W
Exposures Achieved at Maximum Tested Dose	Single Dose	In the NHV study (Study AFX01-0401), IV dose = 0.1 mg/kg; n = 9[a] - mean Cmax 2.56 (10.27% CV) ug/mL; - mean AUC(0-∞) 137.61 (14.05% CV) ug-h/mL In pre-dialysis, ESA-naïve CKD patients (Study AFX01-02), IV dose = 0.1 mg/kg; n = 2 - mean Cmax 2.31 (42.56% CV) ug/mL; -mean AUC(0-∞) 193.53 (43.63% CV) ug-h/mL [a] Total number of NHV in the 0.1 mg/kg cohort was 10, PK parameters derived from 9 subjects less one outlier
	Multiple Dose	- There is limited PK information for AF37702 Injection in hemodialysis patients given multiple IV doses greater than 0.1 mg/kg from Study AFX01-03. Cmax and AUC determinations were assessed from a total of 3 patients; dose ranged from 0.13 to 0.15 mg/kg/dose) . - Dose normalized Cmax: 0.030 kg/mL (42.08% CV) - Dose normalized AUC(0-∞): 1.63 kg-h/mL (12.51% CV)
Range of linear PK	- 0.0125 mg/kg to 0.1 mg/kg in NHV (Study AFX01-0401); - 0.025 mg/kg to 0.1 mg/kg in ESA-naïve, pre-dialysis patients with CRF (Study AFX01-02). - No PK information is available yet at doses much greater than 0.1 mg/kg	
Accumulation at steady state	No accumulation with Q4W dosing ($T_{1/2}$ ~40 to 50 hours in patients)	

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Metabolites	No metabolism study has been conducted to date. In vitro metabolism studies (CYP450 inhibition and induction studies) have been planned. (b) (4) [redacted] The PEG constituent of AF37702 is considered to be largely inert. Multiple pathways appears to be involved in the low rate of PEG metabolism including an oxidative process mediated by alcohol and aldehyde dehydrogenases as well as by hepatic P450-dependent oxidative enzymes.	
Absorption	Absolute/Relative Bioavailability	The bioavailability of AF37702 Injection administered SC compared to IV is approximately 44% in patients with CRF.
	Tmax	• average 72 hours following SC injection in patients with CRF not on dialysis • immediate (≤ 15 minutes) following IV injection in patients with CRF on dialysis • not determined for metabolites (peptide fragments)
Distribution	Vd/F or Vd	Volume of distribution following IV dosing: - 29.2 mL/kg (14.7%CV) in NHV (Study AFX01-0401, n = 9, IV dose = 0.1 mg/kg) [b]; - 44.5 mL/kg (39.0%CV) in ESA-naïve, pre-dialysis patients with CKD (Study AFX01-02, n = 2, IV dose = 0.1 mg/kg) [b] and 39.3 mL/kg (42%CV) in hemodialysis patients (Study AFX01-03, n = 6, IV dose = 0.1 mg/kg) [b] Vd is generally the same among NHV, pre-dialysis, and hemodialysis patients, and approximates plasma volume suggesting limited distribution outside the circulation. [b]Study data reported in IND 63,257/S-047
	% bound	Percent bound for AF37702 Injection has not been determined.
Elimination	Route	• renal clearance has been shown to be a primary elimination route

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	Terminal t½	• $T_{1/2}$ from IV injections are 23.7 h (22.8 %CV) in NHV (Study AFX01-0401, n =9, IV dose = 0.1 mg/kg) [b]; 59.2 h (5.02%CV) in patients with CRF not on dialysis (Study AFX01-02, n = 2, IV dose = 0.1 mg/kg) [b]; and 50.8 h (28.2%CV) in hemodialysis patients (Study AFX01-03, n = 6, IV dose = 0.1 mg/kg)[b] A prolonged $T_{1/2}$ is observed for SC injections and indicates rate limited absorption. $T_{1/2}$ from SC dosing are ~45 h (n = 8) and ~69.2 h (n = 8) in NHV and pre-dialysis patients, respectively [b]. • not determined for metabolites (peptide fragments) [b]Study data reported in IND 63,257/S-047
	CL/F or CL	Absolute clearance rates (CL) for AF37702 following IV dosing are 60.9 mL/h (13.6 %CV) in NHV (Study AFX01-0401, n =9, IV dose = 0.1 mg/kg) [b]; 38.5 mL/h (43.6 %CV) in predialysis patients (Study AFX01-02, n = 2, IV dose = 0.1 mg/kg) [b]; and 40.6 mL/h (41.4 %CV) in hemodialysis patients (Study AFX01-03, n = 6, IV dose = 0.1 mg/kg)[b] [b]Study data reported in IND 63,257/S-047
Intrinsic Factors	Age	Effect of age on the PK of AF37702 has not been tested
	Sex	No significant gender differences in PK from NHV study
	Race	Effect of race on the PK of AF37702 Injection has not been tested
	Hepatic & Renal Impairment	Change in AUC with renal impairment was calculated using CL of AF37702 in NHV and in patients with CRF not on dialysis and on hemodialysis. As demonstrated in animal studies, renal impairment is predicted to increase AUC by approximately 1.4 fold. Because AF37702 Injections are administered via parenteral administration (IV or SC), Cmax is dependant only on dose and volume of distribution and is not expected to be affected by hepatic and renal impairment. As above mentioned, Vd is generally the same among NHV, pre-dialysis, and hemodialysis patients, and approximates plasma volume. No hepatic impairment study has been conducted to date.
Extrinsic Factors	Drug interactions	Drug-drug interaction studies have not been conducted. In vitro CYP450 inhibition/induction studies are planned.

