FDA Briefing Document for the
Oncologic Drugs Advisory Committee (ODAC)
December 7, 2011

Meeting Date:	December 7, 2011
NDA:	202799
Applicant:	Affymax, Inc. 4001 Miranda Ave. Palo Alto, CA 94304
Drug:	Peginesatide injection
Proposed Indication:	Treatment of Anemia due to Chronic Kidney Disease in Adult Patients on Dialysis

The attached document(s) contain background material prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee (AC). We have brought this issue -- consideration of the benefits and risks of peginesatide treatment for the anemia associated with chronic kidney disease – to this AC to gain the committee's insights and opinions. The background package may not contain all issues relevant to the final regulatory recommendation. It is intended to focus on issues identified by the Agency for discussion by the AC. The FDA will not issue a final determination on the issues at hand until input from the AC process has been considered and all internal reviews have been finalized. The final determination may be affected by issues not discussed at this meeting.

This document is based on the applicant's information as provided up to September 22, 2011.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY 4
2. BACKGROUND 7
3. PEGINESATIDE PRINCIPAL TRIALS 10
3.1 Peginesatide AFX01-12 and AFX01-14 (On - Dialysis) 11
3.2 Peginesatide Trials AFX01-11 and AFX01-13 (Not On Dialysis) 14
3.3 Peginesatide Safety Analyses 16
3.4 Additional Exploratory Analyses 19
3.5 Immunogenicity 21
4. CONCLUSIONS 21
6. Appendix 23

Table of abbreviations

CHF	Congestive heart failure
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency Trial
CI	Confidence interval
CKD	Chronic kidney disease
CREATE	Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin-beta
CRF	Chronic renal failure
CSE	Composite safety events (applicant's primary safety endpoint)
CV	Cardiovascular
CVA	stroke
DA	Darbepoetin alfa
DSMB	Data Safety Monitoring Board
eGFR	Estimated glomerular filtration rate
ESA	Erythropoiesis stimulating agents (epoetin or darbepoetin)
ESRD	End stage renal disease
Hgb	Hemoglobin
Hct	hematocrit
HR	Hazard ratio
ITT	Intention to treat analysis population
MACE	Major adverse cardiac events (all-cause death, MI, stroke)
mcg	microgram
MI	Myocardial infarction
NHS	Normal Hematocrit Study
RBC	Red blood cell (transfusion)
TREAT	Trial to Reduce Cardiovascular Events with Aranesp® Therapy

TABLE OF TABLES

Table 1: ESA Trial Results for patients with CKD 5
Table 2: Principal Peginesatide clinical trials 10
Table 3: Baseline Demographics AFX01-12 and AFX01-14 (On Dialysis) 12
Table 4: Primary efficacy analysis for trials 12 and 14 13
Table 5: Secondary Efficacy Analysis – Proportion of Patients Receiving Transfusions during the titration and evaluation intervals 13
Table 6: Secondary Efficacy Analysis – Proportion of Patients with Hgb in Target Range during the evaluation interval 14
Table 7: Peginesatide Injection Active Control Trials (non-dialysis) 15
Table 8: Demographics in Studies AFX01-11 and AFX01-13 combined 15
Table 9: Primary Efficacy Analysis AFX01-11 and AFX01-13 (Not On Dialysis) 16
Table 10: Adverse Events AFX01-12 and AFX01-14 Combined (On Dialysis) 17
Table 11: Adverse Events AFX01-11 and AFX01-13 Combined (Not On Dialysis) 17
Table 12: Applicant's Composite Safety Endpoint (On Dialysis) 18
Table 13: Composite Safety Endpoint for trials 11 and 13 combined (Non Dialysis) 18
Table 14: Time to First Event Analysis – MACE events 19
Table 15: MACE outcomes by History of Coronary Artery Disease (CAD) for AFX01-11 and AFX01-13 combined 20
Table 16: MACE outcomes by History of Coronary Artery Disease (CAD) for AFX01-12 and AFX01-14 combined 20
Table 17: MACE outcomes by History of Diabetes for AFX01-11 and AFX01-13 combined 20
Table 18: MACE outcomes by History of Diabetes for AFX01-12 and AFX01-14 combined 20
Table19: Laboratory Excursions - Pooled Analyses……..…..21

Tables were created by FDA unless otherwise indicated.

1. EXECUTIVE SUMMARY

FDA requests that this advisory committee consider the benefits and risks of peginesatide injection, based on the New Drug Application (NDA) 202799, for the applicant's proposed indication:

- Treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

The applicant also proposes that the prescribing information state that:

- Peginesatide is not indicated for use in CKD patients not on dialysis, in patients with cancer receiving chemotherapy, or as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

Currently in the United States there are two approved and marketed erythropoietin based products, i.e., epoetin alfa (Epogen and Procrit) and darbepoetin alfa (Aranesp). Both epoetin and darbepoetin share the following labeled indications:

- Treatment of anemia due to chronic kidney disease, in patients on dialysis and patients not on dialysis
- Treatment of anemia due to the effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy

Since the original approvals of epoetin and darbepoetin, new safety concerns have arisen regarding their use. These concerns are for serious adverse events, including all-cause mortality and arterial thromboses related in some way to the use of ESAs to raise hemoglobin (Hgb) levels in CKD. The main sources of this new safety information were controlled clinical trials published between 1998 and 2009, namely the "Normal Hematocrit Study" (NHS study) (Besarab et al. 1998), the "Correction of Hemoglobin Outcomes in Renal Insufficiency (CHOIR) study" (Singh et al. 2006) and the "Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT)" (Pfeffer et al. 2009). These studies, designed to show superiority in cardiovascular outcomes by targeting higher Hgb levels with the ESAs, demonstrated that this method of therapy increased the risk of cardiovascular adverse events, including – all cause mortality, MI, and/or stroke in those patients treated with ESAs to achieve higher hemoglobin (Hgb) target levels. Current scientific knowledge remains unclear to what extent the ESA dose, the ESA regimen, the hemoglobin rate of rise, the achieved hemoglobin value, the failure to achieve the target hemoglobin (thus requiring additional ESA dose), or some other factor(s) may account for the observed effects in these trials. The Agency reviewed these trials and subsequently revised the prescribing information (PI) for the use of ESAs for the anemia of CKD. The following table is from the current ESA labels'

section 5.1, Warnings and Precautions entitled *Mortality, Myocardial Infarction, Stroke and Thromboembolism*. Further details of these trials are provided in the appendix.

