

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202799Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL TEAM LEADER REVIEW MEMO

NDA/ Serial Number: 202-799/ 0000

Drug Name: Peginesatide injection (OMONTYS®)

Indication(s): Treatment of anemia in adult patients with chronic kidney disease

Applicant: Affymax Inc

Date(s): Letter Date: May 27 2011
Stamp Date: May 27 2011
PDUFA Goal Date: March 27, 2012

Review Priority: Standard

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Keywords: Active-controlled studies, cardiovascular risk

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1. EXECUTIVE SUMMARY

1.1 Background on the Submission

This submission consists of data and final study reports from four randomized, active-controlled, open label trials, which compared peginesatide injection with other ESAs in patients having chronic kidney disease (CKD). Two trials (AFX01-12 and AFX01-14) studied patients with CKD on dialysis and two trials (AFX01-11 and AFX01-13) studied patients with CKD not on dialysis. The AFX01-12 study had epoetin alfa as the control therapy, while epoetin alfa and epoetin beta were used as the control therapies in the AFX01-14 study. Darbepoetin alfa was used as the control therapy in the AFX01-11 and AFX01-13 studies. For studies AFX01-12 and AFX01-14, subjects were to have been on stable IV epoetin alfa maintenance therapy continuously prescribed for a minimum of 8 weeks prior to randomization. Stability was defined as $\leq 30\%$ change from the maximum prescribed weekly dose (i.e., $[\text{max}-\text{min}]/\text{max} \leq 0.3$) with no change in prescribed frequency. The applicant is seeking an indication only for CKD patients on dialysis. The applicant's proposed indication is:

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

The applicant also proposes that the prescribing information in the product label 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.

The primary efficacy endpoint for all trials was the mean change in hemoglobin from baseline to the evaluation period. A non-inferiority margin of 1.0 g/dL was used for all trials. For the dialysis trials, peginesatide would be considered non-inferior to the comparator if the lower limit of the two-sided 95% CI for the difference between the two treatment groups' mean changes of hemoglobin (peginesatide - control) from baseline was ≥ -1.0 g/dL. For the combined analysis of the non-dialysis each peginesatide arm would be considered non-inferior to the comparator if the lower limit of the two-sided 97.5% CI for the difference between the two treatment groups' mean changes of hemoglobin (peginesatide - control) from baseline was ≥ -1.0 g/dL. Efficacy was easily demonstrated in each trial. That is, peginesatide tended to maintain hemoglobin levels in CKD patients on dialysis, and tended to raise hemoglobin levels in CKD patients not on dialysis.

For each disease area (i.e., on dialysis and not on dialysis), there was a primary safety objective. For each disease area (pooling the two studies) a comparison was done on a composite safety endpoint (CSE) having components, death, stroke, myocardial infarction, congestive heart failure, angina, and arrhythmia. The applicant's pre-specified objective was to rule out a 30% increase by peganesatide compared to control in the instantaneous risk of a CSE event based on a 90% confidence interval for the

peginesatide vs. control hazard ratio. The results of these analyses are summarized in Tables 1 and 2. The applicant's primary safety objective was met in the dialysis population and was not met in the non-dialysis population. In fact, for the non-dialysis population the 90% confidence interval for the peginesatide vs. darbepoetin alfa hazard ratio was entirely greater than 1, indicative of increased risk of a CSE event by peginesatide compared to darbepoetin alfa.

Table 1. Results for the Primary Safety Endpoint (On Dialysis Studies Combined)

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

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

Table 2. Results for the Primary Safety Endpoint (Non Dialysis Studies Combined)

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

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

For further details on the design of these studies and their results, see the statistical review of Dr. Qing Xu.

1.2 Regulatory History of ESAs

Currently in the United States there are two approved and marketed erythropoiesis-stimulating agents (ESAs) - epoetin alfa (Epogen and Procrit) and darbepoetin alfa (Aranesp). Epogen/Procrit and Aranesp 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 Epogen/Procrit and Aranesp, safety concerns have arisen regarding their use. These concerns for patients with chronic kidney disease include increased risk of all-cause mortality, myocardial infarction, stroke and arterial thromboses. Main sources of this new safety information included 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, which were designed to show improvement in cardiovascular outcomes by targeting higher hemoglobin levels with the ESAs, demonstrated instead increased risk of cardiovascular events, including – all cause mortality, myocardial infarction, and/or stroke in those patients treated with ESAs to achieve higher hemoglobin target levels. Due to the cardiovascular safety concerns from these completed studies, the use of ESAs in patient with chronic kidney disease was discussed at advisory committees in September 2007 and October 2010. The Agency reviewed these trials and subsequently revised the prescribing information for the use of ESAs for the anemia of CKD. The following table (Table 3) 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 below. Additionally, the safety concerns of ESAs have been brought to advisory committees for patients with cancer in May 2004, May 2007, and March 2008.

Table 3. 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	All-cause mortality	All-cause mortality	Stroke

Group			
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 Effects of Normal versus Anemic Hematocrit on Outcomes of Cardiac Disease in Dialysis Patients (Normal Hematocrit Study) study was an open-label trial of epoetin alfa in end-stage renal disease patients on hemodialysis with a history of either heart failure or ischemic heart disease. Subjects were evenly randomized to receive epoetin alfa to maintain a target hemoglobin level of 14 g/dL or a target of 10 g/dL. The hypothesis tested was that a higher target would decrease the incidence of all-cause mortality and non-fatal myocardial infarction. The trial, conducted between 1993 and 1996, enrolled 1265 subjects who previously received epoetin alfa and were being maintained at a hemoglobin level of 10 g/dL. The trial was terminated early after an interim analysis by the independent data monitoring committee yielded a higher hemoglobin target to lower hemoglobin target hazard ratio on overall survival was 1.30 based on 404 events (nominal p-value of 0.009; 99.5% CI of 0.98-1.72 and 95% CI of 1.07 - 1.58) with a data cutoff date of March 31, 1996.

The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) Trial was an open-label trial of epoetin alfa in subjects with hemoglobin levels below 11 g/dL and with moderate to severe CKD not on dialysis. Subjects were evenly randomized to a group with a higher target hemoglobin level of 13.5 g/dL or to a group with a lower target hemoglobin level of 11.3 g/dL. The primary endpoint was time to the composite of all-cause death, non-fatal MI, hospitalization for congestive heart failure (CHF), and non-fatal stroke. The trial, conducted between 2003 and 2005, enrolled 1432 subjects who had not previously received therapy with epoetin alfa. The study was terminated early after an interim analysis by the Data and Safety Monitoring Board (DSMB) after a median follow-up period of 16 months. At the time of study termination, 125 (17.5%) of the 715 subjects in the higher hemoglobin target group experienced an endpoint event as compared to 97 (13.5%) of the 717 subjects in the lower hemoglobin target group (hazard ratio 1.34; 95% CI 1.03-1.74; p=0.03). Death and hospitalization for CHF accounted for 75% of the events. The analysis of overall survival yielded a higher hemoglobin target to lower hemoglobin target hazard ratio of 1.49 based on 88 events.

The TREAT study was a randomized, prospective, double-blind, placebo-controlled, Phase III study to evaluate if treatment of anemia to a target of 13g/dL with darbepoetin alfa would reduce all-cause mortality and non-fatal cardiovascular events, or delay progression to end-stage renal disease, in patients with CKD and type 2 diabetes mellitus. The trial enrolled 4038 patients with baseline hemoglobin $\leq$ 11 g/dL. Time to first cardiovascular event, a composite of all-cause mortality, MI, stroke, CHF requiring medical attention, or hospitalization for myocardial ischemia, yielded a darbepoetin alfa to placebo hazard ratio of 1.05 (95% CI 0.94, 1.17) based on 1234 events. Time to a renal event, a composite of occurrence of end-stage renal disease or all-cause mortality, yielded

a darbepoetin alfa to placebo hazard ratio of 1.06 (95% CI 0.95, 1.19) based on 1270 events. There was a statistically significant increase in stroke with 101 subjects (5%) suffering a stroke in the darbepoetin alfa group compared to 53 (2.6%) subjects in the placebo group, resulting in a time to stroke hazard ratio of 1.92 (95% CI 1.38-2.68, nominal p value of < 0.0001).

Collectively, these studies raised substantial safety concerns associated with ESA therapy for the anemia of patients with CKD. In 2007, the ESA labels were revised to include boxed warnings which stated that patients with CKD experienced greater risks of death and serious cardiovascular events when administered ESAs to target higher hemoglobin versus lower hemoglobin levels. It was then also recommended that prescribers individualize dosing to achieve and maintain hemoglobin within the range of 10 to 12 g/dL. In June 2011, the ESA labels were further amended to include the warning that in controlled clinical trials there were greater risks for death, serious adverse cardiovascular reactions, and stroke when targeting hemoglobin levels greater than 11 g/dL (which is consistent with applicant's proposed product label).

1.3 Issues and Findings

I have no major disagreements with the statistical review of Dr. Qing Xu. Key issues, findings and my comments are provided below.

1. Studies overpowered for the primary endpoint of change in hemoglobin level
 - In each of studies AFX-012 and AFX-014, and the combined analysis of the non-dialysis studies, based on the observed patient-level standard deviation for the change in hemoglobin, the probability of failing to rule out a non-inferiority margin of 1 g/dL when both study arms have equal effects on the change in hemoglobin was less than 1.2×10^{-26} . Twenty-one subjects per treatment arm would be needed to rule out a non-inferiority margin of 1 g/dL for 90% power when both study arms have equal effects on the change in hemoglobin.
2. The non-inferiority margin of 1 g/dL
 - There is no issue that peginesatide tended to maintain hemoglobin levels in CKD patients on dialysis, and tended to raise hemoglobin levels in CKD patients not on dialysis. The choice of a non-inferiority margin of 1 g/dL is not based on previous studies of ESAs given in the setting of these active controlled trials. Differences between the current studies and past studies involve the requirement in the dialysis studies that subjects already have stable dosing on epoetin and the “targeted” hemoglobin levels and/or dosing adjustments.
3. Open-label studies
 - These were open-label studies, which can be subject to bias. Additionally, in the dialysis studies, the control therapy was administered more frequently than the experimental therapy. This may or may not affect diagnosis.

4. Use of an active control for safety evaluation
 - It is unusual to have a “non-inferiority” safety analysis to an active-control, where there have been safety concerns involving the active-controls on cardiovascular events. In June 2011, based on the results of the NHS, CHOIR, and TREAT studies, the labeling for administration to patients with CKD on dialysis was changed from “Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL” to “Initiate ESA treatment when the hemoglobin level is less than 10 g/dL. If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of ESA.” How the control ESAs were given in the peganesatide studies is not consistent with current labeling. Additionally, it is not clear why ruling out a 30% increase in the instantaneous risk of a CSE event relative to a currently approved ESA implies or is equivalent to a demonstration of safety.
5. Changes to the Darbepoetin alfa label during the studies
 - In 2009, while these trials were ongoing, the ESA product labels were amended to include a warning on the increase in the risk of stroke from the TREAT study in non-dialysis CKD subjects. It is not clear, how or whether the change in the product label affected the treatment of subjects on darbepoetin alfa in studies AFX01-11 and AFX01-13 with respect to dose and dose adjustments.
6. Presence of selection bias
 - At an End of Phase 2 meeting held on February 23, 2007, It was recommended that the sponsor, “Demonstrate that your product is not importantly inferior in safety or efficacy to available products.” In addition it was recommended that, “Results across studies must show consistency with regard to safety and efficacy in order to support the proposed indication.” When an evaluation (or indication) does not include all studies, but is based on studies that were chosen due to their outcomes, there will be a selection bias. The area having the studies with the best (worst) results will tend to overstate (understate) the true effects. When there are two studies each in two different disease settings, there is a one-third probability due to chance that the two best observed effects will be within the same disease setting. The relative effect on CSE by peginesatide is likely to be smaller than that observed in the AFX-012 and AFX-014 studies.
7. Correspondence between achieved hemoglobin and safety
 - The results from these four peganesatide studies were consistent with the results from the NHS, CHOIR, and TREAT studies, in that the treatment arm that achieved the greater observed mean change in hemoglobin level also had the greater observed risk of a cardiovascular event or death. While the reason for this correlation of differences may not be completely understood, such results can be suggestive that mechanism of action not only influences hemoglobin, but may influence safety outcomes. There are other possible explanations. See the statistical review of Dr. Qing Xu for the details on the comparisons on achieved hemoglobin.

8. Prognostic factors for safety outcomes (age, NYHA failure class)
 - Per analyses done by the statistical reviewer, Dr. Qing Xu, there were two baseline factors – age and New York Heart Association failure class - that stood out across the two disease settings in their prognostic value for the risk of a cardiovascular event.
9. Baseline imbalances not impactful on the comparison of safety
 - There were some baseline imbalances due to the randomization. Age was fairly balanced between arms in all studies. New York Heart Association failure class was a stratification factor in all studies and in the respective models as a stratification factor for the primary safety analyses. Adding other covariates to the model (where the model already includes the stratification factors) did not greatly alter the results (see the statistical review of Dr. Qing Xu).
10. Difficult to assess for variability of effects across baseline subgroups
 - There is no baseline factor that stands out for examination for differences between arms in the risk of a cardiovascular event. Additionally, the sample sizes are small to assess for such heterogeneity in relative risk. Additionally, there is limited historical information on the changes in risk of the active controls across subgroups.
11. Demographic differences across disease settings
 - The fact that the distribution for the demographics is different between the dialysis and non-dialysis studies is not sufficient for the results in one area to be applicable to the other area. These were active-controlled trials, not placebo-controlled studies. Both arms (peginesatide and currently approved ESA) are affected by the background risk. There have been issues of safety of ESAs previously in both subjects on dialysis and subjects not on dialysis. Additionally, the demographic breakdowns in the peginesatide non-dialysis studies are similar to previous large studies in patients not on dialysis.
12. Differences in the subjects studied and the sought indication
 - The subjects on the AFX-012 and AFX-014 studies had to have stable dosing on epoetin for a minimum of 8 weeks prior to randomization. However, the applicant is seeking an indication that does not require prior stabilization on epoetin alfa.
13. Proposed dosing recommendations in product label different from that studied
 - The dosing recommendations in the label are noticeably different from those used in studies AFX-012 and AFX-014. The proposed labeling states “If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of OMONTYS®.” However, for studies AFX-012 and AFX-014 the algorithm for dose adjustments of peginesatide (i.e., OMONTYS®) was the following:
 - If Hgb is < 9.5 g/dL or is below baseline by 1.0 to 1.5 g/dL, the dose should be increased by 25%.
 - If Hgb is below baseline by > 1.5 g/dL, the dose should be increased by 50%.
 - If Hgb is 12.5 to 12.9 g/dL, the dose should be reduced by 25%.

- If Hgb $\geq$ 13.0 g/dL, the dose should be delayed until Hgb is $<$ 13.0 g/dL and the dose should then be reduced by 25%.
- If Hgb has increased by $>$ 1.0 g/dL over the past two weeks, the dose should be reduced by 25%.

2. RECOMMENDATIONS

Should peganesatide get approved for CKD patients on dialysis, my recommendation is that the indication correspond with the inclusion/exclusion criteria of the AFX-012 and AFX-014 studies, which includes subjects having stable dosing on epoetin for a minimum of eight weeks. Additionally, studies with CKD patients on dialysis should be conducted to assess the safety (and efficacy) of peganesatide corresponding to the usage specified in the label. Studies should also be conducted evaluating initial use for the treatment of anemia in patients with CKD on dialysis. For safety evaluation purposes, I recommend that the studies be stratified by age and New York Heart Association failure class.

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02/07/2012

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02/07/2012



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/ Serial Number: 202-799/ 0000

Drug Name: Peginesatide injection

Indication(s): Treatment of anemia in adult patients with chronic renal failure

Applicant: Affymax Inc

Date(s): Letter Date: May 27 2011
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Review Priority: Standard

Biometrics Division: Division of Biometrics V

Statistical Reviewer: Qing Xu, Ph.D

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Keywords:
Cox model, Survival Analysis, Missing data, ANOVA

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1. EXECUTIVE SUMMARY

The applicant submitted data and final study reports of four phase 3 randomized, controlled, open label, multicenter trials to seek full approval for Peginesatide injection for the indication of “Treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis”. In the NDA, there are two trials (AFX01-11 and AFX01-13) in patients with CKD on dialysis and two trials (AFX01-12 and AFX01-14) in patients with CKD not on dialysis.

The primary efficacy endpoint for all trials was change in hemoglobin between the baseline and the evaluation period. The non-inferiority margin was 1.0 g/dL for all trials. Peginesatide would be considered non-inferior to the comparator 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 non-dialysis trials. Each trial met this non-inferiority criterion.

The phase 3 clinical program includes an assessment of cardiovascular (CV) safety utilizing blinded adjudication of pre-specified CV endpoints. The Phase 3 dialysis and non-dialysis studies were pooled for the primary CSE analysis, as well as analyzed by population (dialysis and non-dialysis). The CSE was defined to consist of the following six component events: death, stroke, myocardial infarction (MI), congestive heart failure (CHF), angina and arrhythmia. Composite endpoint (defined as the first occurrence of death, stroke or myocardial). The time to first CSE event was analyzed by estimating HRs using stratified Cox regression for each study. This analysis was used to conclude if a hazard ratio of the upper limit of the two-sided 90% CI was than 1.3 could.

The safety outcomes in both on-dialysis trials (AFX01-12 and AFX01-14) appear similar for both treatment groups for both the CSE (HR=0.94, 95% CI= (0.76, 1.16)) and the MACE (HR=0.84, 95% CI= (0.66, 1.09)) 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. The HR was 1.28 with 95% CI of (0.94, 1.75) for CSE endpoint, and the HR was 1.34 with 95% CI of (0.88, 2.05) for MACE endpoint.

Given the different findings in the dialysis and non-dialysis populations, the sponsor proposed limiting the indication to dialysis patients. The question is whether the observed safety findings in the non-dialysis patients can be extrapolated to dialysis patients. Based on current data, compared with dialysis patients, the non-dialysis studies have smaller sample sizes, longer exposure time, older subjects, different dose usages, and different baseline characteristics. In addition, it is unclear if the same biological mechanism applies to both dialysis and non-dialysis patients in using the drug. Therefore, it may not be appropriate to apply safety findings from non-dialysis trials to the risk evaluation of drug in dialysis population.

In exploratory analyses, we also observed that poor initial response is in correspondence with lower hemoglobin level at week 12 and through out the study, despite that higher dose of treatments were being given to poor initial responders. Poor initial hematopoietic response to Peginesatide is also associated with higher rates of the composite CSE and MACE endpoint, as

compared with better response. However, such associations are dependent on both the definition of poor initial response and key baseline characteristics in the model analysis. Therefore, caution should be taken in the interpretation of such analysis, since the poor initial response to ESA treatment is probably a marker of baseline illness severity. In further perspective, well controlled studies may be needed to evaluate these findings, to identify factors influencing ESA responsiveness so that avoiding excessive doses. In addition, justification of poor response definition with clinical meaningfulness is necessary to be provided in future trials.

Given all those safety concerns observed in non-dialysis trials, a randomized active controlled trial is recommended for further exploring safety profiles for dialysis patients; however, determination of non-inferiority margin and interpretation of results from non-inferiority studies for safety is challenging. The data submitted in this application supports applicant's claim of the efficacy and safety of Peginesatide in dialysis patients who are stable on ESA.

The Oncology drugs advisory committee meeting discussed study results on December 07, 2011. For the question:

1. Is there a favorable benefit to risk evaluation for Peginesatide for use in patients with anemia associated with chronic renal failure who are on dialysis?-Committee voted: Yes 15, No 1, Abstentions 1.

2. INTRODUCTION

The clinical registration program for Peginesatide was designed to support an indication for the treatment of anemia in chronic renal failure (CRF) both for patients on dialysis and those not on dialysis. Four Phase 3 pivotal randomized controlled studies were conducted. Two each in CRF patients on dialysis and CRF patients not on dialysis, respectively.

2.1 Regulatory History of ESAs

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 [1].

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) [1].

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 [1].

2.2 Overview

There are five randomized, active-controlled CRF studies, of which three dialysis subjects studies comprise the core controlled clinical development program (Table 1).

- Phase 3 dialysis studies AFX01-12 and AFX01-14 compared Peginesatide and Epoetin in the maintenance of Hgb levels in dialysis subjects following conversion from Epoetin therapy. Phase 2 study AFX01-15 compared Peginesatide and Epoetin in the treatment of anemia in dialysis subjects not on ESA treatment (Table 1).
- Phase 3 non-dialysis studies AFX01-11 and AFX01-13 provide supportive information and compared different Peginesatide starting doses to darbepoetin in subjects not on dialysis and not on ESA treatment.