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	Food Effects	Not applicable, intended routes of administration for AF37702 are IV and SC. Oral route of administration not planned.
Expected High Clinical Exposure Scenario	An overdose of AF37702 Injections in either NHVs or patients would result in an increase in absolute Hgb levels (polycythemia) to excessive levels and/or result in an excessive rate of rise of Hgb, either of which can result in cardiovascular events such as hypertension and thrombotic events. Excessive absolute Hgb levels or excessive rate of rise of Hgb would be treated by urgent and possibly repeated phlebotomy.	

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/s/

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02/07/2012

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02/08/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-799	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	May 27, 2011		
Division:	Hematology Products	**Biopharmaceutics Lead:** Angelica Dorantes, Ph.D.	
Sponsor:	Affymax Pharmaceuticals, Inc.	**Second Signature:** Sandra Suarez Sharp, Ph.D.	
Trade Name:	Omontys (Peginesatide) Injection	**Date Assigned:**	June 7, 2011
Generic Name:	Peginesatide Solution	**Date of Review:**	January 18, 2012
Indication:	Treatment of anemia associated with chronic renal failure in adult patients on dialysis	**Type of Submission:** Original New Drug Application	
Formulation/strengths:	Single Dose Vial (SDV): 2 mg/0.5 mL (4 mg/mL) 3 mg/0.5 mL (6 mg/mL) 4 mg/0.5 mL (8 mg/mL) 5 mg/0.5 mL (10 mg/mL) 6 mg/0.5 mL (12 mg/mL) Prefilled Syringe (PFS): 1 mg/0.5 mL (2 mg/mL) 2 mg/0.5 mL (4 mg/mL) 3 mg/0.5 mL (6 mg/mL) 4 mg/0.5 mL (8 mg/mL) 5 mg/0.5 mL (10 mg/mL) 6 mg/0.5 mL (12 mg/mL) Multiple Dose Vial (MDV): 10 mg/1 mL 20 mg/2 mL		
Route of Administration	Intravenous, Subcutaneous		

THE SUBMISSION

This is a 505(b)(1) New Drug Application for single-dose vial (SDV) (2 mg/0.5 mL to 6 mg/0.5 mL), prefilled syringe (PFS) (1 mg/0.5 mL to 6 mg/0.5 mL), and multi-dose vial (MDV) (10 mg/mL, 1 mL vial and 20 mg/ 2mL, 2 mL vial) for Omontys (Peginesatide) indicated for the treatment of anemia associated with chronic renal failure in adult patients on dialysis.

The proposed commercial formulation for the MDV presentations differs from that used in the Phase 1 and 2 trials. A BE study was conducted to bridge these two formulations (refer to Clinical Pharmacology review). The composition of the commercial formulation for the SDV and the PFS presentations are the same as those tested in the Phase 3 trials. However, a higher strength (12 mg/mL) not tested in the Phase 3 clinical trials is being proposed for commercialization. To support the approval of the 12 mg/mL strength, a BE study between the 16 mg/mL SDV formulation and the 10 mg/mL SDV was conducted. Note that a BE study between the 2 mg/mL SDV formulation vs. the 10 mg/mL SDV formulation was also conducted, and according to the Applicant, supports the approval of the lower strengths for these two presentations. However, based on 21CFR 320.22 (b)(1), a waiver for the BA/BE requirements may be granted for all the lower strengths given that the proposed product is a solution and the composition of the commercial formulation is similar to that tested in the Phase 3 trials.