Table 1: ESA Trial Results for patients with CKD

	NHS (N = 1265)	**CHOIR (N = 1432)**	**TREAT (N = 4038)**
Time Period of Trial	1993 to 1996	2003 to 2006	2004 to 2009
Population	CKD patients on hemodialysis with coexisting CHF or CAD, hematocrit 30 ± 3% on epoetin alfa	CKD patients not on dialysis with hemoglobin < 11 g/dL not previously administered epoetin alfa	CKD patients not on dialysis with type II diabetes, hemoglobin ≤ 11 g/dL
Hemoglobin Target – Higher vs. Lower (g/dL)	14.0 vs. 10.0	13.5 vs. 11.3	13.0 vs. ≥ 9.0
Median (Q1, Q3) Achieved Hemoglobin level (g/dL)	12.6 (11.6, 13.3) vs. 10.3 (10.0, 10.7)	13.0 (12.2, 13.4) vs. 11.4 (11.1, 11.6)	12.5 (12.0, 12.8) vs. 10.6 (9.9, 11.3)
Primary Endpoint	All-cause mortality or non-fatal MI	All-cause mortality, MI, hospitalization for CHF, or stroke	All-cause mortality, MI, myocardial ischemia, heart failure, and stroke
Hazard Ratio or Relative Risk (95% CI)	1.28 (1.06 - 1.56)	1.34 (1.03 - 1.74)	1.05 (0.94 - 1.17)
Adverse Outcome for Higher Target Group	All-cause mortality	All-cause mortality	Stroke
Hazard Ratio or Relative Risk (95% CI)	1.27 (1.04 - 1.54)	1.48 (0.97 - 2.27)	1.92 (1.38 - 2.68)

The applicant, Affymax Inc., has submitted the results of 4 trials (2 trials in patients with CKD on dialysis and 2 trials in patients with CKD not on dialysis) to support this NDA. AFX01-12 and AFX01-14 are phase 3 randomized, controlled, open label, multicenter studies in patients with CKD on dialysis. AFX01-11 and AFX01-13 are phase 3

randomized, controlled, open-label, multicenter studies in patients with CKD not on dialysis. The primary efficacy analysis for all four trials was a comparison of the mean change in hemoglobin between the baseline and the evaluation period (weeks 29 to 36 for studies AFX01-12 and14 and weeks 25-36 for studies AFX01-11 and 13). By the protocol specified analysis, peginesatide would be considered non-inferior to the comparator (epoetin for the on-dialysis trials and darbepoetin for the non-dialysis trials) if the lower limit of the two-sided 95% CI for the difference between the two treatment groups' mean changes of hemoglobin (peginesatide - epoetin) from baseline was ≥ -1.0 g/dL for the on-dialysis trials and if the lower limit of the two-sided 97.5% CI for the difference between the two treatment groups' mean change of hemoglobin (peginesatide - darbepoetin) from baseline was ≥ -1.0 g/dL for the non-dialysis trials (with two peginesatide treatment groups).

For the two "on-dialysis" trials, based on the pre-specified efficacy analysis plan for each trial, the applicant has concluded and FDA agrees that Peginesatide is non-inferior to epoetin.

For the two "not-on-dialysis" trials, based on the pre-specified efficacy analysis plan for each trial, the applicant has concluded and FDA agrees that Peginesatide is non-inferior to darbepoetin.

The major concern raised by these trials is the uncertainty about the evidence for the safety of peginesatide. The trials were sized to assess safety, and the applicant pre-specified that the primary analysis of the safety outcomes for each trial should be performed using a safety composite endpoint and that the results should be compared using 90% confidence intervals. The composite safety endpoint (CSE), defined as the first occurrence of any one event of death, stroke, myocardial infarction, congestive heart failure, unstable angina, or arrhythmia, was the primary protocol specified safety endpoint for analysis. An additional planned safety analysis was to be performed assessing the MACE composite endpoint – major adverse cardiac events (defined as the first occurrence of death, stroke or myocardial infarction).

The safety outcomes in both on-dialysis trials (AFX01-12 and AFX01-14) appear similar for both treatment groups for both the CSE and the MACE endpoints.

However, in the two non-dialysis trials (AFX01-11 and AFX01-13), there are differences in the safety outcomes, with results unfavorable for peginesatide. Differences in baseline characteristics unfavorable to peginesatide are acknowledged. Using the applicant's pre-specified primary safety analysis plan and the CSE outcomes, the safety of peginesatide appears to be statistically significantly inferior to darbepoetin. However, using the applicant's secondary analysis plan comparing MACE outcomes, and using a 95% confidence interval, the safety outcomes for peginesatide are numerically worse, but they are not statistically significantly different from that of the darbepoetin-treated group. Statistical testing of the safety outcomes is appropriate since these were pre-specified outcomes for analysis and were considerations in determining the sample sizes. Also, the trial results must be considered in the context of safety of the ESA

comparator (in this case, darbepoetin), which in and of itself is confounded by safety concerns as were discussed above.

FDA is asking the committee's advice about the benefit risk profile of peginesatide for patients with CKD, given the safety findings and in light of the prior history with agents that stimulate the erythropoietin receptor.

2. BACKGROUND

Erythropoietin, the primary growth factor for erythroid development, is produced in the kidney, released into the bloodstream, and functions as a protein hormone. It binds to the erythropoietin receptor on erythroid progenitor cells, activating signaling pathways which stimulate red blood cell production, or erythropoiesis, and inhibiting apoptosis, resulting in an increase in red blood cell levels. In patients with CKD, while anemia can be multi-factorial, anemia due to the CKD occurs primarily because production of erythropoietin is impaired by the kidney disease.