Table 1 Controlled Phase 3 and Phase 2 Dialysis Studies

Study ID (Phase, Country, Sites)	Study Design	Treatment Group	N (Full Analysis Population) ¹	Route
Maintenance of Hgb in subjects on dialysis previously treated with Epoetin				
AFX01-12 (Phase 3, US, 92 sites)	Multiple-dose, OL, MC, R, AC, titrated dose	52+ weeks treatment Conversion to AF37702 Inj starting dose (0.04, 0.08, 0.12, or 0.16 mg/kg Q4W from Epoetin alfa) with 1-week ESA-free interval: Epoetin alfa 1-3 x per week	Total : 793 524 269	IV
AFX01-14 (Phase 3, US, EU, 86 sites)	Multiple-dose, OL, MC, R, AC, titrated dose	52+ weeks treatment Conversion to AF37702 Inj starting dose (0.04, 0.08, 0.12, or 0.16 mg/kg Q4W from Epoetin) with 1-week ESA-free interval: Epoetin (alfa or beta) 1-3x per week	Total : 815 542 273	IV or SC
Correction of anemia in subjects on dialysis and not on ESAs				
AFX01-15 (Phase 2, Russia, 17 sites)	Multiple-dose, OL, MC, R, AC, titrated dose	28 weeks treatment AF37702 Inj 0.04 mg/kg Q4W starting dose AF37702 Inj 0.08 mg/kg Q4W starting dose Epoetin 50 U/kg TIW starting dose	Total: 114 39 37 38	IV

AC = active control, MC = multicenter, OL = open-label, R = randomized

Source: Applicant's clinical overview Table 1

The Phase 3 dialysis studies AFX01-12 and AFX01-14 were designed to evaluate the efficacy of Peginesatide compared to Epoetin using a non-inferiority design. Subjects were randomized 2:1 to receive study treatment and underwent a 28-week titration period followed by an 8-week evaluation period. Additional long term safety and efficacy (LTSE) data were evaluated from weeks 37 to 52+. Phase 2 study AFX01-15 evaluated two starting doses of Peginesatide compared to Epoetin. Subjects were randomized 1:1:1 to receive study treatment and underwent a 20-week correction period followed by an 8-week evaluation period. The primary efficacy endpoint in all controlled CRF studies was the mean change from baseline in Hgb during the evaluation period; the treatment difference between the Peginesatide groups and active control was assessed.

The design of the clinical development program was discussed with Agency in a number of meetings. The phase 3 program was designed to include prospective analysis of predefined CV CSE based on pooled data from four phase 3 studies, as well as separate analyses for the dialysis and non-dialysis populations. The events to be included in the CSE analysis included all-cause death, myocardial infarction (MI), stroke, and SAE of congestive heart failure (CHF), unstable angina, and arrhythmia. Events were adjudicated by an Independent Event Review Committee (ERC).

2.3 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The data sets were well documented and included definition files. The analysis dataset was not adequate and required data management, programming and information request. The clinical study reports and datasets are located at the following location:

[\\CDSESUB1\EVSPROD\NDA021825\021825.ENX](#)

Data sources include all material reviewed, e.g. Applicant study reports, data sets analyzed, and literature referenced.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor submitted SDTM datasets for all Phase 2 and Phase 3 studies included in the submission. In addition, SDTM datasets that include the CSE adjudication results were included. The sponsor also submitted ADaM datasets for all Phase 3 studies and for the Phase 2 study AFX01-15 (treatment of anemia in hemodialysis patients not on ESA treatment). In addition, ADaM datasets to support analyses conducted for the CSE, ISS, and the ISE were included.

Individual patient data listing were included in all clinical study reports (CSRs). Data listings for AFX01-11 through AFX01-15 are based on the SDTM.

The reviewer was able to perform all analyses using the submitted data. This reviewer requested time-to-transfusion data during the review process. No additional data submission was requested.

3.2 Evaluation of Efficacy

The applicant defined the following key terms relating to analysis populations or measurements or observations:

Fully Analysis Population: defined as all randomized patients who received at least one dose of study treatment, with patients analyzed based upon the treatment assigned by randomization (“as randomized”). This is the primary efficacy analysis population.

Randomized Population: defined as all patients randomized into the study with patients analyzed based upon the treatment assigned by randomization.

Safety Population: defined as all randomized patients who received at least one dose of their assigned study treatment (“as treated”). The analysis of AEs and other safety related endpoints will be performed using the safety population.

Per-Protocol Population (PP): defined as patients in the full analysis population that meets the certain criteria.

Reviewer’s comments

It is not appropriate to use the fully analysis population as the primary efficacy analysis set for the primary efficacy endpoint; it is against the intent-to-treat principle, as the response-evaluable population is a subset of the ITT population. The randomized population should be the primary basis for making treatment comparison in maintaining the integrity of the randomization. However, since there is only minor difference between ITT population and fully analysis population (98.8%), and this difference does not impact the overall conclusion from full analysis population, we accept to report analysis from protocol pre-specified full analysis population as the primary population.

3.2.1 Study Design and Endpoints

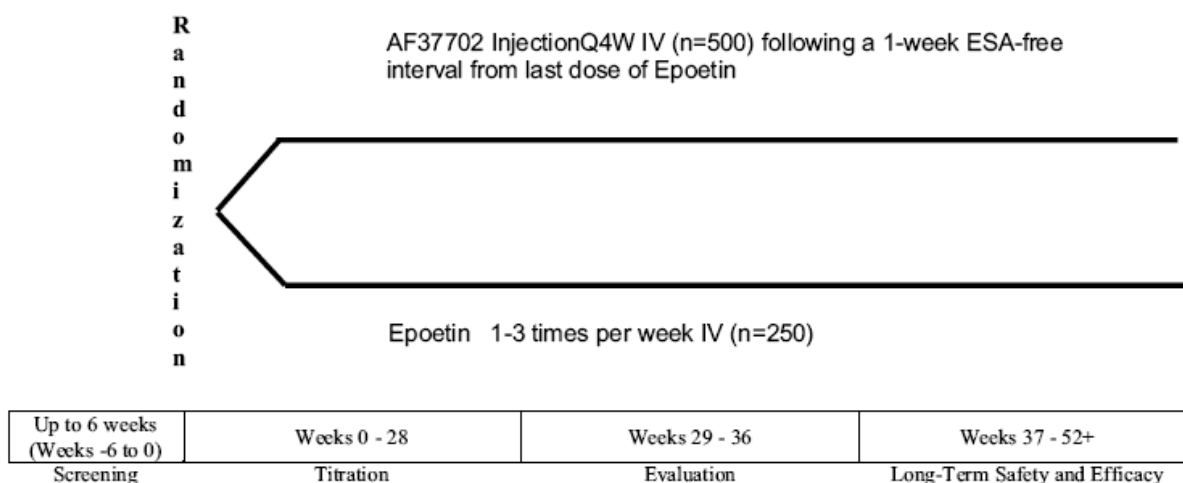
Since the sponsor does not intend to claim indication for Study AFX 01-11 and AFX01-13 (Non-dialysis) patient population in the labeling, this report did not include detailed review of the efficacy for Non-dialysis patient population but only safety review.

Study AFX01-12

This is a phase 3, randomized, active-controlled, open-label, and multicenter study of the efficacy and safety of Peginesatide for the maintenance treatment of anemia due to chronic renal failure (CRF) in hemodialysis patients. A total of approximately 750 eligible patients were to be enrolled at approximately 120 sites. Patients were randomized in a 2:1 ratio: Peginesatide IV injection every 4 weeks (Q4W) at a starting dose of 0.04 mg/kg to 0.16 mg/kg based on the patient’s prior Epoetin alfa dose, or continued treatment with Epoetin alfa 1-3 times per week IV. Randomization was stratified by the mean screening hemoglobin (Hgb) (≤ 11.4 g/dL, ≥ 11.5 g/dL) and the New York Heart Association (NYHA) Heart Failure (HF) Class (no HF-Class I,

Classes II-IV). Following randomization, patients were to be followed for a minimum of 52 weeks. Duration on study will vary across patients depending on the time of patient accrual. All randomized patients were to be followed until the last patient enrolled has been followed for 52 weeks.

Figure 1 Four Sequential Study Periods of Study AFX01-12



Note: "Week 0" was not an actual 7-day period, but instead referred to the baseline visit at which baseline assessments were collected and the patient was randomized.

Source data: Applicant's clinical study report Figure 1

- Screening period: the screening period consisted of up to 6 weeks (week-6 to week 0) of continued Epoetin alfa treatment prior to randomization.
- Titration period (28 weeks): the titration period consisted of 28 weeks (week 0 through week 28) of study treatment dosing following randomization.
- Evaluation period (8 weeks): the evaluation period consisted of 8 weeks (week 29 through week 36) of continued study treatment dosing following the titration period. The Hgb assessments taken during this period were used to determine the primary efficacy endpoint. Study visits were scheduled every week, and Hgb levels were evaluated weekly.
- Long-term safety and efficacy period (Figure 1)

The primary efficacy endpoint was the mean change in Hgb between baseline (the mean of the four most recent Hgb values prior to randomization) and the evaluation period (mean Hgb from week 29 through 36).

The major secondary efficacy endpoints include:

- Proportion of patients who receive red blood cell (RBC) transfusions.
- Mean proportion of Hgb values within target range of 10.0-12.0 g/dL during the evaluation period.
- Mean weekly Hgb during 4-week intervals.
- Mean Hgb change from baseline during 4 week intervals.
- Proportion of patients who maintain Hgb within 1.5g/dL below or above baseline during the evaluation period.
- Mean proportion of Hgb values within 1.5 g/dL below or above baseline during the Evaluation period.

A non-inferiority approach was used to establish the efficacy of Peginesatide as compared with Epoetin. Non-inferiority was established if the lower limit of the two sided 95% confidence interval for the difference between the means of primary endpoint in Peginesatide treatment group and Epoetin treatment group (Peginesatid injection minus Epoetin) was ≥ -1.0 g/dL.

Reviewer's Comments

The sponsor had provided the statistical rationale for choice of non-inferiority margin. The estimate was based on summary information from the Darbepoetin alfa development program, the most recent ESA registration with publicly available summary data the time of Peginesatide Phase 3 study planning. Based on these data, the estimated treatment effect of ESA therapy in the dialysis population with a 10-12 g/dL target range (at lease -2.0 g/dL) was considered to be appreciably less than -1.0g/dL, with a standard deviation of 1.5 g/dL.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Study AFX01-12

A total of 803 patients were randomized to treatment with either Peginesatide or Epoetin. Of the 803 randomized patients, 793 patients (98.8%) received at least one dose of study medication: 524 (98.5%) patients in the Peginesatide (AF37702) group and 269 (99.3%) patients in the Epoetin group. Of the 803 randomized patients, 568 (70.7%) completed the study: 366 (68.8%) patients in the Peginesatide group and 202 (74.5%) patients in the Epoetin group. Of the 568 patients who completed the study, 530 (66.0%) completed the study on-drug: 334 (62.8%) patients in the Peginesatide group and 196 (72.3%) patients in the Epoetin group, respectively (Table1).

A total of 793 patients were included in the Full Analysis Population and the Safety Analysis Population. A total of 506 patients were included in the Per-Protocol Population (Table 2)

Table 2 Summary of Patient Disposition

	AF37702 N=532	Epoetin Alfa N=271	Total N=803
# of patients who received study drug	524 (98.5%)	269 (99.3%)	793 (98.8%)
Full set	524 (98.5%)	269 (99.3%)	793 (98.8%)
Safety set	524 (98.5%)	269 (99.3%)	793 (98.8%)
Per-Protocol Population	341 (64.1%)	165 (60.9%)	506 (63.0%)
# of patients who completed study	366 (68.8%)	202 (74.5%)	568 (70.7%)
On-drug	334 (62.8%)	196 (72.3%)	530 (66.0%)
Off-drug	32 (6.0%)	6 (2.2%)	38 (4.7%)

There were 600 (74.7%) patients who received at least one year of dosing with study drug, 382 (71.8%) patients in the Peginesatide group and 218 (80.4%) patients in the Epoetin group (Table 3)

Table 3 Summary of Number of Patient Receiving Last Dose of Study Drug by Period (Full Analysis Set)

Frequency Row Pct	AF37 N=524	EPO N=269	Total N=793
Evaluation Period	17 (3.2%)	11 (4.1%)	28 (3.5%)
LTSE (Weeks 37-52)	42 (7.9%)	17 (6.3%)	59 (7.3%)
LTSE (Weeks >52)	382 (71.8%)	218 (36.33%)	600 (74.7%)
Titration Period	83 (15.6%)	23 (8.5%)	106 (13.2%)
Total	524 (98.5%)	269 (99.3%)	793 (98.8%)

Reviewer's Comments:

A higher proportion of patients in the Peginesatide group received their last dose of study drug during the titration period compared to the Epoetin group.

A total of 235 (29.3%) of the 803 patients who enrolled in the study prematurely terminated participation in the study, 166 (31.2%) in the Peginesatid group and 69 (24.4%) in the Epoetin alfa group. the proportion of patients who terminated the study prematurely was slightly higher in the Peginesatide group compared to the Epoetin alfa group (Table 4).

Table 4 Summary of the Primary Reason for Prematurely Terminated from Study

Frequency Row Pct	AF37 N=532	EPO N=271	Total N=803
Consent Withdrawn for all Study Activities	35 (6.6 %)	12 (4.4 %)	47
Death	55 (10.3%)	29 (10.7%)	84
Lost to Follow Up	10 (1.9%)	3 (1.1%)	13
Other	66 (12.4 %)	25(9.2 %)	91
Total	166 (31.2%)	69 (24.4%)	235 (29.3%)

Reviewer's Comments:

The proportion of patients who were terminated from the study prematurely was slightly higher in the Peginesatide group (166 (31.2%)) compared to the Epoetin alfa group (69 (25.5%)). Overall, the most frequently cited reason for termination was 'other' and death. There were more deaths in the Peginesatid group compared to the Epoetin alfa group.

Table 5 shows summary of patient demographic using full analysis population. The mean age of patients in the study was 57.4 years, with a range of 20 to 91 years. Most of patients (70.6%) were under 65 years age.

Table 5 Summary of Patient Demographic (Full Analysis Population)

Demographic/ Baseline Characteristics	Statistic	AF37702 Inj. IV Q4W (N=524)	Epoetin alfa IV 1-3 Times per Week (N=269)	Total (N=793)
Age (year)	N	524	269	793
	Mean (SD)	57.3 (13.96)	57.5 (13.68)	57.4 (13.86)
	Median	58	57	58
	Q1 - Q3	49 - 67	50 - 67	49 - 67
	Min - Max	20 - 91	22 - 90	20 - 91
Age				
<65 Years	N (%)	370 (70.6%)	190 (70.6%)	560 (70.6%)
>= 65-< 75 Years	N (%)	97 (18.5%)	44 (16.4%)	141 (17.8%)
>= 75 Years	N (%)	57 (10.9%)	35 (13.0%)	92 (11.6%)
Sex				
Male	N (%)	293 (55.9%)	144 (53.5%)	437 (55.1%)
Female	N (%)	231 (44.1%)	125 (46.5%)	356 (44.9%)
Race				
American Indian or Alaskan Native	N (%)	2 (0.4%)	4 (1.5%)	6 (0.8%)
Asian	N (%)	16 (3.1%)	9 (3.3%)	25 (3.2%)
Black	N (%)	234 (44.7%)	136 (50.6%)	370 (46.7%)
Native Hawaiian or Other Pacific Islander	N (%)	7 (1.3%)	2 (0.7%)	9 (1.1%)
White	N (%)	263 (50.2%)	116 (43.1%)	379 (47.8%)
Other	N (%)	1 (0.2%)	2 (0.7%)	3 (0.4%)
Missing	N (%)	1 (0.2%)	0 (0.0%)	1 (0.1%)

Note: Number of patients specified in the header of each column is used as the denominator for all percentage calculations.

Source data: Applicant's study report table 9

Reviewer's Comments:

There were more white patients in the Peginesatide group (50.2%) compared to Epoetin alfa group (43.1%); there were fewer black patients in the Peginesatide group (44.7%) compared to Epoetin alfa group. Age and gender distributions were generally balanced between the treatment groups for the full analysis population.

Table 6 shows summary of patient baseline characteristics. For each patient, the baseline Hgb value was defined as the mean of 5 Hgb values: the most recent Hgb values taken prior to the day of randomization and the value obtained on the day of randomization. The mean baseline Hgb was 11.31 g/dL and similar between treatment groups; 55.0% of the patients had a baseline Hgb that was $\leq$ 11.4 g/dL.

Table 6 Summary of Patient Baseline Characteristics (Full Analysis Population)

Demographic/ Baseline Characteristics	Statistic	AF37702 Inj. IV Q4W (N=524)	Epoetin alfa IV 1-3 Times per Week (N=269)	Total (N=793)
Baseline Hgb (g/dL)[1]	N	524	269	793
	Mean (SD)	11.30 (0.523)	11.32 (0.493)	11.31 (0.513)
	Median	11.4	11.4	11.4
	Q1 - Q3	10.9 - 11.7	11.0 - 11.7	10.9 - 11.7
	Min - Max	9.9 - 12.4	10.0 - 12.3	9.9 - 12.4
<= 11.4 g/dL	N (%)	290 (55.3%)	146 (54.3%)	436 (55.0%)
> = 11.5 g/dL	N (%)	234 (44.7%)	123 (45.7%)	357 (45.0%)
Ferritin (ng/mL) (Normal Range: Female: 10-291; Male: 22-322)	N	524	269	793
	Mean (SD)	697.6 (349.31)	657.0 (347.36)	683.8 (348.96)
	Median	666	609	642
	Q1 - Q3	458 - 869	409 - 844	427 - 862
	Min - Max	44 - 2245	47 - 1913	44 - 2245
TSAT (%) (Normal Range: 20-55)	N	524	269	793
	Mean (SD)	30.9 (10.68)	29.1 (9.58)	30.2 (10.34)
	Median	29	28	28
	Q1 - Q3	24 - 35	22 - 34	23 - 35
	Min - Max	11 - 82	9 - 83	9 - 83

Note: Number of patients specified in the header of each column is used as the denominator for all percentage calculations.

[1] Source is from central laboratory data in the clinical database.

Source data: Applicant's study report Table 9

Reviewer's Comments:

The mean and median of serum ferritin values are higher in the Peginesatide group compared to Epotin alfa group; the mean of serum ferritin for the patients with Peginesatide treatment is 697.6 ng/mL and the mean of serum ferritin for the patients with Epotin alfa treatment is 657.0 ng/mL. The median of serum ferritin for the patients with Peginesatide treatment is 666 ng/mL and the median of serum ferritin for the patients with Epotin alfa treatment is 609 ng/mL.

Table 7 shows the summary of baseline renal disease characteristics using full analysis population.

Table 7 Summary of Baseline Renal Disease Characteristics (Full Analysis Population)

Baseline Disease Characteristics	Statistic	AF37702 Inj. IV Q4W (N=524)	Epoetin alfa IV 1-3 Times per week (N=269)	Total (N=793)
Primary Cause of Chronic Renal Failure				
Diabetes	N (%)	222 (42.4%)	118 (43.9%)	340 (42.9%)
Hypertension	N (%)	184 (35.1%)	97 (36.1%)	281 (35.4%)
Autoimmune Disease	N (%)	13 (2.5%)	10 (3.7%)	23 (2.9%)
Polycystic Kidney Disease	N (%)	11 (2.1%)	6 (2.2%)	17 (2.1%)
Pyelonephritis	N (%)	1 (0.2%)	1 (0.4%)	2 (0.3%)
Interstitial Nephritis	N (%)	5 (1.0%)	1 (0.4%)	6 (0.8%)
Urologic	N (%)	4 (0.8%)	1 (0.4%)	5 (0.6%)
Unknown	N (%)	21 (4.0%)	6 (2.2%)	27 (3.4%)
Other*	N (%)	63 (12.0%)	29 (10.8%)	92 (11.6%)

Note: Number of patients specified in the header of each column is used as the denominator for all percentage calculations.

Source data: Applicant's study report Table10

Reviewer's Comments:

Baseline renal disease characteristics were balanced between Peginesatide group and Epotin alfa group.

Table 8 shows the summary of baseline cardiovascular disease characteristics between two groups using full analysis population.

Table 8 Summary of Baseline Cardiovascular Disease Characteristics (Full Analysis Population)

Baseline Disease Characteristics	Statistic	AF37702 Inj. IV Q4W (N=524)	Epoetin alfa IV 1-3 Times per week (N=269)	Total (N=793)
Cardiovascular Risk History [1]	N (%)	519 (99.0%)	268 (99.6%)	787 (99.2%)
At Least One Cardiovascular Risk History without Hypertension [2]	N (%)	491 (93.7%)	258 (95.9%)	749 (94.5%)
Hypertension	N (%)	517 (98.7%)	266 (98.9%)	783 (98.7%)
Diabetes	N (%)	298 (56.9%)	151 (56.1%)	449 (56.6%)
CAD**	N (%)	238 (45.4%)	100 (37.2%)	338 (42.6%)
MI	N (%)	88 (16.8%)	30 (11.2%)	118 (14.9%)
Angina	N (%)	108 (20.6%)	49 (18.2%)	157 (19.8%)
Coronary Artery Bypass Graft	N (%)	64 (12.2%)	26 (9.7%)	90 (11.3%)
PCI or Coronary Stent Placement	N (%)	73 (13.9%)	32 (11.9%)	105 (13.2%)
Arrhythmia**	N (%)	102 (19.5%)	65 (24.2%)	167 (21.1%)
AF, Flutter or SVT	N (%)	66 (12.6%)	35 (13.0%)	101 (12.7%)
VT or Fibrillation	N (%)	18 (3.4%)	13 (4.8%)	31 (3.9%)

Note: Number of patients specified in the header of each column is used as the denominator for all percentage calculations.

Source data: Applicant's study report Table 10.

Reviewer's Comments:

Baseline Cardiovascular disease characteristics were balanced between Peginesatide group and Epotin alfa group.