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The Biopharmaceutics review for this NDA is focused on the evaluation of these data provided to support granting a biowaiver for the lower strengths and the highest strength of the SDV and PFS presentations.

The proposed formulations for the SDV and PFS are similar in composition to the unpreserved 10 mg/mL SDV formulation used in Phase 1, Phase 2, and Phase 3 clinical trials. Additionally, the BA/BE data demonstrates that 1) the 2 mg/mL SDV formulation is bioequivalent to the 10 mg/mL SDV formulation and 2) the 16 mg/mL SDV formulation is bioequivalent to the 10 mg/mL SDV formulation (refer to clinical pharmacology review by Dr. Young-Jin Moon). Although the BE study considering the 2 mg/mL and 10 mg/mL SDV formulations was not needed from the regulatory perspective, it confirms the bioequivalency for the intermediate strengths (4 - 8 mg/mL) of the proposed commercial SDV and PFS products. Also, the BE study for the 10 mg/mL and 16 mg/mL SDV formulations provides an adequate bridge for the highest strength (12 mg/mL) of the proposed commercial SDV and PFS products. Thus, a biowaiver for the proposed products is granted.

RECOMMENDATION

This application is recommended for approval from a Biopharmaceutics standpoint. A waiver for the CFR BA/BE requirement is granted for the following strengths of the proposed products:

- SDV: 2 mg /0.5 mL, 3 mg /0.5 mL, 4 mg /0.5 mL, and 6 mg/0.5 mL
- PFS: 1 mg /0.5 mL, 2 mg /0.5 mL, 3 mg /0.5 mL, 4 mg /0.5 mL, and 6 mg/0.5 mL

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez Sharp, Ph.D.
Senior Biopharmaceutics Reviwer
Office of New Drug Quality Assessment

cc: Angelica Dorantes

BIOPHARMACEUTICS INFORMATION ASSESSMENT

1. Background

Peginesatide (AF37702) is a synthetic, dimeric peptide covalently linked to polyethylene glycol (PEG). It acts as an erythropoiesis stimulating agent (ESA) that acts on the erythropoietin receptor (EPOr). The structure of Peginesatide is show in Figure 1.

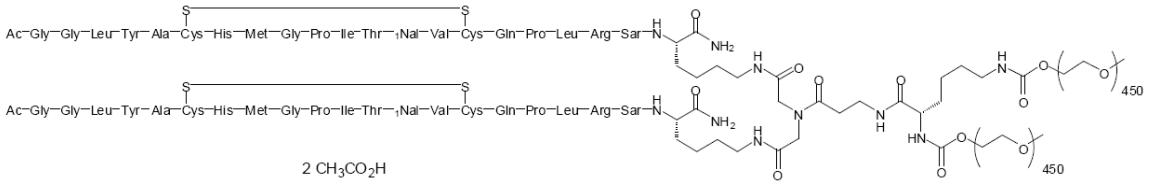

Figure 1. Structure of Peginesatide

The proposed dosing regimen for initial treatment of Peginesatide (to patients not being treated with an ESA) is 0.04 to 0.08 mg/kg body weight administered once monthly. This proposal is based on Phase 2 Study AFX01-15, which evaluated these two AF37702 Injection starting doses (as compared to Epoetin) in dialysis subjects, and data from the Evaluation Period of Phase 3 Dialysis Studies AFX01-12 and AFX01-14. Note that the patients' body weights varied from 63 kg to 227 kg (Table 1.4.3 in the submission). For patients currently being treated with an ESA, the Applicant proposes a nine-tiered dose conversion chart in which each tier provides the AF37702 Injection dose (mg/month) which corresponds to a specific range of doses of Epoetin (U/week) and darbepoetin (μ g/week). The data from Phase 3 studies AFX01-12 and AFX01-14 were analyzed and a relationship was determined between

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Epoetin dose (U/week) and AF37702 Injection dose (mg/month) dose. This relationship is the underlying basis of the proposed dose conversion from Epoetin to AF37702 Injection. Use of a derived darbepoetin-AF37702 Injection relationship, supported by the darbepoetin-to-AF37702 Injection conversion Study AFX01_202, yielded the corresponding proposed conversion from darbepoetin to AF37702 Injection (Table 1).