The erythropoiesis-stimulating agents (ESAs) currently licensed and marketed in the U.S. are recombinant erythropoietins and stimulate red blood cell production similar to the endogenous protein. The first ESA, epoetin alfa, was approved in 1989 for patients with the anemia of chronic renal disease to raise the hemoglobin level and reduce the need for red blood cell transfusions. There are two ESA products currently approved and marketed in the U.S., epoetin alfa (Epogen/Procrit) and darbepoetin alfa (Aranesp), all of which are polypeptides with amino acid sequence homology to endogenous erythropoietin. These ESAs share the following principal indications:

- Treatment of anemia associated with CKD, including patients on dialysis and patients not on dialysis.
- Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy

Peginesatide is a synthetic, pegylated dimeric peptide molecule comprised of two [redacted] amino acid chains covalently bonded to a linker derived from [redacted]. The peptide structure shares no homology with erythropoietin and for this reason the applicant claims that peginesatide has a decreased risk of pure red cell aplasia (PRCA).

PRCA is a rare adverse reaction that can occur with ESA treatment resulting in a life-threatening anemia. The mechanism involves an immune reaction during therapy with administered erythropoietins in which an anti-erythropoietin antibody cross-reacts with endogenous erythropoietin and blocks erythropoietin function. McKoy et al in 2008 reported that, since 2002, FDA safety databases included reports on 59 new cases of PRCA.

The applicant's proposed indication for peginesatide is as follows:

- Treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

The applicant also proposes that the prescribing information state that:

- Peginesatide is not indicated for use in CKD patients not on dialysis, in patients with cancer receiving chemotherapy, or as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

At the End of Phase 2 meeting with the applicant on February 23, 2007, the 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 must show consistency with regard to safety and efficacy.

Since the original approval of epoetin alfa and darbepoetin alfa, new safety concerns have arisen regarding their use. The concerns relate to increased risks for certain serious adverse events, i.e., all cause mortality and arterial thrombotic events, but the relationship of these events to factors such as target hemoglobin levels, dosage of ESA, underlying diseases or other factors is unclear. The main sources of this new safety information were three major trials, the "Normal Hematocrit Study" (NHS study) (Besarab et al. 1998), the "Correction of Hemoglobin Outcomes in Renal Insufficiency (CHOIR) study" (Singh et al. 2006), and the "Trial to Reduce Cardiovascular Events with Aranesp® Therapy" (TREAT) (Pfeffer et al. 2009).

The NHS study was an open-label study that enrolled 1265 patients with anemia due to CKD receiving hemodialysis and with a history of either chronic heart failure or ischemic heart disease. The baseline hematocrit (Hct) levels were 27% to 33%. Epoetin alfa was administered in both study arms, and patients were randomized to maintain a target Hct of 42 +/- 3%, i.e., a "normal" hematocrit or to maintain a target Hct of 30 +/- 3%, i.e., a low hematocrit. The primary efficacy endpoint was the time to death or first non-fatal myocardial infarction. The trial was terminated prematurely for adverse safety outcomes. There were 183 deaths and 19 first non-fatal myocardial infarctions (MIs) in the normal Hct group compared with 150 deaths and 14 non-fatal MIs in the low Hct group. The risk ratio for all-cause mortality was 1.27 (95% CI = 1.04 - 1.54) showing a significantly greater mortality in the group targeted to the normal hematocrit level.

The CHOIR trial was an open label study that enrolled 1432 patients with anemia due to CKD not receiving dialysis. The baseline hemoglobin (Hgb) was < 11 g/dL. These patients were treated with epoetin alfa and randomized to maintain a target Hgb of either 13.5g/dL, i.e., a higher Hgb group or to a target Hgb of 11.3 g/dL, i.e., a lower Hgb group. The primary efficacy endpoint was a composite endpoint of the time to death or time to first event of non-fatal MI, hospitalization for congestive heart failure, or stroke. The trial was terminated prematurely for adverse safety outcomes. There were

125/715 (18%) patients in the high Hgb group compared to 97/717 (14%) in the low Hgb group that experienced the composite endpoint. The hazard ratio for the composite primary endpoint was 1.34 (95% CI =1.03, 1.74), significantly favoring the lower Hgb group.

The TREAT trial was the first double blind study (for both Hgb levels and ESA/placebo dosing) and enrolled 4038 patients with anemia due to CKD and with type 2 diabetes who were not receiving dialysis. The baseline Hgb was ≤ 11 g/dL. Further details are noted in the appendix. There were two primary efficacy endpoints: (1) a composite outcome of death or cardiovascular events, and (2) a composite outcome of further renal deterioration to end stage renal disease or cardiovascular events. Patients were randomized to receive darbepoetin to maintain a Hgb target of 13 g/dL or to a matched placebo. Placebo patients also received "rescue" with darbepoetin treatment if and while their Hgb was below 9 g/dL. The determination of Hgb levels and the dosing with darbepoetin or placebo in both groups was based on a computer algorithm and was a blinded procedure. In TREAT, there were 632/2012 (31%) of patients in the darbepoetin group and 602/2026 (30%) of patients in the control group who had a composite cardiovascular primary endpoint event. The hazard ratio was 1.05 (95% CI = 0.94, 1.17), favoring the placebo group. For the renal composite primary endpoint, there were 652 (32%) of patients in the darbepoetin group and 618 (31%) of patients in the placebo group that had a primary endpoint event. The hazard ratio was 1.06 (95% CI = 0.95, 1.19) favoring the placebo group. Notably in this study, fatal or non-fatal stroke, a pre-specified individual primary endpoint event for analysis, occurred in 101 patients assigned to darbepoetin and 53 patients assigned to control therapy. The hazard ratio was 1.92 (95% CI = 1.38, 2.68), significantly favoring the control group. Since 46% of placebo patients also received darbepoetin during the trial, the true hazard ratio for stroke may be greater than that observed in TREAT.