Study AFX01-14

A total of 823 patients were randomized to treatment with either Peginesatide or Epoetin. Of the 823 randomized patients, 815 patients (99.0%) received at least one dose of study medication: 542 (98.7%) patients in the Peginesatide (AF37702) group and 273 (99.6%) patients in the Epoetin group. Of the 823 randomized patients, 632 (76.8%) completed the study: 421 (76.7%) patients in the Peginesatide group and 211 (77.0%) patients in the Epoetin group. Of the 632 patients who completed the study, 605 (73.5%) completed the study on-drug: 403 (73.4%) patients in the Peginesatide group and 202 (73.7%) patients in the Epoetin group, respectively

A total of 823 patients were included in the Full Analysis Population and the Safety Analysis Population. A total of 506 patients were included in the Per-Protocol Population (Table 9)

Table 9 Summary of Patient Disposition

	AF37702 N=549	Epoetin Alfa N=274	Total N=823
# of patients who received study drug	542 (98.7%)	273 (99.6%)	815(99.0%)
Full set	542 (98.7%)	273 (99.6%)	815(99.0%)
Safety set	542 (98.7%)	273 (99.6%)	815(99.0%)
Per-Protocol Population	372 (67.8%)	141 (51.5%)	513 (62.3%)
# of patients who completed study	421 (76.7%)	211 (77.0%)	632 (76.8%)
On-drug	403 (73.4%)	202 (73.7%)	605 (73.5%)
Off-drug	18 (3.3%)	9 (3.3%)	27 (3.3%)

There were 651 (79.9%) patients who received at least one year of dosing with study drug, 439 (67.43%) patients in the Peginesatide group and 212 (32.57%) patients in the Epoetin group (Table 10).

Table 10 Summary of Number of Patient Receiving Last Dose of Study Drug by Period

	AF37	EPO	Total
Evaluation Period	15 (71.43%)	6 (28.57%)	21
LTSE (Weeks 37-52)	29 (63.4%)	17 (36.96%)	46
LTSE (Weeks >52)	439 (67.43%)	212 (32.57%)	651
Titration Period	59 (60.82%)	38 (39.18%)	97
Total	542	273	815

Reviewer's Comments:

A higher proportion of patients in the Peginesatide group received their last dose of study drug during the titration period compared to the Epoetin group.

The Table 11 shows the summary of the primary reason for patients prematurely terminated from study. A total of 191 (23.4%) of the 815 patients who enrolled in the study prematurely terminated participation in the study. 128 (23.6%) in the Peginesatid group and 63 (23.0%) in the Epoetin alfa group.

Table 11 Summary of the Primary Reason for Patients Prematurely Terminated from Study

	AF37	EPO	Total
Consent Withdrawn for all Study Activities	44 (78.57%)	12 (21.43%)	56
Death	53 (63.86%)	30 (36.14%)	83
Lost to Follow Up	2 (33.33%)	4 (66.67%)	6
Other	29 (63.04%)	17 (36.96%)	46
Total	128 (23.1%)	63 (23.07%)	191

Reviewer's Comments:

Overall, the most frequently cited reason for termination was 'other' and death. There were more deaths in the Peginesatide group compared to the Epoetin alfa group.

Table 12 shows the summary of patient demographics. The mean age of patients in the study was 59 years, with a range of 22 to 97 years. Most of patients (64.2%) were under 65 years age.

Table 12 Summary of Patient Demographic (Full Analysis Population)

Demographic/ Baseline Characteristics	Statistic	AF37702 Inj. IV or SC Q4W (N=542)	Epoetin alfa/beta IV or SC 1-3 Times per Week (N=273)	Total (N=815)
Age (year)	N	542	273	815
	Mean (SD)	58.8 (14.47)	58.6 (13.73)	58.8 (14.22)
	Median	59	59	59
	Q1 - Q3	50 - 69	50 - 68	50 - 68
	Min - Max	22 - 93	22 - 97	22 - 97
<65 Years	N (%)	350 (64.6%)	173 (63.4%)	523 (64.2%)
>=65-<75 Years	N (%)	110 (20.3%)	67 (24.5%)	177 (21.7%)
>=75 Years	N (%)	82 (15.1%)	33 (12.1%)	115 (14.1%)
Sex				
Male	N (%)	331 (61.1%)	153 (56.0%)	484 (59.4%)
Female	N (%)	211 (38.9%)	120 (44.0%)	331 (40.6%)

Note: Number of patients specified in the header of each column is used as the denominator for all percentage calculations.

[1] Source is from central laboratory data in the clinical database.

For the reported TSSAT values, n=1000/ it was included in the summary as 1000/

Source data: Applicant's study report table 11

Table 13 shows summary of patient baseline characteristics. The mean baseline Hgb was 11.30 g/dL and similar between treatment group; 63.1% of the patients had a baseline Hgb that was ≤ 11.4 g/dL.

Table 13 Summary of Patient Baseline Characteristics (Full Analysis Population)

Demographic/ Baseline Characteristics	Statistic	AF37702 Inj. IV or SC Q4W (N=542)	Epoetin alfa/beta IV or SC 1-3 Times per Week (N=273)	Total (N=815)
Baseline Hgb (g/dL)[1]	N	542	273	815
	Mean (SD)	11.20 (0.553)	11.21 (0.546)	11.21 (0.550)
	Median	11.2	11.3	11.3
	Q1 - Q3	10.8 - 11.6	10.9 - 11.6	10.8 - 11.6
	Min - Max	10.0 - 13.0	9.3 - 12.2	9.3 - 13.0
<= 11.4 g/dL	N (%)	336 (62.0%)	178 (65.2%)	514 (63.1%)
>= 11.5 g/dL	N (%)	206 (38.0%)	95 (34.8%)	301 (36.9%)
Height (cm)	N	542	272	814
	Mean (SD)	168.55 (9.724)	167.78 (10.086)	168.29 (9.847)
	Median	168.6	168.0	168.0
	Q1 - Q3	162.6 - 175.3	160.5 - 175.0	162.6 - 175.3
	Min - Max	140.0 - 193.0	127.0 - 193.0	127.0 - 193.0
Weight (kg)	N	542	273	815
	Mean (SD)	79.65 (22.317)	78.74 (20.414)	79.35 (21.690)
	Median	76.0	76.0	76.0
	Q1 - Q3	63.3 - 91.3	64.5 - 87.0	63.5 - 90.0
	Min - Max	38.0 - 187.5	43.5 - 163.0	38.0 - 187.5

Note: Number of patients specified in the header of each column is used as the denominator for all percentage calculations.

[1] Source is from central laboratory data in the clinical database.

Source data: Applicant's study report Table 11

Reviewer's Comments:

The percentage of subjects with lower baseline hgb (<=11.4 g/dL) is lower in the Peginesatide group (62%) compared with that of Epoetin alfa group (65.2%)

Table 14 shows the summary of baseline cardiovascular disease characteristics between two groups using full analysis population.

Table 14 Summary of Baseline Cardiovascular Disease Characteristics (Full Analysis Population)

Baseline Disease Characteristics	Statistic	AF37702 Inj. IV or SC Q4W (N=542)	Epoetin alfa/beta IV or SC 1-3 Times per Week (N=273)	Total (N=815)
Cardiovascular Risk History [1]	N (%)	534 (98.5%)	270 (98.9%)	804 (98.7%)
At Least One Cardiovascular Risk History without Hypertension [2]	N (%)	448 (82.7%)	227 (83.2%)	675 (82.8%)
Hypertension	N (%)	522 (96.3%)	266 (97.4%)	788 (96.7%)
Diabetes	N (%)	238 (43.9%)	124 (45.4%)	362 (44.4%)
CAD**	N (%)	209 (38.6%)	91 (33.3%)	300 (36.8%)
MI	N (%)	78 (14.4%)	29 (10.6%)	107 (13.1%)
Angina	N (%)	94 (17.3%)	43 (15.8%)	137 (16.8%)
Coronary Artery Bypass Graft	N (%)	51 (9.4%)	19 (7.0%)	70 (8.6%)
PCI or Coronary Stent Placement	N (%)	60 (11.1%)	25 (9.2%)	85 (10.4%)
Arrhythmia**	N (%)	122 (22.5%)	40 (14.7%)	162 (19.9%)
AF, Flutter or SVT	N (%)	77 (14.2%)	28 (10.3%)	105 (12.9%)
VT or Fibrillation	N (%)	14 (2.6%)	4 (1.5%)	18 (2.2%)

Note: Number of patients specified in the header of each column is used as the denominator for all percentage calculation.

Source data: Applicant's study report Table 12.

Reviewer's Comments:

Baseline Cardiovascular disease characteristics were balanced between Peginesatide group and Epotin alfa group.

3.2.3 Statistical Methodologies

Study AFX01-12

Sample Size Consideration

The sample size for this study has been determined based on a two group evaluation of non-inferiority using the t-distribution with a non-inferiority margin of -1.0 g/dL. A sample size of approximately 750 (Peginesatide group of 500 and Epoetina alfa group of 250) will provide at least 99% power for the evaluation of non-inferiority, assuming an expected treatment difference of 0.0g/dL and a standard deviation of 1.5 g/dL.

Statistical Methods

The primary analysis was an analysis of variance (ANOVA) cell means model for the Hgb change from baseline to the Evaluation Period (Week 29 through 36). The ANOVA model included treatment and terms based upon the 4 individual strata formed by combination of the 2 randomization stratification variables (per the IVRS): mean of the four most recent screening Hgb values prior to randomization and New York Heart Association CHF. An estimate of the difference between the means of the primary efficacy variable for the Peginesatide treatment group and Epotin alfa group and two-sided 95% confidence intervals for this estimate were calculated using ANOVA model. The approach used was similar to that used to generate a p-

value using Type II Sums of Squares in the SAS Procedure Mixed (i.e., weights proportionate to the stratum sizes). The analysis of the primary efficacy endpoint was conducted in the Full Analysis, Randomized, Per-Protocol and Supplemental Per-Protocol Populations. The result obtained using the Full Analysis Population was considered primary, with result obtained from the latter three populations considered as providing supportive information.

A Cochran-Mantel-Haenszel (CMH) statistic (as implemented by SAS PROC FREQ) stratified by the two randomization stratification factors will be computed for each of these two binary endpoints. Ninety-five percent confidence intervals for the ratios of these stratified proportions (i.e., relative risks) will be calculated to characterize the relative differences between the treatment groups.

Study AFX01-14

Sample Size Consideration (Identical to that in study AFX01-12)

Statistical Methods (Identical to that in study AFX01-12)

3.2.5 Results and Conclusions

Study AFX01-12

Results of Primary Efficacy Endpoint

The primary analysis was based on an adjusted mean difference between Peginesatide group and Epotin alfa group. The adjusted mean difference was calculated by weighting differences between the Peginesatide group and Epotin alfa group means for each of the four randomization strata proportional to the total sample size for the stratum. From baseline to the Evaluation Period, the magnitudes of the mean changes in Hgb ($\pm$ SD) were similar in the two treatment groups; -0.24 ± 0.956 g/dL in the Peginesatide group and -0.09 ± 0.922 g/dL in the Epotin alfa treatment group, respectively. The adjusted mean difference (95% CI) between Peginesatide group and the Epoetin treatment group was -0.15 g/dL with 95% CI of $(-0.30, -0.01)$, the lower limit of 95% CI for Peginesatide mean minus Epoetin mean was greater than -1.0 g/dL, indicating that the primary endpoint satisfied the protocol-specified criterion for the non-inferiority of efficacy relative to Epoetin (Table 15).

Table 15 Summary Efficacy Analysis Result of Change in Hgb from Baseline to the Evaluation Period (Full Analysis Population)

Evaluation Period (Weeks 29-36)	AF37702 N=445	Epotin N=248	Total N=693
Mean (SD)	11.06 (0.932)	11.25 (0.846)	11.13 (0.906)
Median	11.0	11.3	11.1
Change from baseline			
Mean (SD)	-0.24 (0.956)	-0.09 (0.922)	-0.19 (0.946)
Median	-0.3	-0.1	-0.2
Difference from Epoetin			
LS Mean (SE)	-0.15 (0.072)		
2-sided 95% CI	(-0.30, -0.01)		

Reviewer's Comments:

There were 100 patients who had no Hgb values available during the Evaluation Period (Weeks 29-36), 79 patients in the Peginesatide group and 21 patients in the Epoetin treatment group. The impact of these missing data on the analysis of the primary efficacy endpoint was examined by some modifications: (1) a change from baseline in Hgb of 0.0 g/dL was assigned to patients with no available Hgb values during the Evaluation Period and (2) the mean of the last five Hgb values recorded was assigned as the mean Hgb during the Evaluation Period for patients with no available Hgb values during the Evaluation Period. The results for the primary efficacy endpoint were given in the Table 16. However, those pre-specified missing data imputations are not 'imputation under the null' methods; it may be in favor of Epoetin alfa group.

Table 16 Primary Efficacy Analysis of Hgb Change from Baseline to the Evaluation Period using Different Strategy of Missing data Imputation

	Mean difference	95% CI
Change from baseline in Hgb of 0.0 g/dL	-0.12 g/dL	-0.24, 0.01
Mean of the last five Hgb values	-0.17	-0.31, -0.03

The sponsor provided the statistical rationale for choice of non-inferiority margin in their report. Non-inferiority was established if the lower limit of the two-sided 95% CI for the difference between the means of the primary endpoint in the Peginesatide group and the Epoetin treatment group. Statistical support for the choice of non-inferiority margin was provided by estimating a lower bound for the effect of standard therapy on Hgb in the treatment of anemia in CRF based on historical data

The sponsor used Full Analysis Population as the primary efficacy analysis population. However, the Full Analysis Population is the subset of randomized population. For keeping the principle of randomization, any efficacy evaluations in a randomized trial should be based upon all randomized patients. The results for the primary efficacy analysis of the Hgb change from baseline using randomized population were given in the Table 17. The results were similar between Randomized Population and Full Analysis Population

Table 17 Primary Efficacy Analysis of the Hgb Change from Baseline to the Evaluation Period (ITT Population)

Evaluation Period (Weeks 29-36)	AF37702 N=446	Epoetin N=248	Total N=693
Mean (SD)	11.06 (0.931)	11.25 (0.846)	11.13 (0.905)
Median	11.1	11.3	11.1
Change from baseline			
Mean (SD)	-0.24 (0.956)	-0.09 (0.922)	-0.19 (0.946)
Median	-0.3	-0.1	-0.2

Difference from Epoetin LS Mean (SE) 2-sided 95% CI	-0.15 (0.072) (-0.29, -0.01)
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The primary endpoint was also conducted by using CMH method; the mean difference between treatment groups for the change in Hgb from baseline to the Evaluation period was -0.15 g/dL with 95% CI of -0.29, -0.02). the results are similar from the ANOVA method.

Results of the Major Secondary Efficacy Endpoints

Fifty-four (10.3%) patients in the Peginesatide group and 23 (8.6%) patients in the Epoetin treatment group received one or more transfusions during the Titration and Evaluation Periods; the relative risk was 1.21 with 95% CI of (0.76, 1.92) (Table18).

Table 18 RBC Transfusion During the Titration and Evaluation Period

Transfusion Rate (%)	Statistic	AF37702 Inj. IV Q4W (N=524)	Epoetin IV 1-3 Times per Week (N=269)	Total (N=793)
No. of Patients Who Received ≥ 1 Transfusion During the Titration and Evaluation Periods				
N (%)		54/524 (10.3%)	23/269 (8.6%)	77/793 (9.7%)
Relative Risk (RR) from Epoetin [1][2]				
RR		1.21		
2-Sided 95% CI for RR		(0.76, 1.92)		
No. of Patients Who Received ≥ 1 Transfusion During the Titration Period				
N (%)		45/524 (8.6%)	19/269 (7.1%)	64/793 (8.1%)
Relative Risk (RR) from Epoetin [1][2]				
RR		1.21		
2-Sided 95% CI for RR		(0.73, 2.03)		

Note: RBC or whole blood transfusions are included.

[1] Relative risk estimate and CI were obtained from the CMH test including terms for treatment group and the randomization stratification factors.

[2] Relative risk from Epoetin = AF37702 Injection treatment group / Epoetin group.

Source Data: Applicant's study report Table 15

Reviewer's Comments:

In order to assess the time effect of the transfusion use, this reviewer performed time to first event analysis for transfusion using Cox Proportional Hazard model stratified by treatment group and the randomization stratification factors during titration and evaluation period. The results show that the HR is 1.27 with 95% CI of (0.78, 2.06). However, there are several limitations that would cause biases:

- Criterion for transfusion usage vary among different clinicians and clinics
- Additionally, patients who died from cardiovascular or renal disease were no longer at risk of transfusion (competing risk).

Results of the Secondary Efficacy Endpoints-proportion of patients whose mean hemoglobin level during the evaluation period was within the target range of 10.0 to 12.0g/dL

During the evaluation period, 330/524 (63.0%) vs. 193/269 (71.7%) patients in the Peginesatide and Epoetin treatment groups, respectively, had a mean Hgb level within target range. The relative response rate (with 'response' defined as a Hgb in the target range during the Evaluation Period) of Peginesatide relative to Epoetin was 0.88 with 95% CI of (0.79, 0.97).

Study AFX01-14

Results of Primary Efficacy Endpoint

The primary analysis was based on an adjusted mean difference between Peginesatide group and Epoetin alfa group. The adjusted mean difference was calculated by weighting differences between the Peginesatide group and Epoetin alfa group means for each of the four randomization strata proportional to the total sample size for the stratum. From baseline to the Evaluation Period, the magnitudes of the mean changes in Hgb ($\pm$ SD) were similar in the two treatment groups; -0.07 ± 1.009 g/dL in the Peginesatide group and -0.17 ± 1.000 g/dL in the Epoetin alfa treatment group, respectively. The adjusted mean difference (95% CI) between Peginesatide group and the Epoetin treatment group was -0.10 g/dL with 95% CI of $(-0.05, 0.26)$, the lower limit of 95% CI for Peginesatide mean minus Epoetin mean was greater than -1.0 g/dL, indicating that the primary endpoint satisfied the protocol-specified criterion for the non-inferiority of efficacy relative to Epoetin (Table 19).

Table 19 Summary Efficacy Analysis Result of Change in Hgb from Baseline to the Evaluation Period (Full Analysis Population)

Evaluation Period (Weeks 29-36)	AF37702 N=488	Epoetin N=237	Total N=725
Mean (SD)	11.20 (0.553)	11.21 (0.546)	11.21 (0.550)
Median	11.2	11.3	11.3
Change from baseline			
Mean (SD)	-0.07 (1.009)	-0.17 (1.000)	-0.10(1.006)
Median	-0.1	-0.2	-0.1
Difference from Epoetin			
LS Mean (SE)	0.10 (0.078)		
2-sided 95% CI	(-0.05, 0.26)		

Reviewer's Comments:

There were 90 patients who had no Hgb values available during the Evaluation Period (Weeks 29-36), 54 (9.8%) patients in the Peginesatide group and 36 (13.1%) patients in the Epoetina treatment group. The impact of these missing data on the analysis of the primary efficacy endpoint was examined by some modifications: (1) a change from baseline in Hgb of 0.0 g/dL was assigned to patients with no available Hgb values during the Evaluation Period and (2) the mean of the last five Hgb values recorded was assigned as the mean Hgb during the Evaluation Period for patients with no available Hgb values during the Evaluation Period. The results for the primary efficacy endpoint were given in the Table 19. However, those pre-specified missing

data imputations are not ‘imputation under the null’ methods; it may be in favor of Epoetin alfa group.

Table 20 Primary Efficacy Analysis of Hgb Change from Baseline to the Evaluation Period using Different Strategy of Missing data Imputation

	Mean difference	95% CI
Change from baseline in Hgb of 0.0 g/dL	0.09 g/dL	-0.05, 0.22
Mean of the last five Hgb values	0.08 g/dL	-0.06, 0.23

The sponsor provided the statistical rationale for choice of non-inferiority margin in this report. Non-inferiority was established if the lower limit of the two-sided 95% CI for the difference between the means of the primary endpoint in the Peginesatide group and the Epoetin treatment group. Statistical support for the choice of non-inferiority margin was provided by estimating a lower bound for the effect of standard therapy on Hgb in the treatment of anemia in CRF based on historical data

The sponsor used Full Analysis Population as the primary efficacy analysis population. However, the Full Analysis Population is the subset of randomized population. For keeping the principle of randomization, any efficacy evaluations in a randomized trial should be based upon all randomized patients. The results for the primary efficacy analysis of the Hgb change from baseline using randomized population were given in Table 21. The results were similar between Randomized Population and Full Analysis Population

Table 21 Primary Efficacy Analysis of the Hgb Change from Baseline to the Evaluation Period (ITT Population)

Evaluation Period (Weeks 29-36)	AF37702 N=549	Epoetin N=274	Total N=823
Change from baseline			
Mean (SD)	-0.07 (1.009)	-0.17 (1.000)	-0.10 (1,006)
Median	-0.1	-0.2	-0.1
Difference from Epoetin			
LS Mean (SE)	-0.10 (0.078)		
2-sided 95% CI	(-0.05, -0.26)		

Results of the Major Secondary Efficacy Endpoint-Transfusion

Fifty-four (7.7%) patients in the Peginesatide group and 27 (9.9%) patients in the Epoetin treatment group received one or more transfusions during the Titration and Evaluation Periods; the relative risk was 0.79 with 95% CI of (0.50, 1.24) (Table 22).