Table 1. Proposed Dose Conversion Chart for Patients Converting from Epoetin or Darbepoetin to AF37702 Injection

Previous Weekly Epoetin alfa Dose (Units/week)	Previous Weekly Darbepoetin alfa Dose (µg/week)	AF37702 Injection Dose Once Monthly (mg/month)
<2,500	<12	2
2,500 to <4,300	12 to <18	3
4,300 to <6,500	18 to <25	4
6,500 to <8,900	25 to <35	5
8,900 to <13,000	35 to <45	6
13,000 to <19,000	45 to <60	8
19,000 to <33,000	60 to <95	10
33,000 to <68,000	95 to <175	15
≥68,000	≥175	20

Source: The data and analyses relevant to the proposed dose conversion from Epoetin and darbepoetin are described in Sections 2.7.3.4.2 and 2.7.3.4.3, respectively.

A biowaiver is needed for approval of the different presentations and strengths of Peginesatide: single-dose vials (SDV) (2 mg/0.5 mL to 6 mg/0.5 mL), prefilled syringes (PFS) (1 mg/0.5 mL to 6 mg/0.5 mL), and multi-dose vials (MDV) (10 mg/1 mL and 20 mg/2 mL).

To support the biowaiver, the Applicant provided the following information/data:

- A comparison of the SDV and PFS marketed formulations to the unpreserved 10 mg/mL SDV formulation used in Phase 1, Phase 2, and Phase 3 clinical trials; and
- BA/BE data comparing the 2 mg/mL SDV product vs. the 10 mg/mL SDV product and the 16 mg/mL SDV product vs. the 10 mg/mL SDV product for SC administration.

The formulation proposed for use in the SDV and PFS marketed formulations is the same as the unpreserved 10 mg/mL SDV formulation used in Phase 1, Phase 2, and Phase 3 clinical trials (refer to Table 2). The MDV formulation is different.

Table 2. AF37702 Formulations Used in Clinical Development vs. Proposed Commercial Presentations

	Phase 1 & 2			Phase 2	Phase 3	Commercial		
Component	SDV	SDV	MDV	SDV	SDV	SDV	PFS	MDV
AF37702 API concentration and fill volume	10 mg/mL,1 mL	2 mg/mL, 0.5mL 16 mg/mL, 0.5mL	10 mg/mL, 1 mL	10 mg/mL , 1 mL 30 mg/mL[a] , 1 mL 50 mg/mL[a], 1 mL	10 mg/mL, 1mL	4 mg/mL, 0.5 mL 6 mg/mL, 0.5 mL 8 mg/mL, 0.5 mL 10 mg/mL, 0.5mL 12 mg/mL, 0.5 mL	2 mg/mL, 0.5 mL 4 mg/mL, 0.5 mL 6 mg/mL, 0.5 mL 8 mg/mL, 0.5 mL 10 mg/mL, 0.5mL 12 mg/mL, 0.5 mL	10 mg/mL, 1 mL 10 mg/mL, 2 mL

(b) (4)

[a] Used in AFX01-05 (A Phase 2, Open-Label, Multi-Center, Dose Escalation Study of the Safety, Pharmacodynamics, and Pharmacokinetics of Subcutaneously Administered AF37702 Injection (Hematide™) in Anemic Cancer Patients Receiving Chemotherapy)

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The Applicant conducted BA/BE studies to bridge the proposed commercial strengths/presentations with the 10 mg/mL SDV product used in Phase 3 clinical trials. Phase 1 studies were performed to evaluate the bioavailability (BA) of AF37702 from the MDV formulation (which contains a preservative) and the BA and pharmacodynamic response from wider range of strengths for the SDV formulation relative to the 10 mg/mL SDV formulation (refer to Table 3). Two Phase 1 studies evaluated the proposed MDV formulation by the intravenous (IV) or subcutaneous (SC) route of administration (Studies AFX01_102 and AFX01_103, respectively), and two Phase 1 studies evaluated the 2 mg/mL and 16 mg/mL strengths of the SDV formulation (Studies AFX01_105 and AFX01_104, respectively).

Table 3. Clinical Studies Bridging Phase 3 Clinical Trial Materials to Commercial Configurations