Taken together, these studies raised substantial safety concerns associated with ESA therapy for the anemia of CKD. Based on an earlier FDA analysis in 2007, the ESA labels were revised to include boxed warnings which stated that patients with CKD experienced greater risks of death and serious CV events when administered ESAs to target higher Hgb versus lower Hgb levels. It was also recommended that prescribers individualize dosing to achieve and maintain Hgb within the range of 10 to 12 g/dL In June 2011, the ESA labels were amended again to include the warning that in controlled clinical trials there were greater risks for death, serious adverse cardiovascular reactions, and stroke when targeting Hgb levels greater than 11 g/dL. The labels recommend that prescribers: individualize dosing for patients with CKD and use the lowest dose sufficient to reduce the need for red blood cell transfusions; to initiate ESA therapy when the Hgb is less than 10 g/dL, and to reduce or interrupt the dose if the Hgb approaches or exceeds 10 - 11 g/dL. No trial has identified a Hgb target level, ESA dose, or dosing strategy that does not increase these risks. Notably, this advice does not define how far below 10 g/dL may be appropriate for an individual to initiate ESA therapy, since physicians and patients must weigh the benefits and risks of ESA therapy versus transfusion therapy for each individual. This advice also does not

recommend that the goal is to achieve a Hgb of ≥ 10 g/dL or a specific target level, for the same reasons.

3. PEGINESATIDE PRINCIPAL TRIALS

The principal active control comparative trials that were submitted to support the approval of peginesatide are shown in the table below. Studies AFX01-11 and AFX01-13 were similarly designed studies conducted in patients with anemia due to CKD who were not on dialysis and not on ESA therapy for at least the preceding 12 weeks. Patients were randomized to receive treatment with either peginesatide subcutaneously or with darbepoetin. In the two trials combined, there were 656 patients enrolled into the peginesatide arms and 327 patients enrolled into the darbepoetin arms in the US and EU.

Studies AFX01-12 and AFX01-14 were similarly designed studies conducted in anemic patients with anemia due to CKD who were on dialysis and previously treated with an ESA. Patients were randomized to receive treatment either with peginesatide intravenously or subcutaneously, or with epoetin alpha or beta in the control arm of the study. In the two trials combined, there were a total of 1066 patients enrolled into the Peginesatide arm and 542 patients enrolled into the epoetin treatment arm, combined in the US and Europe.

Table 2: Principal Peginesatide clinical trials

Trial	Subjects with anemia due to CKD	Control	Sample Size (Peginesatide: Control)	Regions
AFX01-11	Non-Dialysis Not on ESA	Darbepoetin	326:164	US
AFX01-13	Non-Dialysis Not on ESA	Darbepoetin	330:163	US/Europe
AFX01-12	On dialysis and previously treated with Epoetin (IV)	Epoetin alfa	524:269	US
AFX01-14	On dialysis and previously treated with Epoetin (IV/SC)	Epoetin alfa or beta	542:273	US/Europe

3.1 Peginesatide AFX01-12 and AFX01-14 (On - Dialysis)

Trials AFX01-12 and AFX01-14 were similarly designed trials in which the primary objective was to determine efficacy and safety while maintaining the hemoglobin level in the 10- 12 g/dL range. These trials were Phase 3, open label, randomized (2:1), multicenter studies conducted in the United States and Europe and enrolled adult patients with CKD and anemia who were iron replete. The key inclusion criteria were that patients had to be on dialysis for ≥ 3 months and were receiving ESA therapy. Also, patients had to have a mean baseline Hgb ≥10g/dL to ≤ 12g/dL. Patients were randomized 2:1 to either peginesatide (starting doses of 0.04 to 0.16 mg/kg based on prior maintenance epoetin dose) administered intravenously (IV) or subcutaneously (SC) once every 4 weeks, following a 1 week ESA free period from last dose of epoetin; or to continuing treatment with epoetin administered at the current dose 1-3 times per week. The studies consisted of a 6 week screening period, up to 28 weeks of dose titration, followed by a 6 week evaluation period and then a longer term safety evaluation period for 15 weeks or more. Hemoglobin levels were measured once during the screening period, every 2 weeks during the titration period, every week during the evaluation period, and every 2 weeks during the long term safety period. The primary efficacy analysis for these studies was a comparison of the mean change in Hgb from baseline to the evaluation period (weeks 29 to 36) between the two treatment groups. Secondary endpoints included proportion of patients receiving a transfusion and the proportion of patients whose Hgb was maintained in the range of ≥ 10g/dL to ≤ 12 g/dL.

The applicant proposed that peginesatide would be considered non-inferior to epoetin if the lower limit of the two-sided 95% CI for the difference between the two treatment group's mean changes of Hgb (Peginesatide - Epoetin) from baseline was ≥ -1.0 g/dL. The applicant provided support for this choice of a non-inferiority margin of 1.0 g/dL by showing that a statistical lower bound for the effect of ESA therapy based on data from historical ESA registration studies was appreciably greater than 1.0 g/dL. The clinical importance of a 1.0 g/dL change in Hgb was also considered in selecting this margin. Further support was provided by citing the impact of evolving clinical practice including the timing of initiation of ESA therapy and changes in Hgb targets. Patients were stratified based on Hgb ≤ 11.4g/dL or ≥ 11.5g/dL and New York Heart Association (NYHA) Heart Failure class 0-1 or class ≥ 2. Enrollment in studies AFX01-12 and AFX01-14 is shown in the preceding table.

The baseline demographics for patients in AFX01-12 and AFX01-14 are shown in the table below. Overall, the pooled treatment groups in the on dialysis population were balanced for baseline characteristics, except a greater percentage of patients in the Peginesatide group (42%) had a history of coronary artery disease at baseline versus those in the epoetin treatment group (35%). Epoetin use at baseline was similar also for both study arms.