Table 22 RBC Transfusion During the Titration and Evaluation Period

Transfusion Rate (%)	Statistic	AF37702 Inj.IV or SC Q4W (N=542)	Epoetin alfa/beta IV or SC 1-3 Times per Week (N=273)	Total (N=815)
No. of Patients Who Received ≥ 1 Transfusion During the Titration and Evaluation Periods				
	N (%)	42/542 (7.7%)	27/273 (9.9%)	69/815 (8.5%)
Relative Risk (RR) from Epoetin alfa/beta[1][2]				
	RR	0.79		
	2-Sided 95% CI for RR	(0.50, 1.24)		
No. of Patients Who Received ≥ 1 Transfusion During the Titration Period				
	N (%)	35/542 (6.5%)	20/273 (7.3%)	55/815 (6.7%)
Relative Risk (RR) from Epoetin alfa/beta[1][2]				
	RR	0.89		
	2-Sided 95% CI for RR	(0.53, 1.48)		

Note: RBC or whole blood transfusions are included.

[1] Relative risk estimate and CI were obtained from the CMH test including terms for treatment group and the randomization stratification factors.

[2] Relative risk from Epoetin alfa/beta = AF37702 Injection treatment group/ Epoetin alfa/beta group.

Source Data: Applicant's study report Table 17

Reviewer's Comments

In order to assess the time effect of the transfusion use, this reviewer performed time to first event analysis for transfusion using Cox Proportional Hazard model stratified by treatment group and the randomization stratification factors. The results show that the HR is 0.78 with 95% CI of (0.48, 1.27), indicating there is no statistical difference between 2 treatment groups during titration and evaluation period. However, there are several limitations that may cause biases:

- *Criterion for transfusion usage vary among different clinicians and clinics*
- *Criteria for transfusion usage also a significantly different by different countries*
- *Additionally, patients who died from cardiovascular or renal disease were no longer at risk of transfusion (competing risk)*

Results of the Secondary Efficacy Endpoints-proportion of patients whose mean hemoglobin level during the evaluation period was within the target range of 10.0 to 12.0g/dL

During the evaluation period, 344/542 (63.5%) vs. 180/273 (65.9 %) patients in the Pegineside and Epoetin treatment groups, respectively, had a mean Hgb level within target range. The relative response rate (with 'response' defined as a Hgb in the target range during the Evaluation Period) of Pegineside relative to Epoetin was 0.96 with 95% CI of (0.87, 1.07).

Study AFX01-11 and AFX01-13 (Non-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 ≥ 8 g/dL and ≤ 11 g/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 μ g/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 ≤ 10.4 g/dL or ≥ 10.5 g/dL and NYHA Heart Failure 0-1 or $\geq$ Class 2.

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 (Table 23).

Table 23 Primary Efficacy Analysis for Non-Dialysis

	Peginesatide 0.025 mg/kg q4wk N= 328	Peginesatide 0.04 mg/kg q4wk N = 328	Darbepoetin 0.75 μ g/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	0.08	0.29	

Darbepoetin by Least Squares mean (2 sided 97.5% CI)	(-0.08, 0.24)	(0.13, 0.45)	
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3.3 Evaluation of Safety

3.3.1 Definition of Endpoints

The primary safety endpoint for the composite safety endpoint (CSE) analyses was the time to first occurrence of a CSE event

The composite safety endpoint (CSE) was defined as a composite of six events (death, stroke, MI, serious events of CHF, unstable angina, and arrhythmia). An Independent Event Review Committee (ERC) provided blinded adjudication of potential CSE events. CSE data by endpoint and component events and by ERC-adjudicated cause of death are presented for the On-Study and On-Drug groups. The primary CSE analysis included (1) CSE events other than death that occurred through the day of termination from the study and (2) death that occurred through 28 days after termination from the study-this is subsequently referred to as the On-Study CSE. It is noted that a separate analysis of death was conducted that included deaths occurring more than 28 days after termination from the study.

An additional post hoc endpoint referred to as the MACE CSE (where MACE refers to Major Adverse Cardiovascular Event) was defined after preliminary Phase 3 and CSE findings were known; the MACE CSE consisted of three of the six CSE events: death, stroke and MI. For each patient who experienced one or more CSE events, the primary CSE was calculated as the number of days from the day of randomization (defined as Day 1) to the day of onset of the first CSE event. In the analysis of this endpoint, for patients who did not experience a CSE event, the time-to-event was censored as of the day of termination from the study.

3.3.2 Analysis Population

The analyses of the CSE were based on all randomized patients who received at least one dose of their assigned study treatment. Thus, the analyses of the CSE were based on the safety analysis population as defined for the individual analyses of each of the Phase 3 studies.

3.3.3 Determination of Sample Size

Assuming a 17.4% annual event rate for the CSE for the pooled dialysis and non-dialysis populations in both groups, a total of 553 patients with CSE events were required for a one-sided 95% confidence interval to exclude a hazard ratio greater than 1.3 with 89% probability; the To observe 553 patients with CSE events required enrolling 2400 patients in Phase 3 studies (1600 in the Peginesatide Injection groups and 800 in the control groups). This sample size estimate was based upon an underlying 17.4% annual CSE event rate for both treatment groups exponential distribution assumed for time to first CSE event), a 12-month accrual period (accrual assumed to be uniform over the period), at least 12 months of follow-up on all patients (a total study period of 24 months), and a 5% annual loss to follow-up (exponential distribution assumed for time to dropout).

3.3.4 Statistical Analysis Method

The primary statistical analysis of the CSE was the estimation of hazard ratios using stratified Cox regression for each study with the study-specific stratification factors, and then combining these estimates over studies using weights inversely proportionate to the variance of the study-specific log-hazard ratio estimates. The primary evaluation for this pooled analysis was based upon a one-sided 95% CI using the normal approximation of the hazard ratio estimated by the stratified Cox regression model. This analysis was used to determine if a hazard ratio greater than 1.3 could be excluded. In the presentation of the statistics for this analysis, a two-sided 90% CI was provided (the one-sided 95% CI was obtained by use of the upper limit of the two-sided 90% CI).

Secondary Analysis (Two-Sided 95% CIs): Although the primary analysis of the CSE was powered based upon the use of a one-sided 95% CI for the hazard ratio, a secondary analysis is presented for the pooled Peginesatide Injection and pooled control group comparison based on a two-sided 95% CI.

Reviewer's Comment

This analysis was requested by FDA at the clinical advice meeting that was held on 14 June 2007.

3.3.5 Analysis Results of Safety Endpoints

3.3.5.1 Patient Disposition

Dialysis

Table 24 shows the summary of phase 3 dialysis population disposition. Of the 1081 randomized subjects in the Peginesatide group, 1066 received study treatment, and of the 545 randomized subjects in the Epoetin group, 542 received study treatment. Similar proportions of subjects complete follow-up through 15 October 2009 between Peginesatid group (78.8%) and Epoetin group (80.1%)

Table 24 Phase 3 Dialysis Population Disposition

	AF37702 Injection	Epoetin
Randomized; n	1081	545
Treated; n (% of randomized)	1066 (98.6%)	542 (99.5%)
Completed Follow-up through 15 October 2009 ¹ n (% of treated)	840 (78.8%)	434 (80.1%)
On Treatment	767 (72.0%)	416 (76.8%)
Off Treatment ²	73 (6.8%)	18 (3.3%)
Early Termination from Study Prior to 15 October 2009 ¹	224 (21.0%)	108 (19.9%)
Reason:		
Death	75 (7.0%)	50 (9.2%)
Withdrew Consent from all Study Activities	66 (6.2%)	21 (3.9%)
Lost to Follow-up	9 (0.8%)	6 (1.1%)
Other ³	74 (6.9%)	31 (5.7%)
Terminated and Contributed a CSE Event	97 (9.1%)	58 (10.7%)
Terminated without Contributing a CSE Event	127 (11.9%)	50 (9.2%)
Vital Status Known	89 (8.3%)	31 (5.7%)
Vital Status Unknown	38 (3.6%)	19 (3.5%)

¹ The Phase 3 studies were closed at individual study sites between 15 October 2009 and 3 February 2010. Thus, 15 October 2009 was considered to be the last date through which subjects were uniformly followed for analysis of CSE events ([Section 3.0](#)).

Source data: Sponsor's ISS report Table 14

Reviewer's Comments:

Larger proportion of subjects in the Peginesatide group discontinued from study prior to 15 Oct 2009 due to withdrew consent from all study activities compared with those from Epoetin group (6.2% vs. 3.9%).

Non-dialysis

Table 25 shows the summary of phase 3 non-dialysis population disposition. A smaller proportion of subjects in the Peginesatide group completed follow-up through 15 October 2009 and completed follow-up through this date on study treatment compared with those from Darbepoetin group.

Table 25 Phase 3 Non-Dialysis Population Disposition Overview

	AF37702 Injection	Darbepoetin
Randomized; n	656	327
Treated; n (% of randomized)	656 (100%)	327 (100%)
Completed Follow-up through 15 October 2009 ¹ n (% of treated)	519 (79.1%)	275 (84.1%)
On Treatment	472 (72.0%)	253 (77.4%)
Off Treatment ²	47 (7.2%)	22 (6.7%)
Early Termination from Study Prior to 15 October 2009 ¹	137 (20.9%)	51 (15.6%)
Reason:		
Death	42 (6.4%)	16 (4.9%)
Withdrew Consent from all Study Activities	44 (6.7%)	14 (4.3%)
Lost to Follow-up	17 (2.6%)	6 (1.8%)
Other ³	34 (5.2%)	15 (4.6%)
Terminated and Contributed a CSE Event	64 (9.8%)	20 (6.1%)
Terminated without Contributing a CSE Event	73 (11.1%)	31 (9.5%)
Vital Status Known	37 (5.6%)	18 (5.5%)
Vital Status Unknown	36 (5.5%)	13 (4.0%)

¹ The Phase 3 studies were closed at individual study sites between 15 October 2009 and 3 February 2010. Thus, 15 October 2009 was considered to be the last date through which subjects were uniformly followed

Reviewer's Comments:

A larger proportion of Peginesatide group discontinued from study prior to 15 Oct 2011 (20.9% vs 15.6%) compared to Darbepoetin group. A larger proportion of subjects in the Peginesatide group were prematurely terminated from the study prior to 15 October 2009 due to death (6.4%) compared with those from Darbepoetin group (4.9%). A larger proportion of subjects in the Peginesatide group were terminated from the study due to CSE (9.8%) compared with those from Darbepoetin group (6.1%).

3.3.5.2 Patient Demographic and Baseline Characteristics

Table 26 shows the summary of phase 3 patient exposure and follow-up

Table 26 Summary of Phase 3 Patient Exposure and Follow-up

	Dialysis Population		Non-Dialysis Population		Dialysis + Non-Dialysis Populations	
	Peginesatide (N=1066)	Epoetin (N=542)	Peginesatide (N=656)	Darbepoetin (N=327)	Peginesatide (N=1722)	Control (N=869)
Patient Exposure ¹						
Total PEY	1,236	653	844	434	2,733	1,106
Average PEY/Patient	1.16	1.20	1.29	1.33	1.21	1.25
Mean Exposure (wks)	61	63	67	69	63	65
Median Exposure (wks)	64	64	74	75	66	68
Patient Follow-Up						
Total PFY	1,317	677	897	460	2215	1137
Average PFY/Patient	1.24	1.25	1.37	1.41	1.29	1.31
Mean Follow-up (wks)	65	65	71	73	67	68
Median Follow-up (wks)	65	66	77	77	69	70

¹ Exposure to study medication was calculated based on the dates of the first and last doses of study medication plus the number of days in the dosing interval (i.e., 28 days peginesatide, 3-7 days for epoetin [dosed 1-3 times per week], and 14 days for darbepoetin).

Source data: Sponsor's briefing document Table 26

Reviewer's Comments:

For both dialysis and non-dialysis studies, the total patients exposure time are lower in the Peginesatide group compared to active control group.

Dialysis Population

The primary cause of Chronic Renal Failure (CRF) in both treatment groups (Peginesatide Injection vs. Epoetin) was diabetes (37.1% vs. 39.5%), followed by hypertension (31.8% vs. 28.4%). Median hsCRP was 5.4 mg/L in the Peginesatide group and 5.8 mg/L in the Epoetin group; hsCRP >10 mg/mL was similar between treatment groups (30.9% Peginesatide vs. 31.5% Epoetin). A larger proportion of subjects in the Peginesatide group had CAD (41.9% vs. 35.2%, with a larger proportion of subjects with MI, CABG, and PCI or coronary stent placement in the Peginesatide group), PVD (24.1% vs. 22.0%), and cigarette use (33.5% vs. 31.5%). Other baseline disease characteristics were similar between treatment groups.

Median baseline Epoetin dose was similar between treatment groups (8,996 U/week [113 U/kg/week] Peginesatide vs. 9,020 U/week [112 U/kg/week] Epoetin). In subjects receiving study treatment IV, median baseline IV Epoetin dose was higher in subjects randomized to the Epoetin group (Peginesatide vs. Epoetin group 9810 U/week); Median baseline Epoetin dose in both the IV and SC groups was approximately two times higher among subjects at US sites compared to subjects at non-US sites. This finding was similar within each treatment group.

Non-dialysis Population

In the Non-Dialysis Population, the primary cause of CRF in both treatment groups (Peginesatide vs. darbepoetin) was diabetes (51.8% vs. 45.0%), followed by hypertension (30.9% vs. 35.2%). Median hsCRP was 3.1 mg/L in the Peginesatide group and 2.8 mg/L in the darbepoetin group; hsCRP >10 mg/L was noted for a larger proportion of subjects in the Peginesatide group (20.7% vs. 18.0%). Differences noted for baseline cardiovascular risk history included a larger

proportion of subjects in the Peginesatide group with at least one cardiovascular comorbidity without hypertension (93.4% vs. 89.6%), diabetes (67.7% vs. 60.2%), CAD (40.2% vs. 38.2%, with larger proportions noted for MI and CABG in the Peginesatide group), arrhythmia (15.9% vs. 13.1%), PVD (27.3% vs. 19.9%), hyperlipidemia (78.2% vs. 74.0%), CHF (27.7% vs. 3.5%), and cigarette use (11.0% vs. 8.3%) There were no cardiovascular risk factors that occurred in larger proportions of subjects in the darbepoetin group.

Summary

Of note, the Non-Dialysis Population was older (on average 10 years older) and had a lower proportion of men and Blacks than the Dialysis Population. In the Non-Dialysis Population, the darbepoetin group had a larger proportion of subjects with hypertension as the primary cause of their CRF compared to the Peginesatide group and both treatment groups in the Dialysis Population whose primary cause of CRF was diabetes. Some baseline CV risk factor differences were noted between the Dialysis and Non-Dialysis Populations. The Non-Dialysis Population had a higher proportion of subjects with hyperlipidemia and diabetes, as compared to the Dialysis Population. In contrast, the Dialysis Population had an increased proportion of subjects with underlying heart failure, increased inflammatory status as measured by hsCRP, and more severe hyperphosphatemia.

3.3.5.3 Studies Results (Dialysis and Non-Dialysis)

Table 27 shows the safety endpoints analyses for the dialysis and non-dialysis using stratified (by study) Cox proportional hazard model adjusting stratification variables (baseline hemoglobin and NYHA CHF class).

Table 27 Summary of Analyses Results for Safety Endpoints (On-Study)

	Dialysis		Non-Dialysis	
	Peginesatide (N=1066)	Epoetin-alfa/beta (N=542)	Peginesatide (N=656)	Darbepoetin (N=327)
CSE				
# of Event	243 (23%)	132 (24%)	141 (22%)	56 (17%)
HR (95% CI)	0.94 (0.76, 1.16)		1.28 (0.94, 1.75)	
MACE				
# of Events	161 (15%)	96 (18%)	80 (12%)	30 (9%)
HR (95% CI)	0.84 (0.66, 1.09)		1.34 (0.88, 2.05)	
All Cause Death				
# of Events	136 (12.8%)	68 (12.5%)	73 (11.1%)	24 (7.3%)
HR (95% CI)	0.97 (0.72, 1.30)		1.52 (0.95, 2.42)	
Stroke				
# of Events	122 (11.4%)	72 (13.3%)	53 (8.1%)	23 (7.0%)
HR (95% CI)	0.86 (0.64, 1.11)		1.16 (0.71, 1.89)	

Reviewer's Comments:

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 disease setting should be performed using a safety composite endpoint and that the results should be compared using 90% confidence intervals. This analysis was used to determine if a hazard ratio of the upper limit of the two-sided 90% CI greater than 1.3 could be excluded.

The safety outcomes in both dialysis trials (AFX01-12 and AFX01-14) appear similar for both treatment groups for both the CSE (HR=0.95, 95% CI= (0.76, 1.16)) and the MACE endpoints ((HR=0.84, 95% CI= (0.66, 1.09)).

However, in the two non-dialysis trials (AFX01-11 and AFX01-13), there are differences in the safety outcomes, with results unfavorable for Peginesatide. The HR was 1.28 with 95% CI of (0.94, 1.75) for CSE endpoint, and the HR was 1.34 with 95% CI of (0.88, 2.05) for MACE endpoint. Peginesatide are numerically worse, but they are not statistically significantly different from that of the Darbepoetin-treated group. 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. Differences in baseline characteristics unfavorable to Peginesatide are acknowledged.

Given the imbalances observed in baseline factors, the best approach is to conduct an analysis adjusting for these baseline factors using Cox-regression model in the safety population. The base model we used was the primary model, which is Cox regression model stratified by study adjusting stratification variables. And then we added these imbalanced baseline factors either separately each time or both of them at the same time into the base model, the adjusted analysis model gave similar results from primary model, indicating there is no clear evidence that imbalanced baseline factors impacts the overall conclusion that a higher risk in the peginesatide treatment compared to darbepoietin in the non-dialysis population

Table 28 shows on-drug sensitivity analyses of safety endpoints using stratified Cox proportional model.

Table 28 Summary of On-drug Sensitivity Analyses Results for Safety Endpoints (On-Drug)

On Drug	Dialysis		Non-Dialysis	
	Peginesatide N=1066	Epoetin N=542	Peginesatide N=656	Darbepoetin N=327
CSE				
# of Event	195 (18.3%)	121 (22.3%)	114 (17.4%)	47 (14.4%)
HR (95% CI)	0.85 (0.68, 1.07)		1.30 (0.92, 1.84)	
MACE				
# of Event	102 (9.6%)	81 (14.8%)	48 (7.3%)	22 (6.7%)
HR (95% CI)	0.65 (0.48, 0.87)		1.14 (0.68, 1.89)	
Death				
# of Event	51 (4.8%)	46 (8.5%)	26 (4.0%)	13 (4.0%)

HR (95% CI)	0.57 (0.38, 0.85)	1.07 (0.55, 2.09)
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Reviewer's Comments

In the phase 3 studies, patients who prematurely discontinued study drug were to remain in the study and continue to be followed for SAEs. Thus, CSE events included in the On-study CSE could occur after discontinuation of study drug. The FDA requested On-drug sensitivity analyses (i.e., censoring at the time at which patients stopped study drug) at the meeting that was hold on 14 June 2007. the results of On-drug sensitivity analyses gave similar conclusion with the primary safety analyses. However, the interpretation of such analyses should take cautious, since these analyses do not maintain the fairness and integrity of the randomization as the actual follow-up time is treatment and outcome related.

3.3.5.4 Analyses of Death Results

In this submission, there are three periods for death.

On study: included deaths through 28 days following discontinuation from study

On drug: included deaths through 28 days following study treatment discontinuation

All deaths: included the on study death and any other deaths occurring more than 28 days after termination from the study.

Table 29 shows the analyses of death for different period in both dialysis and non-dialysis patient population.

Table 29 Summary of Analyses of Death for Three Different Periods

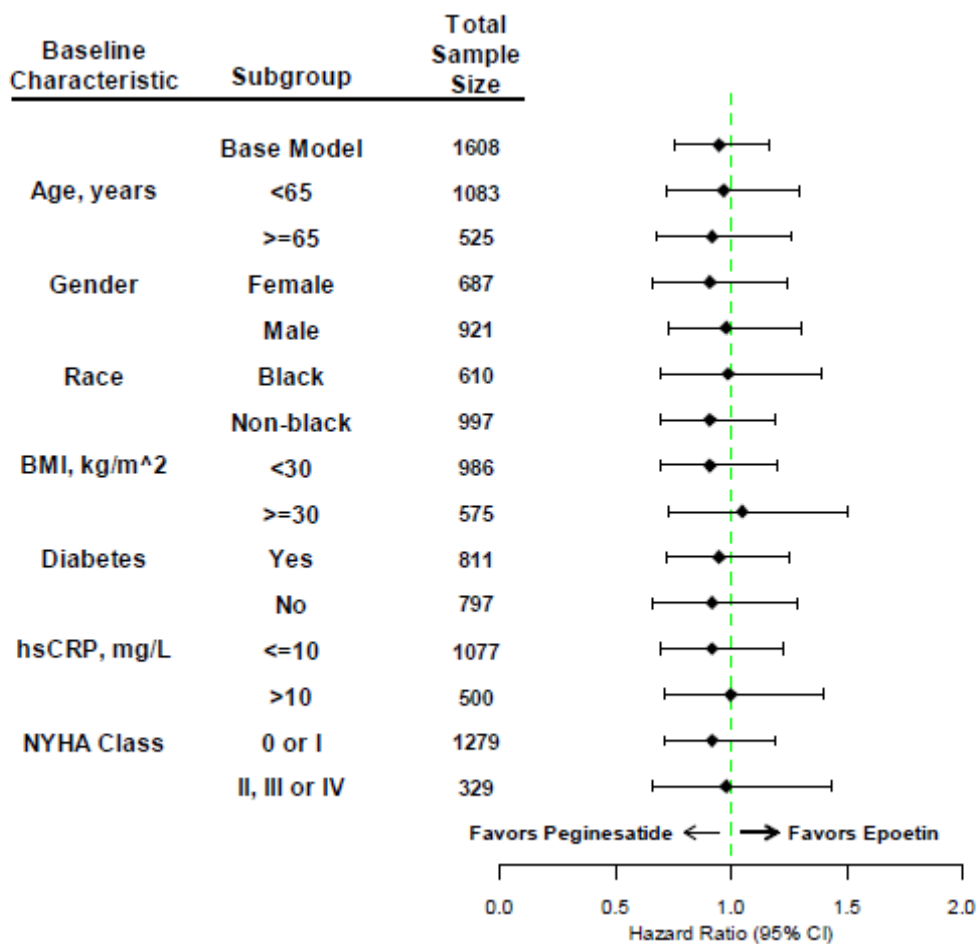
	Non-Dialysis		Dialysis	
	Peg N=656	Dar N=327	Peg N=1066	Epo N=542
All death	73 (11.1%)	24 (7.3%)	136 (12.8%)	68 (12.5%)
	HR=1.52, 95%CI=(0.95, 2.42)		HR=0.97, 95%CI=(0.72, 1.30)	
On study	58 (8.8%)	22 (6.7%)	115 (10.8%)	64 (11.8%)
	HR=1.42, 95%CI=(0.86, 2.35)		HR=0.90, 95%CI=(0.67, 1.23)	
On drug	26 (4.0%)	13 (4.0%)	51 (4.8%)	46 (8.5%)
	HR=1.07, 95% CI=(0.55, 2.09)		HR=0.57, 95% CI=(0.38, 0.85)	

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Subgroup Analysis: Dialysis Population

Figure 2 shows subgroup analysis for CSE dialysis population.