Phase 3 Clinical Trial Material	Commercial Configuration(s) Supported [a]	Clinical Studies (Clinical Trial Material Configurations Used)
10 mg/1 mL SDV	SDV: 2 mg/0.5 mL (4 mg/mL) 3 mg/0.5 mL (6 mg/mL) 4 mg/0.5 mL (8 mg/mL) 5 mg/0.5 mL (10 mg/mL)	AFX01_105 (SC) (1 mg/0.5 mL SDV and 10 mg/mL SDV)
	PFS: 1 mg/0.5 mL (2 mg/mL) 2 mg/0.5 mL (4 mg/mL) 3 mg/0.5 mL (6 mg/mL) 4 mg/0.5 mL (8 mg/mL) 5 mg/0.5 mL (10 mg/mL)	
	SDV: 6 mg/0.5 mL (12 mg/mL)	AFX01_104 (SC) (10 mg/mL SDV and 8 mg/0.5 mL SDV)
	PFS: 6 mg/0.5 mL (12 mg/mL)	
	MDV: 10 mg/1 mL and 20 mg/2 mL (10 mg/mL)	AFX01_102 (IV) (10 mg/1 mL MDV and 10 mg/mL SDV)
		AFX01_103 (SC) (10 mg/1 mL MDV and 10 mg/mL SDV)

[a] Nominal fill volume is 0.5 mL for the SDV and PFS drug product types and 1 mL or 2 mL for the MDV drug product type.

The BA/BE data directly supports the approval of the MDV configurations. Therefore, the Biopharmaceutics review for this NDA is focused on the evaluation of data provided to support granting a biowaiver for lower strengths and the highest strength of the SDV and PFS presentations.

2. BA/BE Studies

BA/BE studies were conducted to compare the proposed commercial SDV 2 mg/mL product vs. 10 mg/mL of the SDV product and a SDV 16 mg/mL formulation vs. 10 mg/mL of the SDV product for SC administration. The goal was that these studies would provide a bridge for the proposed products at the following strengths:

- SDV: 2 mg /0.5 mL, 3 mg /0.5 mL, 4 mg /0.5 mL, and 6 mg/0.5 mL
- PFS: 1 mg /0.5 mL, 2 mg /0.5 mL, 3 mg /0.5 mL, 4 mg /0.5 mL, and 6 mg/0.5 mL

As shown in Table 4, the single dose vials (SDV) and pre-filled syringes (PFS) have the same formulation. They only differ in their container closure systems.

Reference ID: 3073533

Table 4. Commercial SDV and PFS Formulations

Component	Function	Concentration[a]
AF37702	Active ingredient	2[b], 4, 6, 8, 10, 12 mg/mL[c]
(b) (4) Sorbitol, NF	(b) (4)	(b) (4)
Sodium Phosphate monobasic, dihydrate, USP		
Sodium Phosphate dibasic, (b) (4) USP		
Polysorbate 20, NF		
Sodium Hydroxide, NF	pH adjustment	
Water for Injection, USP	(b) (4)	

[a] Commercial formulation is the same as clinical trial formulations with the exception of Studies AFX01-0401, AFX01-02, and AFX01-03 which used an (b) (4) formulation (see Table 3).
[b] PFS formulation only.
[c] Concentrations 2, 4, 6, 8, 10, and 12 mg/mL are equivalent to 1, 2, 3, 4, 5, and 6 mg/0.5 mL, respectively.
(b) (4)
NF = National Formulary, q.s. = quantity sufficient, USP = United States Pharmacopoeia.
Source: Section 3.2.P.1 SDV and Section 3.2.P.1 PFS.

Table 5 presents the data from the BA/BE study for 2 mg/mL of the SDV formulation relative to 10 mg/mL of the SDV formulation. Note that a single SC dose of 0.05 mg/kg AF37702 Injection from the 2 mg/mL or the 10 mg/mL AF37702 Injection Concentration was administered to healthy subjects. Although the AUC parameter did not meet the BE limit standard, the Clinical Pharmacology review team found that the 2mg/mL and 10 mg/mL strengths were determined to be bioequivalent based on their analysis (refer to review by Dr. Young-Jin Moon).

Table 5. BA Estimates for AF37702 from the AF37702 Injection 2 mg/mL Formulation Relative to the 10 mg/mL Formulation (Study AFX01 105)

Parameter	Point Estimate Ratio	90% CI
2 mg/mL Concentration (Test) vs 10 mg/mL Concentration (Reference)		
C_{max}/dose	0.902	(0.8278–0.9820)
AUC_{0-t}/dose	0.857	(0.7897–0.9308)
$AUC_{0-\infty}$/dose	0.821	(0.7797–0.8654)

Source: AFX01_105, Table 14.2.4.1.

Table 6 presents the data from the BA/BE study for 16 mg/mL of the SDV formulation relative to 10 mg/mL of the SDV formulation. Note that a single SC dose of 0.05 mg/kg AF37702 Injection from the 16 mg/mL or the 10 mg/mL AF37702 Injection Concentration was administered to healthy subjects. The Clinical Pharmacology review team found that the 10 mg/mL and 16 mg/mL strengths were determined to be bioequivalent based on their analysis (refer to review by Dr. Young-Jin Moon).