Table 3: Baseline Demographics AFX01-12 and AFX01-14 (On Dialysis)

	Peginesatide (N = 1066) n (%)	Epoetin (N= 542) n (%)
Age ≥ 65 years (%)	346 (33)	179 (33)
Gender Female (%)	442 (42)	245 (45)
Race: Black (%) White (%)	399 (37) 617 (58)	211 (39) 299 (55)
Diabetes	536 (50)	275 (51)
History Coronary Artery Disease	447 (42)	191 (35)
Epoetin dose at screening Median (25th-75th) U/kg/wk	113 (63-194) U/kg/wk	112 (65-216) U/kg/wk

For the primary efficacy analysis for AFX01-12, the mean Hgb change from baseline to weeks 29-36 of the evaluation period was -0.24 g/dL in the peginesatide arm and -0.09 g/dL in the epoetin arm; the between group difference was -0.15 g/dL (95% CI = -0.30, -0.01). For trial AFX01-14, the mean Hgb change from baseline to weeks 29-36 of the evaluation period was -0.07 g/dL in the peginesatide arm and -0.17 g/dL in the epoetin treatment arm; the between group difference was 0.10 g/dL (95% CI = -0.05, 0.26). The results show that Peginesatide can be considered non-inferior to epoetin by the applicant's criteria because the lower limit of the two-sided 95% CI difference between the two treatment group's mean changes of Hgb (Peginesatide - Epoetin) from baseline was > -1.0 g/dL. The primary efficacy results for trials -12 and -14 are shown in the table below.

Table 4: **Primary efficacy analysis for trials 12 and 14**

	AFX01-12		AFX01-14	
	Peginesatide (n=524)	Epoetin (n=269)	Peginesatide (n=542)	Epoetin (n=273)
Mean Hemoglobin at Baseline, g/dL (SE)	11.30 (0.02)	11.32 (0.03)	11.20 (0.02)	11.21 (0.03)
Mean Hemoglobin Week 29-36, Mean g/dL (SE)	11.06 (0.04)	11.25 (0.05)	11.13 (0.05)	11.05 (0.06)
Mean change in hemoglobin g/dL	-0.24	-0.09	-0.07	-0.17
Between group difference (g/dL), Least Squares Mean (95% CI)	-0.15 (-0.30,-0.01)		0.10 (-0.05,0.26)	

The secondary efficacy analysis of the proportion of patients receiving transfusions in studies AFX01-12 and AFX01-14 during the titration and evaluation intervals is shown in the table below. In both studies similar proportions of patients received transfusions in both treatment arms.

Table 5: Secondary Efficacy Analysis – Proportion of Patients Receiving Transfusions during the titration and evaluation intervals

	AFX01-12		AFX01-14	
	Peginesatide (n=524)	Epoetin (n=269)	Peginesatide (n=542)	Epoetin (n=273)
Patients receiving transfusions, n (%)	54 (10%)	23 (9%)	42 (8%)	27 (10%)

The secondary efficacy analysis of the proportion of patients with mean Hgb within the sponsor's target range of 10 g/dL to 12 g/dL during the evaluation period in the dialysis studies is shown in the table below. The table shows the proportions of patients with mean hemoglobin values within the target range in the 2 trials and the ratios of Hgb response rates.

Table 6: Secondary Efficacy Analysis – Proportion of Patients with Hgb in Target Range during the evaluation interval

	AFX01-12		AFX01-14	
	Peginesatide (n=524)	Epoetin (n=269)	Peginesatide (n=542)	Epoetin (n=273)
Patients with mean Hgb within target range (10-12 g/dL) during evaluation period n (%)	330 (63%)	193 (72%)	344 (64%)	180 (66%)
Relative Response Rate*	0.88 (0.79,0.97)		0.96 (0.87,1.07)	

* Peg/Epo by CMH procedure

3.2 Peginesatide Trials AFX01-11 and AFX01-13 (Not On Dialysis)

AFX01-11 and AFX01-13 were similarly designed trials in which the primary objective was to evaluate the efficacy and safety of peginesatide in maintaining the hemoglobin level in the target range of 11-12 g/dL. These trials were Phase 3, open label, multicenter studies conducted in the United States and Europe and adult patients with anemia of CKD who were iron replete. The key inclusion criteria into these studies were that patients were not on dialysis but were previously on stable ESA therapy and all ESA therapy had been discontinued for at least 12 weeks. Also, patients had to have a mean baseline Hgb ≥8g/dL and ≤ 11g/dL. Patients were randomized 1:1:1 to either peginesatide 0.025 mg/kg or 0.04 mg/kg starting doses or to darbepoetin 0.75 µg/kg starting doses. Peginesatide was administered subcutaneously once every 4 weeks. Darbepoetin was administered once every 2 weeks. The studies consisted of a 4 week screening period, up to 24 weeks of dose titration to the target range, followed by the evaluation period (weeks 25 to 36) and then a long term safety evaluation period for 15 weeks or more. Hemoglobin levels were measured once during the screening period, every 2 weeks during the titration period, every week during the evaluation period and every 2 weeks during the long term safety period.

The applicant proposed that the primary endpoint and analysis for these trials was a non-inferiority analysis of the mean change in Hgb from baseline to the evaluation period (Weeks 25 to 36). Peginesatide would be considered non-inferior to epoetin if the lower limit of the two-sided 95% CI for the difference between the two treatment groups' mean changes of Hgb (Peginesatide - Darbepoetin) from baseline was ≥ -1.0 g/dL, similar to that in the dialysis studies. This choice of non-inferiority margin is the same as that described above for the dialysis studies. Patients were stratified based on Hgb ≤ 10.4g/dL or ≥ 10.5g/dL and NYHA Heart Failure 0-1 or ≥ Class 2. The table below shows the enrollment for studies AFX01-11 and AFX01-13.

Table 7: Peginesatide Injection Active Control Trials (non-dialysis)

Study	Patients with CKD	Control	Sample Size (Peginesatide: Control)	Regions
AFX01-11	Non-Dialysis no ESA ≥ 12 wks	Darbepoetin	326:164	US
AFX01-13	Non-Dialysis no ESA ≥ 12 wks	Darbepoetin	330:163	US/Europe

The table below shows that the pooled Phase 3 non-dialysis population had some baseline imbalances which may have been prognostically unfavorable for the peginesatide treatment arm, including a greater proportion of patients with diabetes mellitus, peripheral vascular disease, and coronary artery disease.