Figure 2 Hazard Ratios and Confidence Intervals for CSE Subgroups



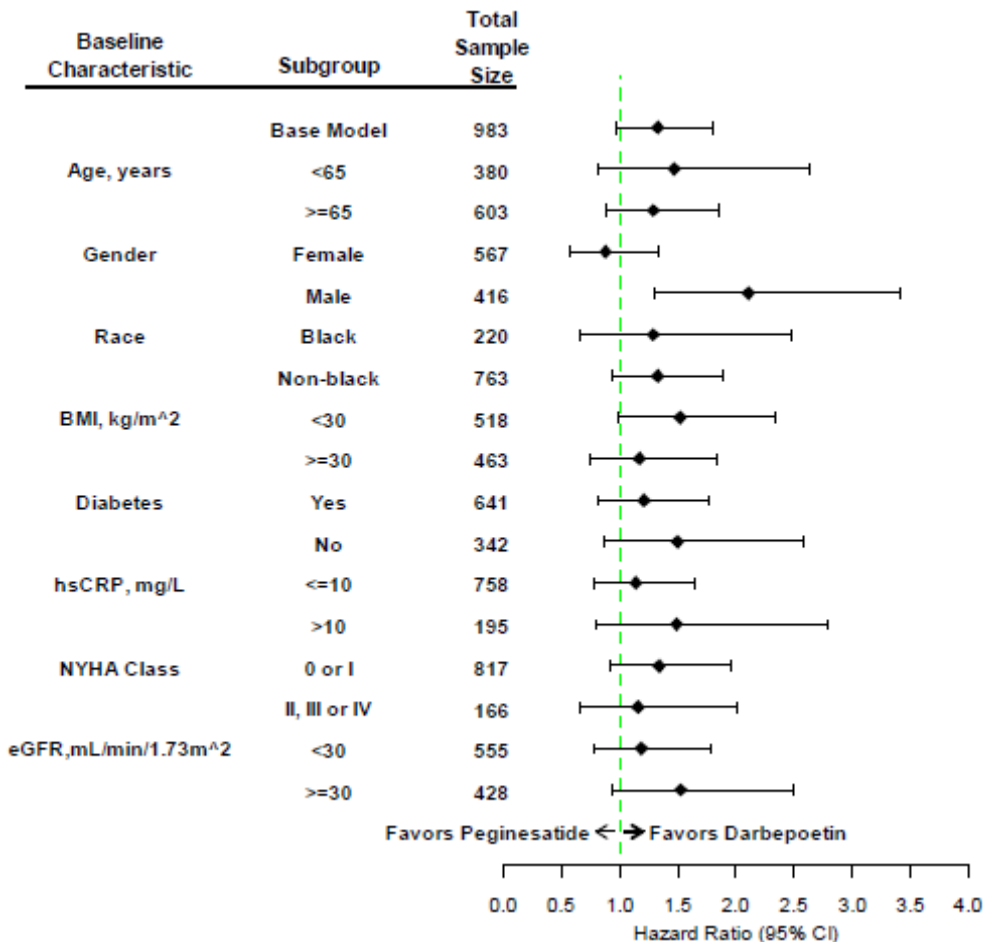
Reviewer's Comments

The hazard ratios for subgroups were generally less than 1, in favor of Peginesatide treatment group for dialysis population. Several hazard ratios for subgroups were greater than one. However, the statistical power for detecting the same magnitude of treatment effect may be insufficient in those subgroup analyses unless the precision of subgroup estimate has been considered properly in planning the sample size or the variability of the response is sufficiently small in the subgroup. Therefore, we recommend that those subgroup analyses are only exploratory and suggestive, but not conclusive.

4.2 Subgroup Analysis: Non-Dialysis Populations

The hazard ratios and 95% confidence intervals for subgroup analysis for CSE in Non-Dialysis Populations are shown in Figure 3. The hazard ratios for CSE endpoint are all greater than 1.

Figure 3 Hazard Ratios and Confidence Intervals for CSE Subgroups in Non-Dialysis Population

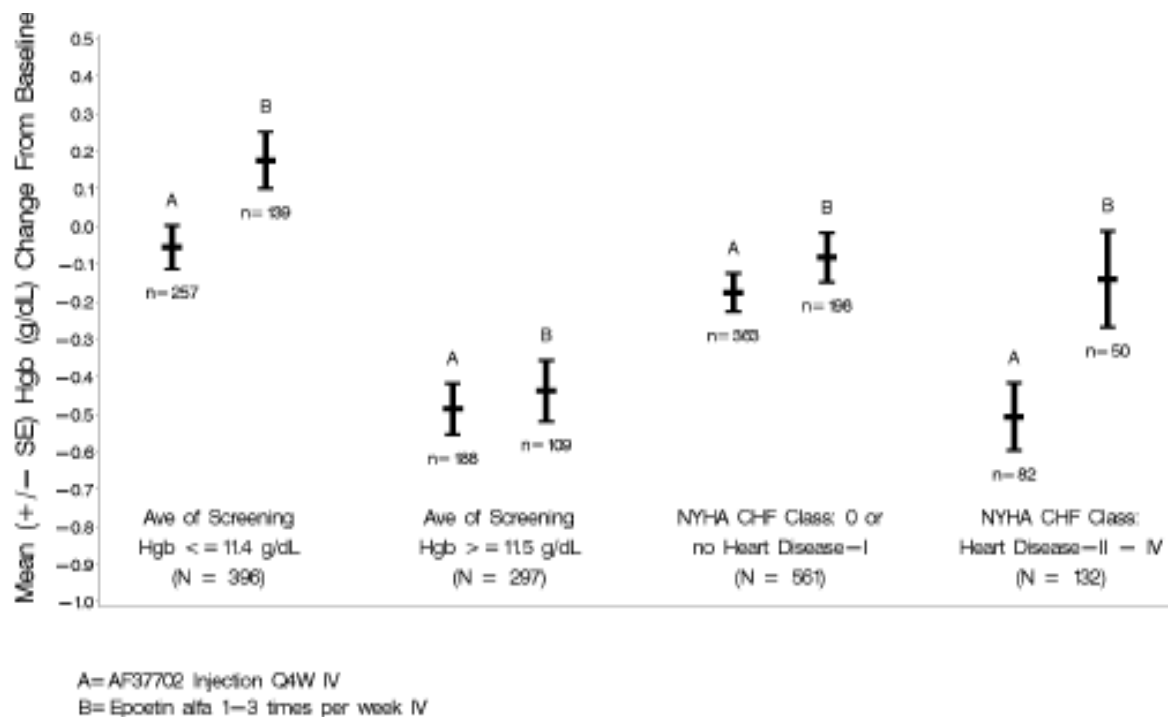


4.3 Other Special/Subgroup Populations

Study AFX01-12

Figure 4 shows the mean ($\pm$ SE of the primary efficacy variable) for the randomization stratification factors.

Figure 4 Primary Efficacy Endpoint by Randomization Stratification Factors (Full Analysis Population)



Source Data: Study Report Figure 3

Reviewer's Comments

The magnitudes of the treatment differences generally were consistent with Full Analysis Population for the subgroups of the stratification factors. However, the difference between treatment groups was larger in the NYHA HF Class subgroups. According to the sponsor's report, determination of functional status based on symptomatology, as is needed for NYHA classification, maybe confounded in dialysis patients by volume overload due to factors independent of cardiac function. The relatively small size of this group and the likely heterogeneity within the group in terms of cardiac function make interpretation of this subgroup finding difficult.

Study AFX01-14

Figure 5 shows the mean ($\pm$ SE of the primary efficacy variable) for the randomization stratification factors.

Figure 5 Primary Efficacy Endpoint by Randomization Stratification Factors (Full Analysis Population)

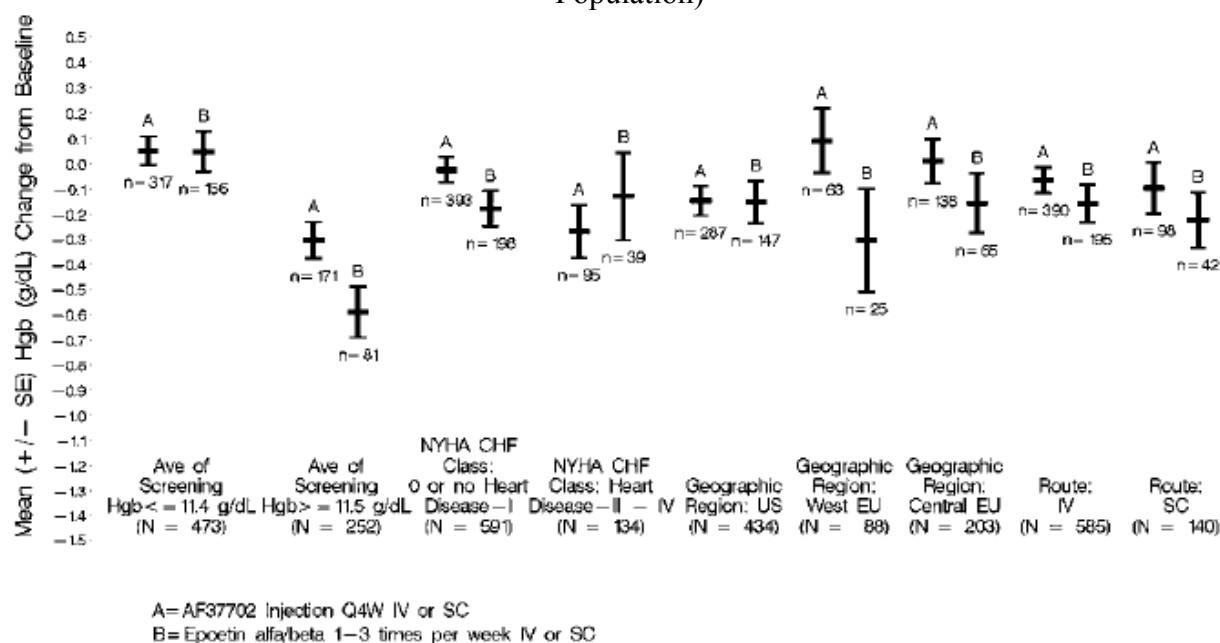


Table 30 and 31 show the post-hoc analyses of CSE endpoint by baseline hemoglobin stratum (≤ 10.4 g/dL or > 10.5 g/dL) for both non-dialysis and dialysis.

Table 30 Analysis of CSE Endpoint for Non-Dialysis by Baseline Hgb

	Peginesatide	Darbepoetin	HR
≤ 10.4 g/dL N=688	21.91% (101/461)	19.38% (44/227)	1.14 (0.78, 1.62)
> 10.5 g/dL N=295	20.51% (40/195)	12% (12/100)	1.88 (0.98, 3.58)

Table 31 Analysis of CSE Endpoint for Dialysis by Baseline Hgb

	Peginesatide	Epoetin	HR
≤ 11.4 g/dL N=950	23.64% (148/626)	23.77% (77/324)	0.99 (0.76, 1.31)
> 11.5 g/dL N=658	21.59 % (95/440)	25.23% (55/218)	0.86 (0.62, 1.2)

Reviewer's Comments

From table 29 and 30 we can see that the non-dialysis cohort has more CSE events compared with the dialysis.

Table 32 shows the summary of mean dose for Peginesatide during the study period.

Table 32 Summary of Mean Dose for Peginesatide Group

	Non-Dialysis		Dialysis	
	Peginesatide N=656	Darbepoetin N=327	Peginesatide N=1066	Epoetin N=542
Mean Dose (SD) Evaluation Period	2.83 (2.76)	48.28 (51.54)	7.63 (8.19)	12703.37 (13682.3)
Mean Dose (SD) (Week 37-52)	2.83 (3.52)	44.27 (50.29)	8.08 (9.60)	13248.95 (14332.20)

Reviewer's Comments

Dialysis patients received substantially higher doses compared with non-dialysis patients.

5. SUMMARY AND CONCLUSIONS**5.1 Statistical Issues and Collective Evidence**

1. For evaluating safety these were active controlled trials, not placebo-controlled trials, where the active control therapy was dosed with respect to old labeling guidelines. The labeled guidelines for dosing the active control treatments were changed due to the concern of increased risk of cardiovascular events or deaths during the course of the study.
2. 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 disease setting should be performed using a safety composite endpoint and that the results should be compared using 90% confidence intervals. This analysis was used to determine if a hazard ratio of the upper limit of the two-sided 90% CI greater than 1.3 could be excluded.

The safety outcomes in both dialysis trials (AFX01-12 and AFX01-14) appear similar for both treatment groups for both the CSE (HR=0.94, 95% CI= (0.76, 1.16)) and the MACE endpoints ((HR=0.84, 95% CI= (0.66, 1.09)).

However, in the two non-dialysis trials (AFX01-11 and AFX01-13), there are differences in the safety outcomes, with results unfavorable for Peginesatide. The HR was 1.28 with 95% CI of (0.94, 1.75) for CSE endpoint, and the HR was 1.34 with 95% CI of (0.88, 2.05) for MACE endpoint. Peginesatide are numerically worse, but they are not statistically significantly different from that of the Darbepoetin-treated group. 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. Differences in baseline characteristics unfavorable to Peginesatide are acknowledged.

3. For Non-dialysis patient population, the baseline characteristic in diabetes and PVD are imbalanced. Given the imbalances observed in baseline factors, the best approach is to conduct an analysis adjusting for these baseline factors using Cox-regression model in the safety population. The base model we used was the primary model, which is Cox regression model stratified by study adjusting stratification variables. And then we added these imbalanced baseline factors either separately each time or both of them at the same time into the base model, the adjusted analysis model gave similar results as the primary model, indicating there is no clear evidence that imbalanced baseline factors impacts the overall conclusion that a higher risk in the Peginesatide treatment compared to Darbepoetin in the non-dialysis population.
4. It is not appropriate to use the fully analysis population as the primary efficacy analysis set for the primary efficacy endpoint; it is against the intent-to-treat principle, as the response-evaluable population is a subset of the ITT population. The randomized population should be the primary basis for making treatment comparison in maintaining the integrity of the randomization. However, since there is only minor difference between ITT population and fully analysis population (98.8%), and this difference doesn't not impact the overall conclusion from full analysis population, we accept to report analysis from protocol pre-specified full analysis population as the primary population.
5. The applicant's analysis of transfusion has several limitations that may cause biases.
 - Criterion for transfusion usage vary among different clinicians and clinics;
 - Criterion for transfusion usage is also significantly different by different countries;
 - Additionally, patients who died from cardiovascular or renal disease were no longer at risk of transfusion (competing risk).

5.2 Conclusions and Recommendations

The applicant submitted data and final study reports of four phase 3 randomized, controlled, open label, multicenter trials to seek full approval for Peginesatide injection for the indication of "Treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis". In the NDA, there are two trails (AFX01-11 and AFX01-13) in patients with CKD on dialysis and two trials (AFX01-12 and AFX01-14) in patients with CKD not on dialysis.

The primary efficacy endpoint for all trials was change in hemoglobin between the baseline and the evaluation period. The non-inferiority margin was 1.0 g/dL for all trials. Peginesatide would be considered non-inferior to the comparator 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 non-dialysis trials. Each trial met this non-inferiority criterion.

The phase 3 clinical program includes an assessment of cardiovascular (CV) safety utilizing blinded adjudication of pre-specified CV endpoints. The Phase 3 dialysis and non-dialysis studies were pooled for the primary CSE analysis, as well as analyzed by population (dialysis and non-dialysis). The CSE was defined to consist of the following six component events: death, stroke, myocardial infarction (MI), congestive heart failure (CHF), angina and arrhythmia. Composite endpoint (defined as the first occurrence of death, stroke or myocardial). The time to first CSE event was analyzed by estimating HRs using stratified Cox regression for each study. This analysis was used to conclude if a hazard ratio of the upper limit of the two-sided 90% CI was than 1.3 could.

The safety outcomes in both on-dialysis trials (AFX01-12 and AFX01-14) appear similar for both treatment groups for both the CSE (HR=0.94, 95% CI= (0.76, 1.16)) and the MACE (HR=0.84, 95% CI= (0.66, 1.09)) 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. The HR was 1.28 with 95% CI of (0.94, 1.75) for CSE endpoint, and the HR was 1.34 with 95% CI of (0.88, 2.05) for MACE endpoint.

Given the different findings in the dialysis and non-dialysis populations, the sponsor proposed limiting the indication to dialysis patients. The question is whether the observed safety findings in the non-dialysis patients can be extrapolated to dialysis patients. Based on current data, compared with dialysis patients, the non-dialysis studies have smaller sample sizes, longer exposure time, older subjects, different dose usages, and different baseline characteristics. In addition, it is unclear if the same biological mechanism applies to both dialysis and non-dialysis patients in using the drug. Therefore, it may not be appropriate to apply safety findings from non-dialysis trials to the risk evaluation of drug in dialysis population.

In exploratory analyses, we also observed that poor initial response is in correspondence with lower hemoglobin level at week 12 and through out the study, despite that higher dose of treatments were being given to poor initial responders. Poor initial hematopoietic response to Peginesatide is also associated with higher rates of the composite CSE and MACE endpoint, as compared with better response. However, such associations are dependent on both the definition of poor initial response and key baseline characteristics in the model analysis. Therefore, caution should be taken in the interpretation of such analysis, since the poor initial response to ESA treatment is probably a marker of baseline illness severity. In further perspective, well controlled studies may be needed to evaluate these findings, to identify factors influencing ESA responsiveness so that avoiding excessive doses. In addition, justification of poor response definition with clinical meaningfulness is necessary to be provided in future trials.

Given all those safety concerns observed in non-dialysis trials, a randomized active controlled trial is recommended for further exploring safety profiles for dialysis patients; however, determination of non-inferiority margin and interpretation of results from non-inferiority studies for safety is challenging. The data submitted in this application supports applicant's claim of the efficacy and safety of Peginesatide in dialysis patients who are stable on ESA.

The Oncology drugs advisory committee meeting discussed study results on December 07, 2011.
For the question:

1. Is there a favorable benefit to risk evaluation for Peginesatide for use in patients with anemia associated with chronic renal failure who are on dialysis?-Committee voted: Yes 15, No 1, Abstentions1.

APPENDX (FDA Exploratory Analysis of Initial Response in Non-Dialysis Patients)

BACKGROUND:

Recently a publication [3] suggested an association between poor initial hematopoietic response to Darbepoetin alfa and an increased risk of cardiovascular events among kidney disease and type 2 diabetes patients. Following a similar approach, this exploratory analysis aims to further investigate such association, as well as the association between response and ESA dosages, in non-dialysis patients with chronicle kidney disease.

METHODS

For this analysis, we combined AFX01-11 and AFX01-13 and divided patients in the Peginesatide and Darbepoetin alfa treatment groups into 4 response categories respectively on the basis of the percent increase in Hgb from baseline to Week 4. To allow a direct comparison with the Solomon findings [2], the definitions of the quartiles for initial Hgb response obtained by Solomon were used to categorize the initial Hgb responses observed in the non-dialysis Phase 3 data. Among the 983 patients in the safety population (656 in the Peginesatide group and 327 in the Darbepoetin alfa group), we excluded from this analysis patients who did not receive the first dose of Peginesatide or first two doses of Darbepoetin alfa, those who had primary event and those whose change in hemoglobin level at the end of week 4 was unknown. 897 (91%) patients were included in this analysis, 597 (67%) in the Peginesatide group and 300 (33%) in the Darbepoetin alfa group.

DEFINITION OF POOR RESPONSE

We defined poor response as the percent increase in Hgb from baseline to Week 4 less than 2%, as compared with those in the upper 3 categories [3] (percent change from baseline to Week 4 from 2% to <8%, from 8% to <15% and $\leq 15\%$). We note that such categorization is just for comparison convenience. In Soloman's study, <2% corresponds to the lower quartile of the Hgb change in their cohort while the lower quartile of Hgb change of our data is 5%. We also performed analysis using different cutoff that corresponds to the lower quartile from this study. The impact of poor response definition will be discussed in the following sections.