Table 6. BA Estimates for AF37702 from the AF37702 Injection 16 mg/mL Formulation Relative to the 10 mg/mL Formulation (Study AFX01 104)

Parameter	Point Estimate Ratio	90% CI
16 mg/mL Concentration (Test) vs 10 mg/mL Concentration (Reference)		
C_{max}/dose	1.018	(0.9309–1.1127)
AUC_{0-t}/dose	1.007	(0.9413–1.0782)
$AUC_{0-\infty}$/dose	0.999	(0.9480–1.0534)

Source: AFX01_104, Table 14.2.4.1.

Reference ID: 3073533

Reviewer Comments:

The proposed commercial formulation for the MDV presentation differs from that used in the Phase 1 and 2 trials (Table 2). A BE study was conducted to bridge these two formulation (refer to Clinical Pharmacology review). The composition of the commercial formulations for the SDV and the PFS presentations are the same as those tested in the Phase 3 trials (Table 3). However, a higher strength (12 mg/mL), not tested in the Phase 3 clinical trials, is being proposed for commercialization. To support the approval of the 12 mg/mL strength, a BE study between the 16 mg/mL SDV formulation to the 10 mg/mL SDV was conducted. Noted that a BE study between the 2 mg/mL SDV formulation vs. the 10 mg/mL SDV formulation was also conducted, and according to the Applicant, supports the approval of the lower strengths for these two presentations. Based on 21CFR 320.22 (b)(1), a waiver for the BA/BE requirements may be granted for all the lower strengths given that the proposed product is a solution and the composition of the commercial formulation is similar to that tested in the phase 3 trials.

All strengths of The SDV and PFS formulations are proportionally similar since they meet the following definition of proportionally similar in the BA/BE Guidance:

"For high potency drug substances, where the amount of the active drug substance in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within + 10 % of the total weight of the strength on which a biostudy was performed), the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients. The changes in the inactive ingredients are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II."

Additionally, the BA/BE data demonstrate that 1) the 2mg/mL SDV formulation is bioequivalent to the 10 mg/mL SDV formulation and 2) the 16 mg/mL SDV formulation is bioequivalent to the 10 mg/mL SDV formulation (refer to clinical pharmacology review by Dr. Young-Jin Moon). Therefore the BE study between the 2 mg/mL and 10 mg/mL SDV formulations supports the bridge for the intermediate strengths (4 - 8 mg/mL) of the proposed commercial SDV and PFS products. Also, the BE study between the 10 mg/mL and 16 mg/mL SDV formulations provide an adequate bridge for the highest strength (12 mg/mL) of the proposed commercial SDV and PFS products. Furthermore, the 12 mg/mL strength is proportionally similar to the 10 mg/mL strength and is within the range of doses tested in Phase 3 clinical trials.

Thus, a biowaiver is granted for the proposed products at the following strengths:

- *SDV: 2 mg /0.5 mL, 3 mg /0.5 mL, 4 mg /0.5 mL, and 6 mg/0.5 mL*
- *PFS: 1 mg /0.5 mL, 2 mg /0.5 mL, 3 mg /0.5 mL, 4 mg /0.5 mL, and 6 mg/0.5 mL*

Reference ID: 3073533

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/s/

KAREEN RIVIERE
01/18/2012

SANDRA SUAREZ
01/18/2012

BIOPHARMACEUTICS FILING REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-799	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	May 27, 2011		
Division:	Hematology Products	**Team Leader:** Angelica Dorantes, Ph.D.	
Sponsor:	Afymax Pharmaceuticals, Inc.	**Supervisor:** Patrick Marroum, Ph.D.	
Trade Name:	Omontys (Peginesatide) Injection	**Date Assigned:**	June 7, 2011
Generic Name:	Peginesatide Solution	**Date of Review:**	July 25, 2011
Indication:	Treatment of anemia associated with chronic renal failure in adult patients on dialysis	**Type of Submission:** Original New Drug Application	
Formulation/strengths	SDV: 2 mg/0.5 mL (4 mg/mL) 3 mg/0.5 mL (6 mg/mL) 4 mg/0.5 mL (8 mg/mL) 5 mg/0.5 mL (10 mg/mL) 6 mg/0.5 mL (12 mg/mL) PFS: 1 mg/0.5 mL (2 mg/mL) 2 mg/0.5 mL (4 mg/mL) 3 mg/0.5 mL (6 mg/mL) 4 mg/0.5 mL (8 mg/mL) 5 mg/0.5 mL (10 mg/mL) 6 mg/0.5 mL (12 mg/mL) MDV:10 mg/1 mL 20 mg/2 mL		
Route of Administration	Intravenous, Subcutaneous		