Table 8: Demographics in Studies AFX01-11 and AFX01-13 combined

	AFX01-11 and AFX01-13 (Non-dialysis)	
	Peginesatide n = 656 N (%)	Darbepoetin n = 327 N (%)
Age ≥ 65 years (%)	403 (61)	200 (61)
Gender Female (%)	366 (56)	201 (61)
Race Black (%) White (%)	142 (22) 482 (74)	78 (24) 231 (71)
Diabetes at baseline	444 (68)	197 (60)
PVD at baseline	179 (28)	65 (20)
History of CAD at baseline	264 (40)	125 (38)

PVD: peripheral vascular disease
CAD: coronary artery disease

For the primary efficacy analysis, the mean Hgb change from baseline to weeks 25-36 (the evaluation period) in AFX01-11 and AFX01-13 in those patients treated with peginesatide 0.025mg/kg was 1.45 g/dL. For those patients treated with peginesatide 0.04 mg/kg the mean Hgb change from baseline at weeks 25-36 in these studies was 1.66 g/dL. In the darbepoetin treatment arm the mean Hgb change from baseline at weeks 25-36 in these studies was 1.36 g/dL. The between group difference was 0.08 g/dL (97.5% CI = -0.08, 0.24) in the peginesatide 0.025mg/kg treatment arm and 0.29 (97.5% CI = 0.13, 0.45) for the 0.04mg/kg peginesatide treatment arm. The results show that Peginesatide can be considered non-inferior to epoetin by the applicant's pre-specified criteria because the lower limit of the two-sided 95% CI difference between the two treatment groups mean changes of Hgb (Peginesatide - Epoetin) from baseline was > -1.0 g/dL. The table below summarizes the primary efficacy analysis for studies AFX01-11 and AFX0-1-13.

Table 9: Primary Efficacy Analysis AFX01-11 and AFX01-13 (Not On Dialysis)

	AFX01-11 and AFX01-13		
	Peginesatide 0.025 mg/kg q4wk N= 328	Peginesatide 0.04 mg/kg q4wk N = 328	Darbepoetin 0.75µg/kg q2wk N = 327
Baseline Hgb g/dL Mean (SE)	10.03 (0.03)	9.99 (0.04)	10.04 (0.04)
Evaluation period mean Hgb g/dL (SE)	11.51 (0.04)	11.66 (0.05)	11.43 (0.04)
Hgb mean change from baseline to Weeks 25-36 g/dL	1.45	1.66	1.36
Difference from Darbepoetin by Least Squares mean (2 sided 97.5% CI)	0.08 (-0.08, 0.24)	0.29 (0.13, 0.45)	

3.3 Peginesatide Safety Analyses

The 2 tables below show the adverse events in the combined AFX01-12 and AFX01-14 (On Dialysis) and the adverse events in the combined AFX01-11 and AFX01-13 (Not On Dialysis) trials. The tables show that overall, in studies AFX01-12 and AFX01-14, there were similar proportions of patients with adverse events, serious adverse events, deaths, adverse events ≥ grade 3 and adverse events leading to permanent discontinuation of the study drug. However, in studies AFX01-11 and AFX01-13 (patients with CKD who were not on dialysis) there was a greater percentage of

peginesatide-treated patients who had adverse events, serious adverse events, deaths, adverse events ≥ grade 3 and adverse events leading to permanent discontinuation of the study drug.

Table 10: Adverse Events AFX01-12 and AFX01-14 Combined (On Dialysis)

	Peginesatide (n=1066) N (%)	Epoetin (n=542) N (%)
Adverse Events	1008 (95)	504 (93)
Serious Adverse Events	572 (54)	309 (57)
Deaths	115 (11)	64 (12)
Adverse Events ≥ Grade 3	549 (52)	286 (53)
Adverse Events Leading To Permanent Discontinuation	136 (13)	65 (12)

Table 11: Adverse Events AFX01-11 and AFX01-13 Combined (Not On Dialysis)

	Peginesatide (n=656) N (%)	Darbepoetin (n=327) N (%)
Adverse Events	614 (94)	299 (91)
Serious Adverse Events	318 (49)	141 (43)
Deaths	58 (9)	22 (7)
Adverse Events ≥ Grade 3	311 (47)	130 (40)
Adverse Events Leading To Permanent Discontinuation	85 (13)	34 (10)

Safety analyses by CSE:
Recall that the applicant's pre-specified primary safety analysis plan was to compare the prospectively defined CSE events (death, stroke, MI, congestive heart failure, unstable angina, and arrhythmia) between the two treatments for all four of the trials using a stratified Cox model and 90% confidence intervals. The results of the safety analyses assessing the primary safety endpoint CSE, are shown in the tables below. Adjudication of all primary safety endpoint events was performed by an independent adjudication committee blinded to treatment group.

Table 12: Applicant's Composite Safety Endpoint (On Dialysis)

	AFX01-12 and AFX 01-14 combined Composite Safety Events*	
	Peginesatide (n=1066) N (%)	Epoetin (n=542) N (%)
Subjects with Events	243 (23)	132 (24)
HR	0.95	
90%CI	(0.79, 1.13)	

*CSE: Death, Stroke, MI, Congestive Heart Failure, Unstable Angina, Arrhythmia

The table above shows the number and proportion of patients with primary composite safety events 243/166 (23%) in the peginesatide treatment arm compared to 132/542 (24%) in the epoetin treatment arm for patients enrolled into studies AFX01-12 and AFX01-14, i.e., the on dialysis studies. The hazard ratio was 0.95 (90% CI = 0.79, 1.13).

However, in trials AFX01-11 and AFX01-13, i.e., the not on dialysis studies, there were 141/656 (22%) of patients treated with peginesatide compared to 56/327 (17%) of patients in the darbepoetin treatment arm who had primary composite safety events. The hazard ratio was 1.32 (90% CI = 1.02, 1.72) which was statistically significantly different favoring darbepoetin as shown in the table below.