In each category, we assessed the mean hemoglobin level at 12 weeks (early phase) and the median dose of the 2 treatment groups, as well as the mean hemoglobin level in the later phase (after 12 weeks) and the median dose of 2 treatments after 12 weeks.

OUTCOME MEASURE

The primary safety outcomes for each trial is 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. An additional planned safety was the MACE composite endpoint which includes three types of major adverse cardiac events (defined as the first occurrence of death, stroke or myocardial infarction). Since the randomization of the original data was lost during the categorization according the response criterion, we also performed comparison

analyses to evaluate the balance of all baseline characteristics that are relevant to the outcomes by response group.

STATISTICAL ANALYSIS

Baseline characteristics between poor responders and normal responders for the 2 treatment groups were compared using descriptive analysis. Bar graphs are plotted to identify potential associations between Hemoglobin level and dose within each treatment group. Kaplan-Meier analysis was used for the comparison of risk of CSE and MACE between poor and normal responders as defined above within each treatment group with nominal p-value calculated from logrank test. Bootstrap re-sampling simulations with the data from the study was performed to calculate the expected probability of detecting a significant difference in the CSE event between poor and normal responders within each treatment. Unadjusted and adjusted Cox proportional hazard models were used to calculate the hazard ratio and its 95% CI between patients of poor and normal responses. The annualized event rates (rate per 100 PFY) and its 95% confidence intervals were calculated by response group within each treatment group.

A two-sided significance level of 0.05 was used for all analyses, and all the nominal p-values are for the information use.

RESULTS

PATIENTS BASELINE AND CHARACTERISTICS

The baseline characteristics of the poor responders were compared with those of the better responders by treatment group, as shown in Tables 1 and 2. For several baseline characteristics, differences were noted between the subjects in the Peginesatide group and those in the Darbepoetin group.

In the Peginesatide group, as compared to the better responders, patients with a poor response were more likely to be female (59% vs 53%), to have history congestive heart failure (34% vs 25%), to have history arrhythmia (20% vs 15%), to have coronary artery disease (46% vs 39%), to have history of cerebrovascular disease (23% vs 18%), to have history of hyperlipidemia (82% vs 78%), to have history of PVD (30% vs 26%) and to have high hsCRP (9.7 vs 7.0) (Table 1) . In the Darbepoetin group, as compared to the better responders, patients with a poor response were more likely to be female (78% vs 59%), to have history arrhythmia (22% vs 12%), to have history of cerebrovascular disease (22% vs 17%), to have history of hyperlipidemia (78% vs 74%) , to have history of PVD (34% vs 18%) and to have lower potassium level (Table 2). In general, those findings are similar with the analysis results of TREAT by Solomon and coworkers [3], in which the poor responders were more likely to have cardiovascular disease history and a marginally higher CRP (Table 33, Table 34).

Table 33 Baseline Characteristics for Peginesatide Group

Variable	Poor Responder (N=93)	Better Responder (N=504)	P Value
Change in Hgb from baseline	<2%	≥2%	
Median-g/dl (min, max)	-0.1 (-3.4, 0.2)	1.1 (0.2, 4.5)	
Age (Yrs) at Reference Start Date	68.4 ± 12.6	67.5 ± 13.3	0.5446
Baseline albumin (g/L)	40.2 ± 3.4	39.6 ± 4.4	0.1854
Baseline BUN (mg/dL)	52.1 ± 22.2	48.4 ± 18.9	0.0900
Baseline Diastolic Blood Pressure (mmHg)	71.0 ± 11.5	69.5 ± 11.4	0.2572
Baseline Serum Ferritin (ng/mL)	277.4 ± 279.5	239.9 ± 214.4	0.1415
Baseline Hgb (g/dL)	10.0 ± 0.6	10.0 ± 0.6	0.9152
hsCRP Baseline	9.7 ± 12.0	7.0 ± 13.1	0.0659
ISS Computed BMI (kg/m)	31.4 ± 8.2	30.5 ± 7.3	0.2483
Baseline Potassium (mmol/L)	4.8 ± 0.6	4.9 ± 0.6	0.5299
Coronary Artery Disease: MI (Num)	1.8 ± 0.4	1.9 ± 0.3	0.0631
Baseline Platelets (X10E9/L)	244.0 ± 85.3	261.6 ± 84.2	0.0876
Baseline Systolic Blood Pressure (mmHg)	137.4 ± 20.1	135.1 ± 18.1	0.2754
Sex [n (%)]			0.3050
F	55 (59%)	269 (53%)	
M	38 (41%)	235 (47%)	
Congestive Heart Failure [n (%)]			0.0649
N	61 (66%)	377 (75%)	
Y	32 (34%)	127 (25%)	
CV Risk History: Arrhythmia [n (%)]			0.1602
N	74 (80%)	430 (85%)	
Y	19 (20%)	74 (15%)	
Coronary Artery Disease [n (%)]			0.1964
N	50 (54%)	307 (61%)	
Y	43 (46%)	197 (39%)	

Variable	Poor Responder (N=93)	Better Responder (N=504)	P Value
CV Risk History: Cerebrovascular Disease [n (%)]			0.3044
N	72 (77%)	413 (82%)	
Y	21 (23%)	91 (18%)	
CV Risk History: Diabetes [n (%)]			0.7971
N	29 (31%)	164 (33%)	
Y	64 (69%)	340 (67%)	
CV Risk History: Hyperlipidemia [n (%)]			0.4189
N	17 (18%)	111 (22%)	
Y	76 (82%)	393 (78%)	
CV Risk History: Peripheral Vasc Dis [n (%)]			0.4578
N	65 (70%)	371 (74%)	
Y	28 (30%)	133 (26%)	
Baseline Iron Supplementation [n (%)]			0.8770
N	51 (55%)	272 (54%)	
Y	42 (45%)	232 (46%)	
Baseline Statin Usage [n (%)]			0.8242
N	31 (33%)	174 (35%)	
Y	62 (67%)	330 (65%)	

a. Mean±SD for continuous variables, p-values calculated from t-test

b. Frequency (%) for categorical variables, p-values calculated from chi-square test, it is for the information use, not adjusted for multiplicity, not to be used for inference.

Table 34 Baseline Characteristics for Darbepoetin alfa

Variable	Poor Responder (N=32)	Better Responder (N=268)	P Value
% Change in Hgb	<2	≥2	
Median of Change -g/dl (min, max)	-0.2 (-3.7, 0.2)	1.15 (0.2, 3.4)	
Age (Yrs) at Reference Start Date	68.9 ± 16.0	66.8 ± 13.9	0.4129
Baseline albumin (g/L)	41.3 ± 2.3	39.6 ± 4.0	0.0186
Baseline BUN (mg/dL)	49.9 ± 24.8	49.1 ± 19.9	0.8305
Baseline Diastolic Blood Pressure (mmHg)	70.1 ± 11.8	70.0 ± 11.4	0.9401
Baseline Serum Ferritin (ng/mL)	274.2 ± 340.9	251.1 ± 278.1	0.6656
Baseline Hgb (g/dL)	10.3 ± 0.5	10.0 ± 0.6	0.0065
hsCRP Baseline	7.2 ± 14.4	7.9 ± 27.2	0.8858
ISS Computed BMI (kg/m)	30.7 ± 7.4	30.5 ± 7.5	0.9139
Baseline Potassium (mmol/L)	4.6 ± 0.7	4.9 ± 0.7	0.0670
Coronary Artery Disease: MI (Num)	1.9 ± 0.2	1.9 ± 0.3	0.5667
Baseline Platelets (X10E9/L)	285.6 ± 85.5	268.2 ± 86.1	0.3131
Baseline Systolic Blood Pressure (mmHg)	128.5 ± 19.6	135.5 ± 17.4	0.0385
Sex [n (%)]			0.0324
F	25 (78%)	157 (59%)	
M	7 (22%)	111 (41%)	
Congestive Heart Failure [n (%)]			0.8365
N	25 (78%)	205 (76%)	
Y	7 (22%)	63 (24%)	
CV Risk History: Arrhythmia [n (%)]			0.1142
N	25 (78%)	236 (88%)	
Y	7 (22%)	32 (12%)	
Coronary Artery Disease [n (%)]			0.3832
N	22 (69%)	163 (61%)	
Y	10 (31%)	105 (39%)	
CV Risk History: Cerebrovascular Disease [n (%)]			0.4727

Variable	Poor Responder (N=32)	Better Responder (N=268)	P Value
N	25 (78%)	223 (83%)	
Y	7 (22%)	45 (17%)	
CV Risk History: Diabetes [n (%)]			0.2062
N	16 (50%)	103 (38%)	
Y	16 (50%)	165 (62%)	
CV Risk History: Hyperlipidemia [n (%)]			0.6341
N	7 (22%)	69 (26%)	
Y	25 (78%)	199 (74%)	
CV Risk History: Peripheral Vasc Dis [n (%)]			0.0268
N	21 (66%)	220 (82%)	
Y	11 (34%)	48 (18%)	
Baseline Iron Supplementation [n (%)]			0.1063
N	22 (69%)	144 (54%)	
Y	10 (31%)	124 (46%)	
Baseline Statin Usage [n (%)]			0.3977
N	11 (34%)	113 (42%)	
Y	21 (66%)	155 (58%)	

a. Mean±SD for continuous variables, p-values calculated from t-test

b. Frequency (%) for categorical variables, p-values calculated from chi-square test, it is for the information use, not adjusted for multiplicity, not to be used for inference.

ASSOCIATION BETWEEN HEMOGLOBIN AND DOSE

The association between hemoglobin levels and initial response categories were examined in terms of mean hgb and dose of both study drugs with 2 periods: (1) Early Phase period, defined as Week 12 and (2) Late Phase period from Week 13 to the end of study.

Figure 6 shows the early phase mean hemoglobin level during Week 12 and the median dose for the Peginesatide or Darbepoetin received before Week 12, by response categories. In both Peginesatide and Darbepoetin groups the same trend of association were observed: Mean Hgb observed at Week 12 increases with increasing initial Hgb response; conversely, median dose of study drug before Week 12 decreases with increasing initial Hgb response. Thus, subjects who had a poor Hgb response to their assigned study drug during the first month tend to have a lower average Hgb at Week 12 than did subjects with better initial Hgb responses, despite the fact that poor initial responders received higher doses of study drug. This is to be expected as doses were titrated to a target Hgb level.

Figure 7 shows late phase mean hemoglobin level and the median dose for the Peginesatide or Darbepoetin received after Week 12 and throughout the remainder of the trial. Similarly trends were observed, i.e., the median dose of treatment during the late phase was substantially higher among patients with a poor initial response than among those with a better initial response. The mean hemoglobin level after 12 weeks remained marginally lower among patients with a poor initial response compared to that of subjects with a better initial response.

Figure 6 Association between Hgb Level and Dose by Response Category (Early Phase)

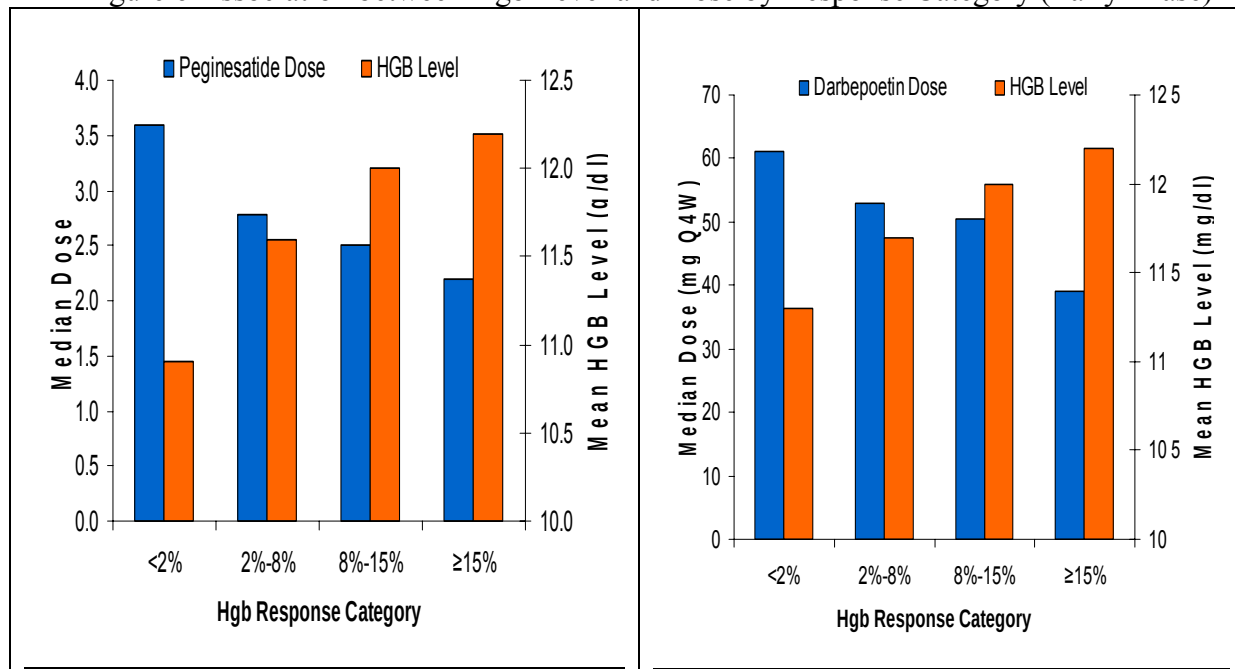
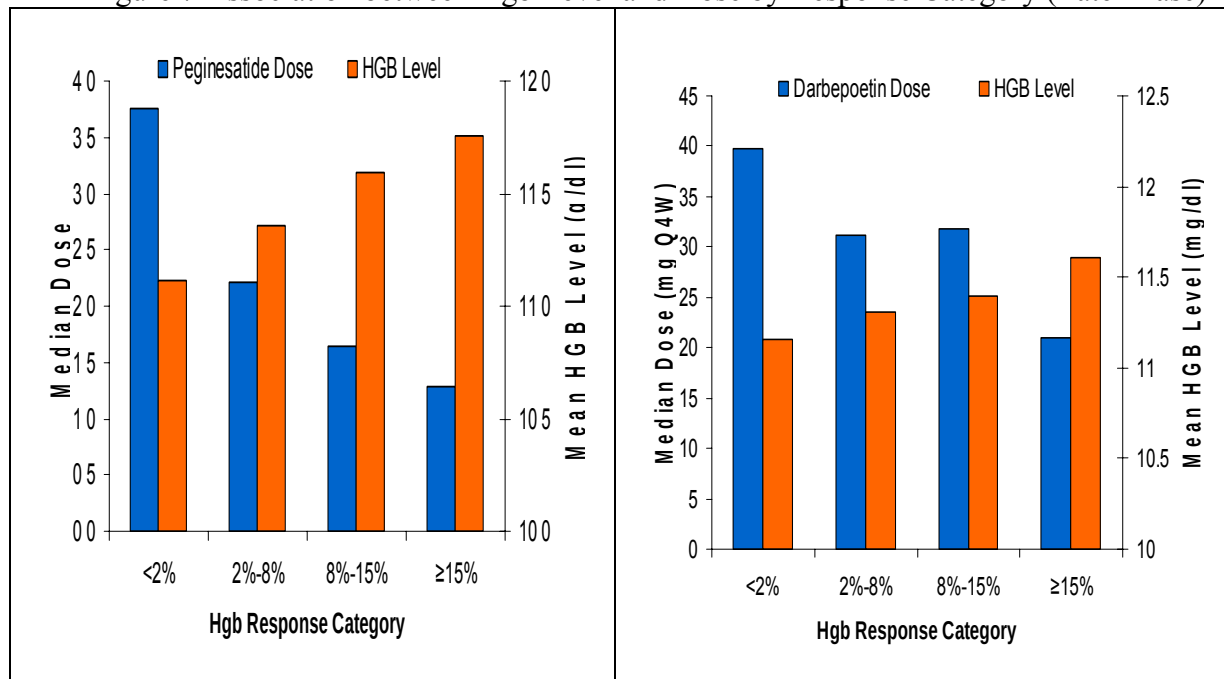


Figure 7 Association between Hgb Level and Dose by Response Category (Late Phase)



ASSOCIATION BETWEEN RESPONSIVENESS AND OUTCOMES

Subjects who had a poor initial Hgb response ($<2\%$ increase in Hgb from baseline to Week 4) were compared to subjects with better initial Hgb responses ($\geq 2\%$ increase in Hgb from baseline to Week 4) with respect to the safety outcomes of CSE event and MACE event. For each of these safety outcomes, the event-free rate over time (Kaplan-Meier survival analysis), annualized event rates, and adjusted hazard ratios (Poor response vs. Better response) were examined. Figure 3 and Figure 4 provide Kaplan-Meier plots of the event-free rates for the comparison of poor responders and better responders by treatment group over time for CSE event and MACE event, respectively.

From these exploratory analyses, in the Peginesatide group, patients with a poor initial response had higher rates of the CSE event and MACE event than patients with a better initial response, with p-value of 0.0029 for CSE and p-value of 0.0098 for MACE using logrank test. In the Darbepoetin group, there is no significant difference between poor response group and better response group; which is different from the findings in Solomon and coworkers' analysis [3], probably due to the relatively small sample size for the Darbepoetin group in this study.

We also performed analysis using an adjusted Cox proportional hazard model to calculate the hazard ratio between the poor and better response groups. Totally 10 baseline covariates relevant to the endpoints (age, congestive heart failure, arrhythmia, coronary artery disease, cerebrovascular disease, hyperlipidemia, PVD, hsCRP, baseline Hgb and baseline potassium) are included as covariates in the model. In the Peginesatide group, the hazard ratio estimated from Cox regression was 1.63 with 95% CI of (0.94, 2.82) for MACE and 1.36 with 95% CI of (0.88, 2.12) for CSE. However, if baseline covariates are unadjusted in the model, significant hazard ratio was obtained, 1.75 with 95% CI (1.15, 2.64) for CSE, and 1.97 with 95% CI (1.17, 3.33). For the Darbepoetin group, using adjusted or unadjusted Cox model all give similar conclusions, i.e., there is no difference between the poor and better response group, although the point estimate of hazard ratio and 95% CI varies.

Annualized event rates were calculated by treatment and response groups (Table 36). The results are consistent with those from adjusted Cox PH model regression. The 95% CI of annualized event rates are not significantly different between response groups for any treatment in terms of CSE, MACE, or death event.

Bootstrap re-sampling simulations with the data from the study was used to calculate the expected probability of detecting a significant difference in the CSE between the hypo-responder and normal responder group. Based on a simulation of 2000 bootstrap samples, the average p-value of testing the null hypothesis that there is no difference between the two groups is 0.046 with 95% confidence interval of (0.039, 0.052). The proportion of p-value that is less than 0.05 among the 2000 simulation is 80.9%.