SUBMISSION:

This is a 505(b)(1) New Drug Application for single-dose vial (SDV) (2 mg/0.5 mL to 6 mg/0.5 mL), prefilled syringe (PFS) (1 mg/0.5 mL to 6 mg/0.5 mL), and multi-dose vial (MDV) (10 mg/1 mL and 20 mg/2 mL) for Omontys (Peginesatide) indicated for the treatment of anemia associated with chronic renal failure in adult patients on dialysis.

BIOPHARMACEUTIC INFORMATION:

The formulation proposed for use in the SDV and PFS marketed formulations is the same as the unpreserved 10 mg/mL SDV formulation used in Phase 1, Phase 2, and Phase 3 clinical trials. The MDV formulation is different.

Phase 1 studies were performed to evaluate the bioavailability (BA) of AF37702 from the MDV formulation (which contains a preservative) and the BA and pharmacodynamic (PD) response from wider range of strengths for the SDV formulation relative to the 10 mg/mL SDV formulation. Two Phase 1 studies evaluated the proposed MDV formulation by the intravenous (IV) or subcutaneous (SC) route of administration (Studies AFX01_102 and AFX01_103, respectively), and two Phase 1 studies evaluated the 2 mg/mL and 16 mg/mL strengths of the SDV formulation (Studies AFX01_105 and AFX01_104, respectively).

The Biopharmaceutics review for this NDA will be focused on the evaluation of data provided to support granting a biowaiver for the intermediate strengths for the SDV and PFS presentations.

Reference ID: 2978335

RECOMMENDATION:
The ONDQA/Biopharmaceutics team has reviewed NDA 202-799 for filing purposes. We found this NDA filable from a Biopharmaceutics perspective. The sponsor has submitted a reviewable submission.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

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

cc: Patrick Marroum, Ph.D.

Reference ID: 2978335

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/s/

KAREEN RIVIERE
07/25/2011

ANGELICA DORANTES
07/25/2011

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	202799/000	**Brand Name**	Omontys
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Peginesatide
Medical Division	OND/OODP/DHP	**Drug Class**	Erythropoiesis-stimulating agent
OCP Reviewer	Young-Jin Moon, Ph.D.	**Indication(s)**	For the treatment of anemia associated with chronic renal failure in adult patients on dialysis
OCP Team Leader	Julie Bullock, Pharm.D.	**Dosage Form**	Single dose vials; Single dose pre-filled syringes; Multiple dose vials
Pharmacometrics Reviewer	Justin Earp, Ph.D.	**Dosing Regimen**	Initial treatment: 0.04 to 0.08 mg/kg body weight administered once monthly
Date of Submission	23-May-2011	**Route of Administration**	IV or SC
Estimated Due Date of OCP Review		**Sponsor**	Affymax
Medical Division Due Date		**Priority Classification**	Standard
PDUFA Due Date	27-Mar-2012		

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	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			**Validation reports: UOR2, UOR3, 05-500, 05-513, NMR2, NMR3, 05-501, BQR2, OFF001, OFF004, TDA0374, P06-17701, P06-17702, TDA0376, TDA0377, P07-17704** **PK bioanalytical reports (in-study): AFX01,-02, -03, -04, -14, -101, -202**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**	**2**		
multiple dose:				
Patients-				
single dose:				
multiple dose:				

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:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**x**	**4**		
Phase 3:	**x**	**4**		
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**6**		**1 dose escalation** **3 dose finding** **2 dose supporting**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**x**	**1**		
Data sparse:	**x**			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**x**	**4**		
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				
Thorough QT study	**x**	**1**		
Chronopharmacokinetics				
Pediatric development plan				
In vitro PD bridge study				
Literature References				
Total Number of Studies		**22**		

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			
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			

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

5	Has a rationale for dose selection been submitted?	x			
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			
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			
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.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

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

Young-Jin Moon, Ph.D	26-July-11
Reviewing Clinical Pharmacologist	Date
Julie Bullock, Pharm. D.	26-July-11
Team Leader/Supervisor	Date

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

Clinical Pharmacology - NDA Filing Memo

Background

This is an original NDA which seeks the approval of an intravenous (IV) or subcutaneous (SC) administration of AF37702 Injection (peginesatide) for the treatment of anemia associated with chronic renal failure in adult patients on dialysis. Peginesatide is a synthetic, dimeric peptide that is covalently linked to polyethylene glycol (PEG). Molecular weight is (b) (4) (b) (4) This NDA is based on the results of two pivotal trials (AFX01-12 and -14). The primary endpoint of both trials was a mean change from baseline in Hgb.