Table 13: Composite Safety Endpoint for trials 11 and 13 combined (Non Dialysis)

	AFX01-11 and AFX01-13 Composite Safety Events*	
	Peginesatide (n=656) N (%)	Darbepoetin (n=327) N (%)
Subjects with Events	141 (22)	56 (17)
HR	1.32	
90%CI	(1.02, 1.72)	

* CSE: Death, Stroke, MI, Congestive Heart Failure, Unstable Angina, Arrhythmia

Safety analyses by MACE:
Analysis of the composite MACE safety events, (death, stroke and MI) is shown in the table below. Also shown are individual event analyses of all cause death and of stroke. This table shows that, for time to first event, there is a numerically higher risk of MACE events, and for all cause death and for stroke in those patients not on dialysis who were treated with peginesatide compared to darbepoetin. However, these results, individually or when combined as the composite MACE outcome, are not statistically significantly different using the conventional 95% confidence interval of possible results.

Table 14: Time to First Event Analysis – MACE events

	Dialysis		**Non-Dialysis**	
	Peginesatide (N=1066)	Epoetin-alfa/beta (N=542)	Peginesatide (N=656)	Darbepoetin (N=327)
MACE				
# of Events	161 (15%)	96 (18%)	80 (12%)	30 (9%)
HR (95% CI)	0.83 (0.65, 1.07)		1.28 (0.84, 1.94)	
All Cause Death				
# of Events	136 (12.8%)	68 (12.5%)	73 (11.1%)	24 (7.3%)
HR (95% CI)	0.99 (0.74, 1.33)		1.37 (0.86, 2.17)	
Stroke				
# of Events	122 (11.4%)	72 (13.3%)	53 (8.1%)	23 (7.0%)
HR (95% CI)	0.84 (0.63, 1.13)		1.10 (0.67, 1.80)	

All hazard ratios are based on a Cox proportional hazards model stratified by study, mean baseline hemoglobin, and New York Heart Association heart failure class

3.4 Additional Exploratory Analyses

Additional analyses were performed to explore the possible impact of imbalances of baseline characteristics on the comparison of safety events between peginesatide and darbepoetin in the not on dialysis trials, in contrast to the similarity in safety outcomes for the on-dialysis trials using epoetin as the comparator.

The differences in baseline characteristics for the treatment groups in the two not-on-dialysis trials have been noted. Analyses of demographic covariates which may have influenced the safety outcomes are shown in the tables below. The history of coronary artery disease is an independent significant covariate, i.e., a history of coronary artery disease would significantly increase the MACE events. However, there is no interaction between the history of coronary artery disease and treatment. That is, whether or not there is the history of coronary artery disease does not appear to change the treatment effect.

Table 15: MACE outcomes by History of Coronary Artery Disease (CAD) for AFX01-11 and AFX01-13 combined

MACE events (11 and 13)	Peginesatide N (%)	Darbepoetin N (%)
History of CAD	41 (15.5%)	17 (13.6%)
No History of CAD	39 (10.0%)	13 (6.4%)

Table 16: MACE outcomes by History of Coronary Artery Disease (CAD) for AFX01-12 and AFX01-14 combined

MACE events (12 and 14)	Peginesatide N (%)	Epoetin-alfa/beta N (%)
History of CAD	97 (21.7%)	45 (23.6%)
No History of CAD	64 (10.3%)	51 (14.5%)

In addition, history of diabetes does not appear to be a significantly different covariate. Also there does not appear to be an interaction between a history of diabetes and safety outcomes on treatment.

Table 17: MACE outcomes by History of Diabetes for AFX01-11 and AFX01-13 combined

MACE events (11 and 13)	Peginesatide N (%)	Darbepoetin N (%)
History of Diabetes	58 (13.1%)	19 (9.6%)
No History of Diabetes	22 (10.4%)	11 (8.5%)

Table 18: MACE outcomes by History of Diabetes for AFX01-12 and AFX01-14 combined

MACE events (12 and 14)	Peginesatide N (%)	Epoetin-alfa/beta N (%)
History of Diabetes	98 (18.3%	54 (19.6%)
No History of Diabetes	63 (11.9%)	42 (15.7%)

The table below analyzes excursions in either leukocytosis, i.e., white blood cell counts > 15,000/μL, or thrombocytosis, platelet counts > 600,000/μL. In particular, in AFX01-11 and AFX01-13, i.e., in the not on dialysis studies, there were similar proportions of patients in each treatment arm with leukocytosis and thrombocytosis. There were approximately 4% of patients treated with peginesatide and 5% of patients treated

darbepoetin who had leukocytosis. There were approximately 1% of patients in each treatment arm with thrombocytosis.

Table19: Laboratory Excursions - Pooled Analyses

CKD On Dialysis - AFX01-12 and AFX01-14		
	Peginesatide (%) N (%)	Epoetin (%) N (%)
Leukocytosis > 15,000/µL	24 (2.3%)	29 (5.5%)
Thrombocytosis > 600,000/µL	13 (1.2%)	2 (0.4%)
CKD Non-Dialysis - AFX01-11 and AFX01-13		
	Peginesatide (%) N (%)	Darbepoetin (%) N (%)
Leukocytosis > 15,000/µL	23 (3.5%)	15 (4.7%)
Thrombocytosis > 600,000/µL	9 (1.4%)	4 (1.2%)

3.5 Immunogenicity

Among 2357 patients who received one or more doses of peginesatide, specific binding antibodies were detected in 29 patients (1.2%). In 21 of these 29, the antibodies neutralized the activity of peginesatide in an *in vitro* test system. In 17 of the 29, a possible impairment of therapeutic effect was concluded based on the occurrence of at least two of the following: drop in Hgb by > 2 g/dL, two or more Hgb values < 9 g/dL, an increase in drug dose, or transfusion use. Hypersensitivity or anaphylactic-type reactions were not reported.

4. CONCLUSIONS

Trials AFX01-12 and AFX01-14 were designed to evaluate the safety and efficacy of peginesatide treatment compared to epoetin treatment in patients with anemia due to CKD who were on dialysis. Trials AFX01-11 and AFX01-13 were designed to evaluate the safety and efficacy of peginesatide treatment compared to darbepoetin treatment in patients with anemia due to CKD who were not on dialysis. In patients on dialysis or not on dialysis, the trials show that peginesatide is non-inferior to epoetin or to darbepoetin, respectively, in its ability to maintain Hgb levels in the protocols' target range of 10-12g/dL. Also, in patients with CKD who are on dialysis, peginesatide appears to show similar safety results when compared to epoetin by both CSE and MACE outcomes.