Table 35 Summary of Analysis of Event Endpoints				
	Peginesatide		Darbepoetin alfa	
	Poor (n=93)	Better (n=504)	Poor (n=32)	Better (n=42)
CSE				
# of Event	30 (32.3%)	92 (18.3%)	5 (15.6%)	42 (15.7%)
HR (95% CI)	1.36 (0.88, 2.12)		0.64 (0.24, 1.70)	
Unadjusted HR (95% CI)	1.75 (1.15, 2.64)		0.90 (0.35, 2.28)	
MACE				
# of Event	19 (20.4%)	53 (10.5%)	1 (3.15%)	23 (8.6%)
HR 95% CI	1.63 (0.94, 2.82)		0.216 (0.03, 1.66)	
Unadjusted HR (95% CI)	1.97 (1.17, 3.33)		0.33 (0.05, 2.45)	

*For MACE, the adjusted Cox model includes age, chf, cvcvd as covariates

Table 36 Annualized Event Rate						
	Peginesatide 0.025 mg/kg		Peginesatide 0.04 mg/kg		Darbepoetin 0.75mcg/kg	
	Poor N=62	Better N=239	Poor N=31	Better N=265	Poor N=32	Better N=268
CSE	22.9 (13.6, 36.1)	12.5 (8.9, 17.0)	33.0 (17.1, 57.7)	15.2 (11.4, 20.0)	11.4 (3.7, 26.7)	11.6 (8.3, 15.7)
MACE	15.6 (8.3, 26.7)	7.9 (5.2, 11.6)	14.9 (5.5, 32.5)	7.4 (4.9, 10.8)	2.2 (0.1, 12.1)	6.1 (3.9, 9.2)
Death	12.8 (6.4, 23.0)	5.1 (3.0, 8.1)	9.5 (2.6, 24.3)	6.0 (3.7, 9.1)	2.2 (0.1, 12.1)	4.2 (2.4, 6.8)

Figure 8 KM Plot for the Comparison of Poor Responder vs. Better Responder for CSE by Treatment

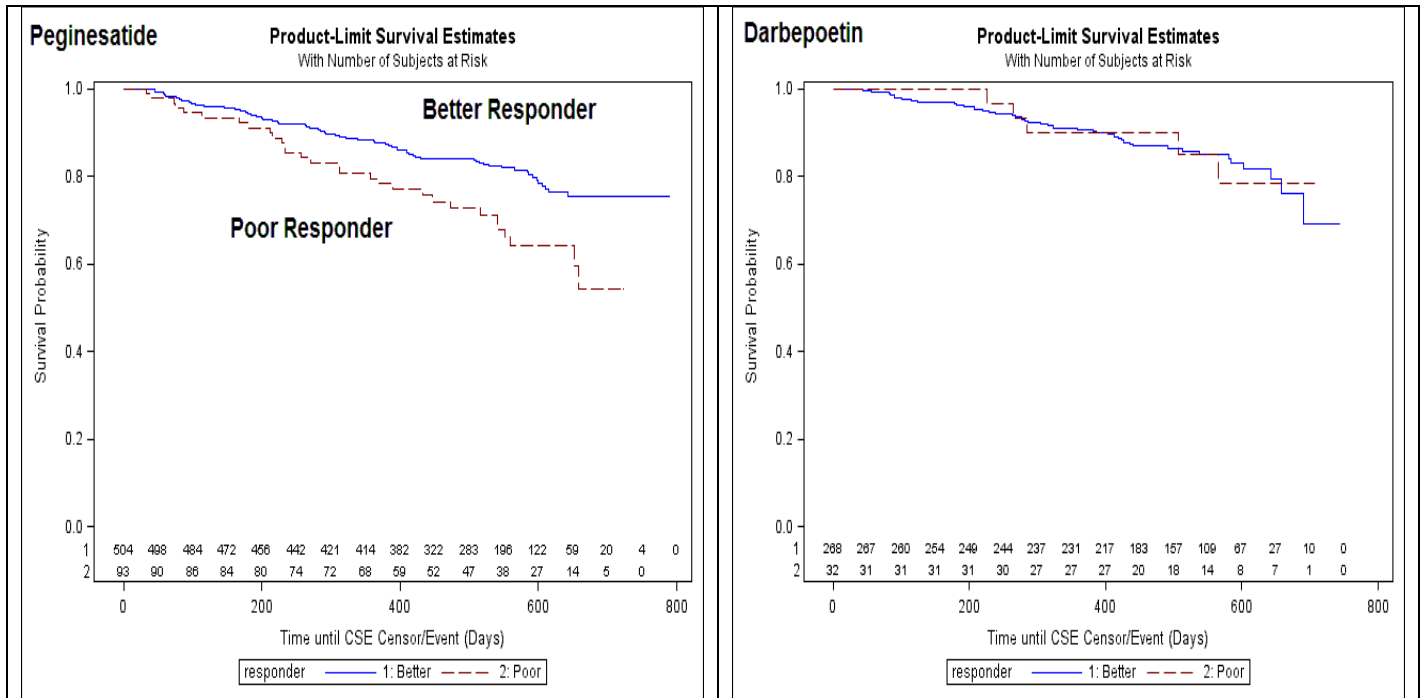
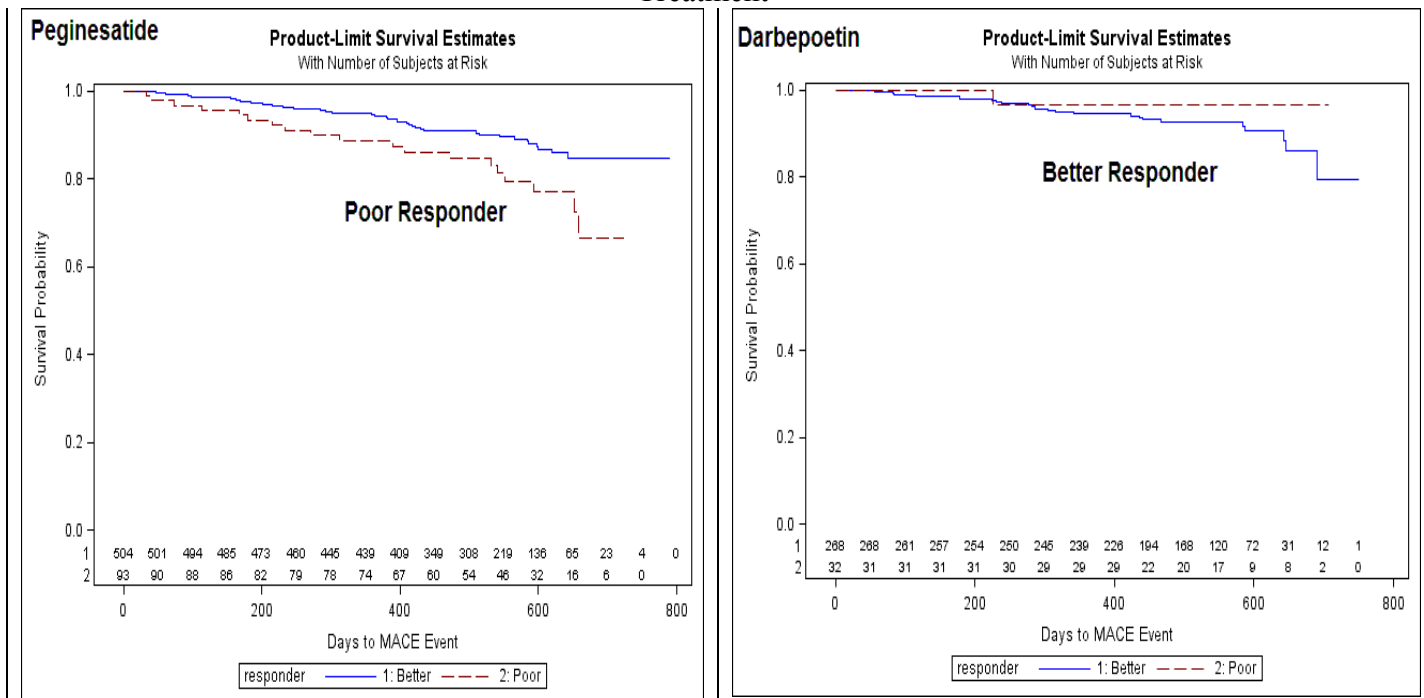


Figure 9 KM Plot for the Comparison of Poor Responder vs. Better Responder for MACE by Treatment



LIMITATIONS

First, the analyses presented in this appendix are based on subgroups categorized post hoc from outcome variable, which is not well controlled and lacks of randomization. It is highly probable that the subgroup effects observed may not be a true effect of treatment but rather the result of inherent imbalance in baseline characteristics of patients that led to particular response or to the development of adverse events. Therefore, the results can be ambiguous and one should take cautious in interpreting them. Second, the results appear to be sensitive to the definition of poor or better responders. Modification in the poor response threshold could change the analysis results and lead to different conclusions. Third, such post hoc analysis cannot determine whether the risk of cardiovascular event is due to the pre-existing clinical conditions or due to the increase in the treatment doses as dose were specified in the protocol to escalate in order to meet target hemoglobin levels.

CONCLUSIONS AND DISCUSSIONS

We observed that poor initial response is in correspondence with lower hemoglobin level at week 12 and through out the study, despite that higher doses of treatments were being given to poor initial responders. Poor initial hematopoietic response to Peginesatide is also associated with higher rates of the composite CSE and MACE endpoint, as compared with normal response. However, such associations are dependent on both the definition of poor initial response employed and key baseline characteristics in the model analysis. Therefore, cautious should be taken in the interpretation of such analyses, since the poor initial response to ESA treatment is probably a marker of baseline illness severity. Well controlled studies are needed to evaluate these findings, to identify factors influencing ESA responsiveness so that excessive doses maybe avoided. In addition, justification of poor response definition with clinical meaningfulness is necessary to be provided in future trials.

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Date: 1/11/2012

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CHECK LIST

Number of Pivotal Studies: 4

Trial Specification

- Phase 3 dialysis studies AFX01-12 and AFX01-14 compared Peginesatide and Epoetin in the maintenance of Hgb levels in dialysis subjects following conversion from Epoetin therapy.
- Phase 3 non-dialysis studies AFX01-11 and AFX01-13 provide supportive information and compared different Peginesatide starting doses to darbepoetin in subjects not on dialysis and not on ESA treatment

Protocol Number (s): AFX01-11, AFX01-12, AFX01-13, AFX01-14

Phase: 3
Control: Active Control
Blinding: Open-Label
Region(s) (Country): Multicenter
Duration: screening period, titration period, evaluation period nervous?

Treatment Arms: Peginesatide

Treatment Schedule: Peginesatide IV injection every 4 weeks (Q4W) at a starting dose of 0.04 mg/kg to 0.16 mg/kg based on the patient's prior Epoetin alfa dose, or continued treatment with Epoetin alfa 1-3 times per week IV (AFX01-12)

Randomization: Yes

Ratio: 2:1

If stratified, then the Stratification Factors: by mean screening hemoglobin and New York Heart Association (NYHA) Heart Failure (HF) Class

Primary Endpoint: The primary efficacy endpoint for all trials was change in hemoglobin between the baseline and the evaluation period

Primary Analysis Population: Fully Analysis Population

Statistical Design: Non-Inferiority

If non-inferiority or equivalence: Was the non-inferiority margin calculated based on historical data? Yes

Margin = 1.0g/dL

Primary Statistical Methodology: The primary analysis was an analysis of variance (ANOVA) cell means model for the Hgb change from baseline to the Evaluation Period

DSMB: Yes

Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? yes

- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No
- Were the **Covariates** pre-specified in the protocol? Yes
- Did the Applicant perform **Sensitivity Analyses**? Yes
- How were the **Missing Data** handled? Missing data imputation
- Was there a **Multiplicity** involved? No
- **Multiple Secondary Endpoints**: Are they being included in the label? No
- **Were Subgroup Analyses Performed : Yes**
- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report?
- Overall, was the study positive? No

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/s/

QING XU
02/06/2012

MARK D ROTHMANN
02/07/2012

RAJESHWARI SRIDHARA
02/07/2012



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NDA Number: 202799
Drug Name: peginesatide
Indication(s): Treatment of anemia associated with chronic renal failure in adult patients on dialysis
Dosage Form: Solution, Injection
Applicant: Affymax Inc
Date(s): Date Received: June 22, 2011
Completion Date: January 17, 2012
Review Priority: Standard
Biometrics Division: VI
Statistical Reviewer: Youngsook Jeon, Ph.D.
Concurring Reviewers: Yi Tsong, Ph.D.
Project Manager: Tu-Van Le Lambert

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1. EXECUTIVE SUMMARY

This review describes statistical findings on Affymax Inc's data from stability study under long-term storage condition (2 – 8 °C) so that FDA office of New Drug Quality Assessment can make informed decisions on the proposed shelf life of the drug product.

Due to large number of strengths, batches, and storage conditions, the sponsor employed a reduced stability design, matrixing design. Based on statistical analysis on 12-month stability data, the sponsor concluded that the shelf life of the drug product can be safely extrapolated up to (b) (4), the proposed shelf life.

The FDA statistician conducted independent statistical analysis on the sponsor's stability data. The shortest among 70 estimated shelf lives is 37 months. Since the drug product is intended to be stored in a refrigerator, the maximum extrapolation that can be considered is 6 months beyond the period covered by long-term data. The sponsor's long-term data is either (b) (4) month long. Therefore, the statistical analysis supports the extrapolation of a shelf life to the proposed (b) (4) for 2 mg, 3 mg, and 4 mg PFS drug products, 2 mg SDV drug product, and 20 mg MDV drug product. However, a shelf life can be extrapolated to only 18 months for 1 mg and 6 mg PFS drug products, 4 mg and 6 mg SDV drug products, and 10 mg MDV drug product. The shelf life for 3 mg SDV drug product cannot be established because one of three primary batches was rejected and excluded from the analysis.

2. INTRODUCTION

2.1 Overview

This review describes statistical findings on Affymax Inc's data from stability study under long-term storage condition (2 – 8 °C) so that FDA office of New Drug Quality Assessment can make informed decisions on the proposed shelf life of the drug product.

The drug product is provided in three drug product (DP) types: Pre-Filled Syringe (PFS), Single Dose Vial (SDV), and Multiple Dose Vial (MDV). There are eleven different commercial drug product configurations including five PFS presentations, four SDV presentations, and two MDV presentations. SDV and MDV are manufactured by Takeda and PFS is manufactured by (b) (4). The summary of the sponsor's stability data can be found in Section 3.1.

Due to large number of strengths, batches, and storage conditions, the sponsor employed a reduced stability design, matrixing design. Based on statistical analysis on 12-month stability data, the sponsor proposed (b) (4) self life for the drug product. The sponsor's stability design and statistical analysis can be found in Section 3.2.

The FDA statistician reviewed the sponsor's study reports and conducted independent statistical analyses on the long-term stability data. The reviewer's assessment can be found in Section 4.

2.2 Data Sources

The sponsor submitted data sets electronically but not in electronic form. The followings are the EDR locations of the folders containing study reports and data sets reviewed in this report.

- Pre-Filled Syringe (PFS): <\\Cdsub1\EVSPROD\NDA202799\0000\m3\32-body-data\32p-drug-prod\pfs\32p8-stab>
- Single Dose Vial (SDV): <\\Cdsub1\EVSPROD\NDA202799\0000\m3\32-body-data\32p-drug-prod\sdv\32p8-stab>
- Multi Dose Vial (MDV): <\\Cdsub1\EVSPROD\NDA202799\0000\m3\32-body-data\32p-drug-prod\mdv\32p8-stab>

3. SPONSOR'S SUBMISSION

3.1 Data

The submitted stability data have two different lengths, (b) (4). The 5mg/0.5mL strength for both PFS and SDV drug products was added to the commercial lineup later in development after the matrix design was finalized. Batch Z377a01 and Z377b01 were manufactured to confirm the process for this strength but were not used to estimate a shelf life. Table 1 – 3 display the summary of the sponsor's data.

Table 1 Summary of Primary Stability Data for PFS

Lot	Strength	Data Available, month	
		2-8°C	25°C/60%RH
Z377B02	1 mg/0.5 mL	(b) (4)	
Z377B03	1 mg/0.5 mL		
Z377B04	1 mg/0.5 mL		
Z377C01	2 mg/0.5 mL		
Z377C02	2 mg/0.5 mL		
Z377C03	2 mg/0.5 mL		
Z377D01	3 mg/0.5 mL		
Z377D02	3 mg/0.5 mL		
Z377D03	3 mg/0.5 mL		
Z377E01	4 mg/0.5 mL		
Z377E02	4 mg/0.5 mL		
Z377E03	4 mg/0.5 mL		
Z377b01	5 mg/0.5 mL		
Z377F01	6 mg/0.5 mL		
Z377F02	6 mg/0.5 mL		
Z377F04	6 mg/0.5 mL		

Source: Table 3 in Sponsor's stability report, stability-data-pfs.pdf (page 6 of 140)

Table 2. Summary of Primary Stability Data for SDV

Lot Number	Strength	Data Available (months)			
		2-8°C		25°C/60%RH	
		Inverted	Upright	Inverted	Upright
Z377401	2 mg/0.5 mL	(b) (4)			
Z377402	2 mg/0.5 mL				
Z377403	2 mg/0.5 mL				
Z377501	3 mg/0.5 mL				
Z377504	3 mg/0.5 mL				
Z377601	4 mg/0.5 mL				
Z377602	4 mg/0.5 mL				
Z377603	4 mg/0.5 mL				
Z377a01	5 mg/0.5 mL				
Z377701	6 mg/0.5 mL				
Z377702	6 mg/0.5 mL				
Z377703	6 mg/0.5 mL				

Source: Table 3 in Sponsor's stability report, stability-data-sdv.pdf (page 5 of 119)

Table 3. Summary of Primary Stability Data for MDV

Lot Number	Strength	Data Available (Months)			
		2-8 °C		25 °C/60% RH	
		Inverted	Upright	Inverted	Upright
Z377801	10 mg/mL	(b) (4)			
Z377802	10 mg/mL				
Z377803	10 mg/mL				
Z377902	20 mg/2 mL				
Z377903	20 mg/2 mL				
Z377904	20 mg/2 mL				

Source: Table 3 in Sponsor's stability report, stability-data-mdv.pdf (page 6 of 86)

3.2 Study Report

3.2.1 Stability Study Design

The sponsor employed a matrixing design because of the large number of strengths, batches, and storage conditions. According to ICH Q1D Guidance (2003), the definition of matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. Table 4 – 6 display the sponsor's matrixing design.

Table 4. Matrixing Design for PFS Primary Batches

Condition	Strength	Stability Intervals (Months)								
		0	1	3	6	9	12	18	24	36
2-8 °C	1mg/0.5mL	All		Z377B03	Z377B02	Z377B04	All	All	All	All
	2mg/0.5mL	All		Z377C03	Z377C01	Z377C02	All	All	All	All
	3mg/0.5mL	All		Z377D01	Z377D03	Z377D02	All	All	All	All
	4mg/0.5mL	All		Z377E02	Z377E01	Z377E03	All	All	All	All
	5mg/0.5mL ^a	All		Z377b01	Z377b01	Z377b01	Z377b01	Z377b01	Z377b01	Z377b01
	6mg/0.5mL	All		Z377F01	Z377F02	Z377F04	All	All	All	All
25°C/60%RH	1mg/0.5mL		All	Z377B03	Z377B02	Z377B04	All			
	2mg/0.5mL		All	Z377C03	Z377C01	Z377C02	All			
	3mg/0.5mL		All	Z377D01	Z377D03	Z377D02	All			
	4mg/0.5mL		All	Z377E02	Z377E01	Z377E03	All			
	5mg/0.5mL ^a		All	Z377b01	Z377b01					
	6mg/0.5mL		All	Z377F01	Z377F02	Z377F04	All			

Source: Table 1 in Sponsor's stability report, stability-summary-pfs.pdf (page 6 of 37)

Table 5. Maxrining Design for SDV Primary Batches

Condition	Strength	Stability Intervals (Months)								
		0	1	3	6	9	12	18	24	36
2-8 °C (Inverted)	2mg/0.5mL	All		Z377402	Z377401	Z377403	All	All	All	All
	3mg/0.5mL	All ^a		Z377504	Z377502 ^a	Z377501	All ^a	All ^a	All ^a	All ^a
	4mg/0.5mL	All		Z377602	Z377601	Z377603	All	All	All	All
	5mg/0.5mL ^b	Z377a01		Z377a01	Z377a01	Z377a01	Z377a01	Z377a01	Z377a01	Z377a01
	6mg/0.5mL	All		Z377701	Z377703	Z377702	All	All	All	All
25°C/60%RH (Inverted)	2mg/0.5mL		All	Z377402	Z377401	Z377403	All			
	3mg/0.5mL		All ^a	Z377504	Z377502 ^a	Z377501	All ^a			
	4mg/0.5mL		All	Z377602	Z377601	Z377603	All			
	5mg/0.5mL ^b		Z377a01	Z377a01	Z377a01					
	6mg/0.5mL		All	Z377701	Z377703	Z377702	All			

Source: Table 1 in Sponsor's stability report, stability-summary-sdv.pdf (page 6 of 37)

Table 6. Matrixing Design for MDV Primary Batches

Condition	Strength	Stability Intervals (Months)								
		0	1	3	6	9	12	18	24	36
2-8 °C (Inverted)	10mg/mL	All		Z377801	Z377803	Z377802	All	All	All	All
	20mg/2mL	All		Z377903	Z377904	Z377902	All	All	All	All

Source: Table 1 in Sponsor's stability report, stability-summary-mdv.pdf (page 6 of 34)

The sponsor's matrixing design is acceptable because it satisfies the following key design consideration points stated in ICH Q1D (2003) Guidance:

- The design is balanced such that each combination of factors is tested to the same extend over the duration of the study,
- Initial and end point values are included for all samples,
- Before application all samples are retested at 12 months,
- At least three time points including initial are available through the first 12 months,
- For accelerated storage condition, 25°C/60%RH, a minimum of three time points are necessary.

3.2.2 Statistical Analysis and Conclusion

The sponsor performed statistical analysis on primary batch data from stability study under long-term storage condition (2 – 8 °C) to estimate a shelf life of the drug product. The sponsor used (b) (4) data for all strengths although (b) (4) data are available for some strength. The following seven test attributes were analyzed for each strength and each DP type:

- Content
- Total Sulfoxidation (Total SO)
- (b) (4)
- Higher Molecular Weights Species (HMW1)
- (b) (4)
- (b) (4)
- Total Degradation Products (TDP)

The sponsor's analysis followed the approach outlined in Appendix B of the ICH Q1E Guidance: Evaluation for Stability Data (2004). Sponsor conducted the batch poolability test and estimated a shelf life using FDA Office of Biostatistics PC-SAS stability program.

The sponsor demonstrated that estimated shelf lives were longer than (b) (4) for all test attributes, all strengths, and all DP types. Therefore, the sponsor concluded that the shelf life of the drug product can be safely extrapolated up to (b) (4) (b) (4) beyond the period covered by long-term data.

4. REVIEWER'S ASSESSMENT

4.1 Statistical Evaluation

The reviewer evaluated the sponsor's long-term stability data in accordance with ICH Q1E Guidance (2004). The reviewer conducted ANCOVA analysis to test batch poolability and to estimate a shelf life of the drug product using Statistical Analysis Software, SAS.

(b) (4) data available for all strengths. For some strengths, however, (b) (4) data are available. While the sponsor used only (b) (4) data for all strengths, the reviewer used all available data, i.e., (b) (4) data for some strengths. As a result, different lengths of data depending on its availability are used for the reviewer's statistical analysis. The data used for the analysis are listed in Table 8.

The reviewer estimated shelf lives for all test attributes, all strengths, and all DP types. There are 70 estimated shelf lives. All of them are longer than the proposed shelf life, (b) (4). The shortest of all is 37 months for HMW1 of 1mg/0.5mL PFS drug product. The summary of 70 estimated shelf lives is displayed in Table 7.