Formulation

Initial clinical development of AF37702 Injection for the treatment of anemia with CRF used a single-dose vial (SDV) sterile parenteral formulation. In the later stages of clinical development, a multidose vial (MDV) parental formulation was developed. Four studies were conducted to assess:

- the relative bioavailability of AF37702 following a single IV dose of AF37702 Injection 0.05 mg/kg derived from the MDV formulation compared with the SDV (AFX01-102)
- the relative bioavailability of AF37702 following a single SC dose of AF37702 Injection 0.05 mg/kg derived from the MDV formulation compared with the SDV formulation (AFX01-103)
- the relative bioavailability and PD of an AF37702 Injection formulation at a higher concentration than what is proposed for marketing (AFX01-104)
- the relative bioavailability and PD of an AF37702 Injection formulation at the lowest concentration proposed for marketing (AFX01-105)

Clinical Studies

The clinical development program for peginesatide includes 20 studies- six phase 1, ten phase 2, and four phase 3 studies- as well as one supportive phase 1 study conducted in Japanese patients. Among them, clinical pharmacology program included 13 clinical studies.

Pharmacokinetics

The pharmacokinetics (PK) of peginesatide were evaluated in seven phase 1 studies in healthy subjects with both intravenous (IV) and subcutaneous (SC) administration. The phase 1 program for peginesatide included a thorough QT/QTc study (AFX01-101) and four biopharmaceutic studies to determine the relative bioavailability of Phase 3 and proposed commercial formulations (AFX01-102, AFX01-103, AFX01-104, and AFX01-105). The phase 1 clinical study conducted in Japan (CPH-001) is considered supportive. PK of peginesatide was further evaluated in phase 2 studies and a phase 3 study:

- Two phase 2 studies in anemic subjects with CRF on hemodialysis with both IV and SC administration (AFX01-03 and AFX01-07)
- Two phase 2 studies in ESA-naïve anemic subjects with CRF not receiving dialysis with both IV and SC administration (AFX01-02 and AFX01-04)
- One phase 2 study in chemotherapy induced anemic subjects with cancer with SC administration only (AFX01-05)

- One phase 3 study in anemic subjects with CRF on hemodialysis with both IV and SC administration (AFX01-14)

Pharmacodynamics

Pharmacodynamic (PD) effects on reticulocyte count and Hgb changes following a single dose of peginesatide were evaluated in four phase 1 studies (AFX01-0401, AFX01-104, AFX01-105, and CPH-001). PD effects on reticulocyte count and Hgb changes following multiple doses of peginesatide were evaluated in five phase 2 studies (AFX01-02, AFX01-03, AFX01-04, AFX01-05, and AFX01-07). In addition, a population PK and PK-PD analysis was conducted utilizing data obtained from four phase 2 studies (AFX01-02, AFX01-03, AFX01-04, AFX01-07) in CRF subjects on and not on dialysis and one phase 3 study (AFX01-14) conducted in CRF subjects on hemodialysis.

***In vitro* studies**

The following *in vitro* studies were evaluated in the clinical pharmacology review:

Distribution

- Partitioning into blood cells in rats, monkeys and humans
- Plasma protein binding

Metabolism

- Metabolism by hepatic and renal microsomes and S9 from humans, rats and monkeys
- Evaluation of two lots of AF37702 as inducers of cytochrome P450 enzymes expressed in cultured human hepatocytes
- Evaluation of two lots of AF37702 (peginesatide) as inhibitors of human cytochrome P450 enzymes in human liver microsome
- Evaluation of induction potential of CYP450 isoforms by AF37702, [redacted] (b) (4) and [redacted] (b) (4) in cryopreserved human hepatocytes
- Inhibitory Effects of AF37702, [redacted] (b) (4) and [redacted] (b) (4) on cytochrome P450 activities in microsomes from insect cells expressing human CYPs

Immunogenicity

Immunogenicity of AF37702 has been characterized in nonclinical and clinical studies using a series of assays designed to detect binding antibodies, to determine whether those antibodies neutralize the functional activity of AF37702, and to assess whether the antibodies are cross-reactive with human EPO. The immunogenicity of AF37702 has been characterized in all clinical studies.

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/s/

YOUNG J MOON
07/13/2011

JULIE M BULLOCK
07/14/2011