However, in patients with CKD not on dialysis (trials AFX01-11 and AFX01-13), there is an imbalance in safety outcomes that was significantly different by the applicant's planned analysis of CSE (HR 1.32 (90% CI = 1.02, 1.72), unfavorable to peginesatide. When assessed by MACE outcomes and with a 95% confidence interval, the difference,

while still numerically unfavorable to peginesatide, was not significantly different in these two trials. There were baseline imbalances unfavorable to peginesatide in the proportion of patients with diabetes, peripheral vascular disease, and coronary heart disease. Whether the difference in safety outcomes can be attributed to the baseline demographic imbalances is uncertain. Exploratory analyses of the imbalances do not identify a treatment interaction.

Adjudication of the safety events was performed by a blinded independent adjudication Committee. Endpoints such as death, MI and stroke as used in the MACE analyses for safety, are considered “hard” endpoints that would be less likely to be subject to bias in adjudication and are of greater clinical consequence. Also there did not appear to be an imbalance in the proportion of patients with abnormal laboratory results such as leukocytosis or thrombocytosis which could potentially increase the risk of thrombosis.

Given the above findings and in light of the recent Agency reassessment/relabeling of the ESAs, the FDA seeks advice from the ODAC and a recommendation as to whether there is a favorable benefit/risk ratio for peginesatide treatment for patients with anemia due to CKD.

5. References

Besarab, A. M.D., Kline Bolton, W., M.D., Browne, J. K., Ph.D., Egrie, J. C., Ph.D., Nissenson, A.R., M.D., Okamoto, D.M., Ph.D., Schwab, S.J., M.D., and Goodkin, D.A., M.D. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Eng J Med. 1998;339:584-90.

Singh, A.K., M.B., B.S., Szczech, L. M.D., Tang, K.L. Ph.D.,Barnhart, H., Ph.D., Sapp, S. M.S., Wolfson, M., M.D., and Reddan, D. M.B., B.S., for the CHOIR Investigators. Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease. N Eng J Med. 2006; 355:2085-2098.

Pfeffer, M.A., M.D., Ph.D., Burdmann, E.A., M.D., Ph.D., Chen, C.-Y., Ph.D., Cooper, M.E., M.D., de Zeeuw, D. M.D., Ph.D., Eckardt, K.-U., M.D., Feyzi, J. M., M.S., Ivanovich, P., M.D., Kewalramani, R., M.D., Levey, A.S., M.D., Lewis, E.F., M.D., M.P.H., McGill, J.B., M.D., McMurray, J.J., M.D., Parfrey, P., M.D., Parving, H.-H., M.D., Remuzzi, G., M.D., Singh, A. K., M.D., Solomon, S.D., M.D., and Toto, R., M.D., for the TREAT Investigators A Trial of Darbepoetin Alfa in Type II Diabetes and Chronic Kidney Disease. N Eng J Med. 2009;361:2019-32.

6. Appendix

Summary of four published prospective controlled trials of ESAs in CKD

Trial	ESA	Design	Primary Efficacy Endpoint	Result
Normal Hematocrit Study	Epoetin alfa	open-label enrolling subjects with CRF receiving hemodialysis with a history of either chronic heart failure or ischemic heart disease; randomization to maintain a target Hct of 42 ± 3% ("normal" Hct) or to maintain a target Hct of 30 ±3% (low Hct)	time to death or first non-fatal myocardial infarction	1265 subjects enrolled; 183 deaths and 19 first non-fatal MIs in the normal Hct group compared with 150 deaths and 14 non-fatal MIs in the low Hct group,; risk ratio for the composite endpoint of 1.3 (95% CI 0.9, 1.9) favoring low HCT treatment
Correction of Hemoglobin and Outcomes in Renal Insufficiency CHOIR	Epoetin alfa	open-label enrolling subjects with CRF not receiving dialysis; randomization to maintain a target Hgb of either 13.5 g/dL (high Hgb group) or 11.3 g/dL (low Hgb group)	time to the composite of death, non-fatal myocardial infarction, hospitalization for congestive heart failure, and stroke	1432 subjects enrolled; 125 (17.5%) of the 715 subjects in the high Hgb group compared to 97 (13.5%) of the 717 subjects in the low Hgb group (HR 1.34; 95% CI 1.03, 1.74; p=0.03)
CREATE*	Erythropoietin beta**	open-label enrolling subjects with CRF not receiving dialysis; randomization to randomized to a high hemoglobin target (13 to 15 g/dL) or a low hemoglobin target (10.5 to 11.5 g/dL); with rescue ESA therapy	composite of eight cardiovascular events: sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization for 24 hours or more or prolongation of hospitalization, complication of peripheral vascular disease (amputation or necrosis), or cardiac arrhythmia resulting in hospitalization for 24 hours or more.	603 subjects enrolled; Overall, a primary endpoint event occurred in 58 of 301 (19.3%) subjects in the high hemoglobin group and 47 of 302 (15.6%) subjects in the low hemoglobin group, with a hazard ratio of 0.78 (95% CI 0.53 to 1.14, p = 0.20). ***
TREAT	Darbepoetin alfa	Double-blind, subjects with CRF not receiving dialysis; randomization to randomized to a high hemoglobin target (13.5 g/dL) or a placebo; with rescue ESA therapy if hemoglobin level falls below 9 g/dl	CV composite endpoint and renal composite endpoint	4038 subjects enrolled; 632 CV (31%) events in the DA group and 602 (30%) events in the placebo group, 1.05 (95% CI 0.94, 1.17); 1270 renal composite endpoint events occurred: 652 (32%) events in the DA group and 618 (31%) events in the placebo group, 1.06 (95% CI 0.95, 1.19), and p-value of 0.29.