Table 7. Estimated Shelf Life (Months)

Container System	Test Strength	Content	Total SO	(b) (4)	HMW1	(b) (4)	(b) (4)	TDP
PFS	1 mg/0.5 mL	55	46	>200	37	70	149	61
	2 mg/0.5 mL	62	>200	126	135	181	116	>200
	3 mg/0.5 mL	117	>200	>200	111	106	117	>200
	4 mg/0.5 mL	62	>200	96	104	150	109	>200
	6 mg/0.5 mL	103	109	74	83	53	96	81
SDV	2 mg/0.5 mL	84	127	125	>200	>200	144	177
	4 mg/0.5 mL	63	>200	>200	68	91	82	113
	6 mg/0.5 mL	80	91	>200	54	>200	71	95
MDV	10 mg/1 mL	147	>200	>200	94	>200	95	>200
	20 mg/2 mL	96	>200	76	>200	82	58	>200

However, for some strengths, shelf lives cannot be extrapolated to (b) (4) because the drug products are intended to be stored in a refrigerator (2 – 8 °C). In this case, the shelf life can be up to one-and-a-half times as long as, but should not be more than 6 months beyond the period covered by long-term data (see Section II.E of ICH Q1E Guidance (2004)). Therefore, the shelf lives can be extrapolated up to either (b) (4) months depending on the availability of the data (Table 8).

Table 8. Available Data and Extrapolated Shelf Life (Months)

Container System	Strength	Available Data	Shelf Life
PFS	1mg/0.5mL	(b) (4)	
	2mg/0.5mL		
	3mg/0.5mL		
	4mg/0.5mL		
	6mg/0.5mL		
SDV	2mg/0.5mL		
	4mg/0.5mL		
	6mg/0.5mL		
MDV	10mg/1mL		
	20mg/2mL		

Another issue in the sponsor's stability analysis is that the sponsor estimated a shelf life for 3 mg/0.5 mL SDV drug product based on only two batches. It is because one of the batches failed to meet the specification for (b) (4). As a result, it was rejected and excluded from the analysis. However, without at least three batches, between-batch variability cannot be assessed. A minimum of three batches are required for shelf life estimation. In addition, an estimated shelf life for 3 mg/0.5 mL SDV drug product would be shorter than the proposed if the failed batch was included in the analysis. Therefore, the shelf life for 3 mg/0.5 mL SDV drug product cannot be established based on the current stability data.

4.2 Summary and Conclusion

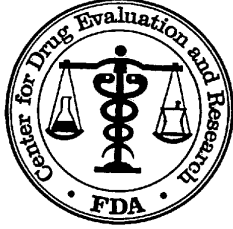
The FDA statistician estimated shelf lives for all test attributes, all strengths, and all DP types of the drug product based on the sponsor's data from the stability study under long-term storage condition (2 – 8 °C). The shortest among 70 estimated shelf lives is 37 months. Since the drug product is intended to be stored in a refrigerator, the extrapolation can be considered up to 6 months beyond the period covered by long-term data. The sponsor's long-term data is either (b) (4) long. Therefore, the statistical analysis supports the extrapolation of a shelf life to the proposed (b) (4) for 2 mg, 3 mg, and 4 mg PFS drug products, 2 mg SDV drug product, and 20 mg MDV drug product. However, a shelf life can be extrapolated to only 18 months for 1 mg and 6 mg PFS drug products, 4 mg and 6 mg SDV drug products, and 10 mg MDV drug product. The shelf life for 3 mg SDV drug product cannot be established because one of three primary batches was rejected and excluded from the analysis.

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/s/

YOUNGSOOK JEON
01/17/2012

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01/18/2012



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation
CARCINOGENICITY STUDIES

IND/NDA Number: IND 63-257 / NDA 202-799

Drug Name: AF37702

Applicant: Sponsor: Affymax, Inc.
4001 Miranda Avenue Palo Alto, CA 94304

Test Facility: [REDACTED] (b) (4)

Documents Reviewed: Electronic data submitted on June 09, 2010.

Review Priority: Standard

Biometrics Division: Division of Biometrics -6

Statistical Reviewer: Min Min, Ph.D.

Concurring Reviewer: Karl Lin, Ph.D.

Office: Office of Oncology Drug Products

Reviewing Pharmacologist: Kimberly Ringgold, Ph.D.

Project Manager: Paul Zimmerman

Keywords: Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in Tg.rasH2 mice. The purpose of rat study was to evaluate AF37702 for carcinogenesis when administered to Sprague-Dawley rats via intravenous injection, once every third week for a period of 2 years. A 26-Week carcinogenicity study was performed using hemizygous Tg.rasH2 mice that were administered AF37702 via intravenous (IV) tail vein injection every three weeks up to 26 weeks, for a total of 10 doses. Results of this review have been discussed with the reviewing pharmacologist Dr. Kropp.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group and one saline control group. Five hundred and ninety-six naive Sprague-Dawley rats were randomly assigned to either the control groups or one of three treatment groups as shown in the tables below.

Toxicology Groups

Group	Dose Level (mg/kg/dose)	Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals	
				Male	Female
1. Saline-Control	0	0	1	53	53
2. Vehicle-Control	0	0	1	53	53
3. Low-dose	0.01	0.01	1	53	53
4. Mid-dose	0.1	0.1	1	53	53
5. High-dose	0.25	0.25	1	53	53

Satellite Groups

Group	Dose Level (mg/kg)	Concentration (mg/mL)	Dose Volume (ml/kg)	Number of Animals	
				Male	Female
6. Saline-Control	0	0	1	3	3
7. Vehicle-Control	0	0	1	3	3
8. Low-dose	0.01	0.01	1	9	9
9. Mid-dose	0.1	0.1	1	9	9
10. High-dose	0.25	0.25	1	9	9

Animals were dosed once every third week (Days 1,22,43,64,85, 106, 127, 148, 169, 190, 211, 232, 253, 274, 295, 316, 337, 358, 379, 400, 421, 442, 463, 484, 505,526,547,568,589,610,631,652 and 673; females in Groups 1-5 and males and females in Groups 6-10 were also dosed on Day 694) by intravenous injection via the lateral tail vein. Mortality and clinical observations were evaluated daily. Due to early deaths encountered in Groups 1-5, the male groups were terminated over three days (Days 680-682) following the Day 673 dose, and the female groups were terminated over four days (Days 706-709) following the Day 694 dose, Selected

tissues were harvested at necropsy and histopathologic evaluation was performed on all tissues for all animals in Groups 1-5.

At scheduled terminal sacrifice, all remaining animals in Groups 1-5 had blood samples collected for evaluation of hematology parameters. Animals were anesthetized by CO₂ inhalation prior to blood collection. After terminal collections by cardiocentesis, animals were euthanized by CO₂ asphyxiation. For all animals necropsied, the tissues listed in the table below were preserved in 10% neutral buffered formalin (except for the testes that were preserved in Bouin's fixative).

Tissues Collected	
Cardiovascular	Urogenital
Aorta	Kidneys
Heart	Urinary Bladder
Digestive	Ovaries
Salivary gland(s)	Uterus
Tongue	Cervix
Esophagus	Vagina
Stomach	Testes
Small Intestine	Epididymides
Duodenum	Prostate
Jejunum	Seminal Vesicles
Ileum	Fallopian tube
Large Intestine	Endocrine
Cecum	Adrenals
Colon	Pituitary
Rectum	Thyroid/Parathyroid
Pancreas	Skin/Musculoskeletal
Liver	Skin
Respiratory	Mammary Glands
Trachea	Skeletal Muscle (thigh)
Larynx	Femur with articular surface
Lung with mainstem bronchus	Zymbal's gland
Nasal cavity	Nervous/Special Sense
Lymphoid/Hematopoietic	Eyes (with optic nerve)
Sternum with bone marrow	Sciatic Nerve
Thymus	Brain

Spleen	Spinal Cord – cervical
Lymph Nodes	Spinal Cord – midthoracic
Mandibular (Cervical)	Spinal Cord – lumbar
Mesenteric	Lacrimal Glands
Other	
Unique Animal Identifier (not for evaluation)	
Abnormalities (gross)	
Injection site(s)	
Bone marrow smears (cytology and M:E ratios)	

2.1. Sponsor's analyses

2.1.1. Survival analysis

Kaplan-Meier estimates of group survival rates were calculated by sex. A log-rank dose response trend test of survival rates was performed utilizing dose coefficients. In addition, a generalized Wilcoxon test for survival was used to make pair-wise comparisons of each treated group with the control group. The trend test and pair-wise comparisons were conducted at the 0.05 significance level and were conducted for each control group individually. Survival times in which the status of the animal's death was classified as an accidental death or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings: Among males there was a significant dose related decreasing trend in survival rates when comparing treated groups to both the saline and vehicle control. In the pair-wise comparisons, the survival rate of the 0.25 mg/kg group was significantly less than that of the saline control. In addition, the survival rate of the 0.1 and 0.25 mg/kg groups were both significantly less than that of the vehicle control. Among females, there was a statistically significant difference in the pair-wise comparison of the 0.1 mg/kg dose group when compared with the saline control. It should be noted that the survival rate of the 0.1 mg/kg was significantly greater than that of the saline control.

2.1.2. Tumor data analysis

The incidence of tumors was analyzed by Peto's mortality-prevalence method, without continuity correction, incorporating the context (incidental, fatal, or mortality-independent) in which tumors were observed. The following fixed intervals were used for incidental tumor analyses: weeks 1-60, 61-80, 8 I-end of study (up to, but not including, scheduled terminal sacrifices), and scheduled terminal sacrifice. The first interval (weeks 1 - 60) was revised from the protocol (week 1-50) because there were multiple groups for which there were no necropsies in the first 50 weeks of the study. All animals that died or were sacrificed after the first animal of that sex was terminally sacrificed were included in the scheduled terminal sacrifice interval for the incidental

finding analyses. For example, among males terminal sacrifices began on study day 680. All male natural deaths and sacrifices that occurred after the first male sacrifice on study day 680 were included in the scheduled terminal sacrifice interval. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis.

Tumors for which the day of detection was earlier than the day of necropsy (eg. ski and mammary gland tumors) were classified as mortality-independent. (Note: The tumor transport file presented death/sacrifice time (DTHSACTM) in days and the detection time (DETECTTM) in weeks. DETECTTM was only presented (non-missing) for mortality independent tumors. To accommodate the statistical analysis, the detection time was converted from weeks to approximate days (week*7) for analysis of tumors which occurred in both a mortality-independent and dependent context.) Each diagnosed tumor type was analyzed separately and, at the discretion of the study director, analysis of combined tumor types was performed. Grouping of tissues was performed for analysis purposes. All analyses were conducted by sex. The incidence of each tumor type that occurred was analyzed with a one-sided trend test using the dose coefficients. In addition, each active treatment group was compared with each control group with one-sided pair-wise comparisons. Lastly, the vehicle control group was compared to the saline control group with a one-sided pair-wise comparison. An exact permutation test was conducted for analyses with low tumor incidence. Statistical significance was determined according to the following guidelines: trend tests were conducted at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. Pair-wise comparisons with the control groups were conducted at the 0.05 significance level for both common and rare tumors. A rare tumor was defined as one in which the historical spontaneous tumor rate was less than 1 %.

In pair-wise comparisons with the vehicle control group in pituitary gland in male rats, there was an increase in the incidence of adenoma and adenoma/carcinoma in the 0.01, 0.1 and 0.25 mg/kg groups. However, the dose-response trend test was not statistically significant. In addition, comparisons with the saline control were not statistically significant. There were no other statistically significant tumor findings among males and there were no statistically significant tumor findings among females.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all four treatment groups (three treated groups and one vehicle control group) were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972). The inter-current mortality data are given in Tables 1A and 1B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for males and females, respectively.

Reviewer's findings: The test results showed statistically significant dose-response relationship and statistically significant pair-wise difference between high dose group and the vehicle control group in survivals in male rats. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pair-wise comparisons of the vehicle control group with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988), and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. For short term study of 26 weeks no such suggestion is available, in the mouse tumor data analysis we chose k=3 here. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for males and females, respectively.

As suggested by the reviewing pharmacologist Dr. Kropp, this reviewer did the analysis of the combinations of all organ/tumors as the following:

Combining Tumors for Statistical Analysis †				
Tissue	Tumor types ^a	Rat		Mouse
All sites	Hemangiomas + hemangiosarcomas	♂	♀	♂ ♀
All sites	Mesotheliomas	♂	♀	♂ ♀
All sites	Leukemias	♂		♂ ♀
All sites	Lymphomas	♂	♀	♂ ♀
All bone ^b	Chondromas + osteosarcomas + osteomas	♂	♀	♂ ♀
Common sites	Lipomas + liposarcomas	♂	♀	♂ ♀
Adrenals	Cortical adenomas + carcinomas			♀
Adrenals	Benign + malignant pheochromocytomas			♀
Alimentary tract (upper) ^c	Adenomas + carcinomas ^c			♂
Alimentary tract (lower) ^d	Adenomas + carcinomas ^d			♂
Alimentary tract (all) ^e	Adenomas + carcinomas ^e			♂
Duodenum	Leiomyomas + leiomyosarcomas		♀	
Harderian gland	Adenomas + adenocarcinomas			♂
Injection site	Fibromas + fibrosarcomas			♂
Injection site	Fibromas + fibrosarcomas + sarcomas + rhabdomyosarcomas			♂
Kidney	Tubular cell adenomas + carcinomas	♂		♂
Liver	Hepatocellular adenomas + carcinomas	♂		♂
Lung	Bronchio-alveolar adenomas + carcinomas			♂
Mammary	Adenomas + carcinomas		♀	
Mammary	Fibroadenomas + fibrocarcinomas		♀	
Mammary gland	Adenomas + adenocarcinomas + adenoacanthomas			♀
Oral cavity +	Squamous cell papillomas + carcinomas	♂	♀	♂ ♀

tongue					
Pancreas	Islet cell adenomas + mixed acinar/islet cell adenomas	♂			
Pancreas	Mixed acinar/islet cell adenomas + acinar cell adenomas	♂			
Pituitary	Anterior lobe adenomas + carcinomas	♂	♀	♂	♀
Skin and subcutis	Basal cell adenomas + carcinomas	♂			
Skin and subcutis	Squamous cell papillomas + carcinomas + keratoacanthomas	♂	♀	♂	
Skin and subcutis	Sarcomas (not specified) + fibrosarcomas + liposarcomas + rhabdomyosarcomas				♀
Testis	Interstitial cell adenomas + mesotheliomas + rete testis adenomas + sex cord stromal tumors	♂		♂	
Thoracic cavity	Hibernomas (benign + malignant)	♂	♀		
Thymus	Thymomas (benign + malignant)	♂			
Thyroid	C-cell adenomas + carcinomas	♂	♀	♂	♀
Thyroid	Follicular cell adenomas + carcinomas	♂	♀	♂	♀
Uterus	Stromal polyps + sarcomas		♀		
Uterus	Stromal polyps + endometrial stromal sarcomas				♀
Uterus	Adenomas + adenocarcinomas		♀		
Uterus	Schwannomas (benign + malignant)				♀
Uterus	Leiomyomas + leiomyosarcomas				♀
Uterus + vagina	Uterus stromal neoplasms + vaginal stromal neoplasms		♀		♀

† Tumor combinations by sex (not combined across sexes or across species)

^a Include separate analyses for individual tumor types

^b For example bone, cranium, femur, etc.

^c Stomach, duodenum, jejunum

^d Colon, cecum

^e Stomach, duodenum, jejunum, colon, cecum

Multiple testing adjustment: Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level $\alpha=0.025$ for rare tumors and $\alpha=0.005$ for common tumors for a submission with two species, and a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the spontaneous tumor rate is less than 1%. The adjustment for multiple pair-wise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by Rahman and Lin (2008) indicate that the criteria apply equally well to the analysis using the poly-3 test.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship and/or pair-wise comparisons between control and each of individual treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons

Organ Name	Tumor Name	Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value			
		N=53	N=53	N=53	N=53	Dos Resp	C vs. L	C vs. M	C vs. H			
Male	PITUITARY GLAND	Adenoma		4	11	12	9		0.125	0.048	0.014	0.057
Female	HEMOLYMPHORETIC	Lymphoma		0	0	2	3		0.023	.	0.265	0.120
	THYROID GLAND	C-Cell Adenoma		8	6	12	13		0.035	0.822	0.259	0.157
	TYROID	CCELL_ADENOMA+CARCIN		9	6	13	13		0.050	0.883	0.270	0.229

Based on the criteria of adjustment for multiple testing of trends proposed by Lin and Rahman, the positive dose-response relationships in the incidence of lymphoma in hemolymphoreticular and c-cell adenoma in thyroid gland in females were considered to be statistically significant because both p-values were less than 0.05. Also based on the criteria of Haseman, none of the pair-wise comparisons of treated groups with the control was considered to be statistically significant in either sex for increased tumor incidence in the treated group. because none of the p-values was less than 0.01.

3. Mouse Study

A 26-Week carcinogenicity study was performed using hemizygous Tg.rasH2 mice that were administered AF37702 via intravenous (IV) tail vein injection every three weeks up to 26 weeks, for a total of 10 doses. The study consisted of one vehicle control group (Group 1), one Positive Control group (Group 2) and three test article groups (Groups 3-5) consisting of 25 male and 25 female mice per group. The mice were treated with either the vehicle (20mM phosphate and 0.003% Tween 20 in 4.7% sorbitol, pH 6.0, Group 1), the Positive Control (urethane in saline administered via 3 separate intraperitoneal (IP) injections on Days 1, 3 and 5) or AF37702 delivered in vehicle via iv injection on Days 1,22,43, 64,85,106, 127, 148, 169 and 190. Dose levels for the test article groups were 0.1, 0.25 and 0.5 mg/lg/dose (Groups 3-5, respectively). Test article and vehicle were administered in a dose volume of 5 mL/kg body weight and the Positive Control was administered in a dose volume of 10 mL/kg body weight. All animals that died on test were necropsied as soon as possible after being found. Carcasses were refrigerated until necropsy. Moribund animals were sacrificed immediately by CO2 overdose and then necropsied. Organs were not weighed at necropsy for interim deaths or moribund sacrificed animals. The following table is copied from sponsor's report for study design. All surviving animals in Groups 1, 3, 4 and 5 were sacrificed by CO2 overdose 5 to 7 days after the last treatment on Days 195-196 for the males and Days 196-197 for the females. Any surviving animals in Group 2 (positive control) were sacrificed by CO2 overdose on Day 114 for the males and Day 113 for the females. All animals (Groups 1 through 5) were subjected to a necropsy examination.

Text Table 5: Study Design

Group	Number of Animals	
	Male	Female
Group 1: Vehicle (control)	25	25
Group 2: Positive control, urethane*	25	25
Group 2: Low dose (0.1 mg/kg/dose)	25	25
Group 4: Middle dose (0.25 mg/kg/dose)	25	25
Group 5: High dose (0.5 mg/kg/dose)	25	25
Total	125	125

* = The Positive Control animals received a total of three i.p. injections on Days 1, 3 and 5.

The following tissues/organs were collected and fixed in 10% neutral buffered formalin:

Adrenal glands	Pancreas
Aorta	Parathyroid glands
Bone (femur and sternum)	Pituitary gland
Bone marrow (femur and sternum)	Prostate gland
Brain	Salivary gland
Epididymides	Sciatic nerve
Esophagus	Seminal vesicles
Eyes	Skeletal muscle (thigh)
Gall bladder	Small intestine (duodenum, jejunum, and ileum)
Gross lesions	Spinal cord (cervical, thoracic, and lumbar)
Harderian glands	Spleen
Heart	Stomach
Kidneys	Testes
Large intestine (cecum, colon, rectum)	Thymus
Liver	Thyroid glands
Lungs and bronchi	Trachea
Lymph nodes (mesenteric, mediastinal, and mandibular)	Urinary bladder
Mammary gland with adjacent skin	Uterus
Nasal cavity	Vagina
Ovaries	

3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data from the mouse study were analyzed by the sponsor using the same statistical methodologies that were used to analyze the survival data from the rat study. All statistical analysis was performed for males and females separately.

Sponsor's findings: Evaluations of trend and heterogeneity of survival data were performed using the Cox-Tarone binary regression on life tables and Gehan-Breslow nonparametric methods using the National Cancer Institute (NCI Life Table Package (Tolll et al, 1977). The Cox-Tarone method is more sensitive to late deaths, and the Gehan-Breslow method is more sensitive to early death due to treatment. As a result, they are both important tools to evaluate observable incidence data. Days 196 and 197 were treated as the end of the study in the NCI package for males and females, respectively. There was no apparent AF37702-related mortality.

The following table is copied from sponsor's report which summarizes the mortalities:

MALES

	Group:	1	2	3	4	5
Day 9-112	Found Dead/Moribund Sacrifice	-	13/25	-	-	-
Day 108	Found Dead	-	-	1/25	-	-
Day 114	Scheduled Sacrifice	-	12/25	-	-	-
Day 154	Found Dead	-	-	-	1/25	-
Day 167	Moribund Sacrifice	1/25	-	-	-	-
Day 195 or 196	Terminal Sacrifice	24/25	-	24/25	24/25	25/25
TOTAL:		25/25	25/25	25/25	25/25	25/25

FEMALES

	Group:	1	2	3	4	5
Day 38-113	Found Dead/Moribund Sacrifice	-	13/25	-	-	-
Day 113	Scheduled Sacrifice	-	12/25	-	-	-
Day 146	Found Dead	-	-	1/25	-	-
Day 195	Found Dead	-	-	1/25	-	-
Day 195, 196 or 197	Terminal Sacrifice	25/25	-	23/25	25/25	25/25
TOTAL:		25/25	25/25	25/25	25/25	25/25

Group 1 M/F 0 mg/kg/dose (Vehicle Control)
 Group 2 M/F Positive Control (1,000 mg/kg urethane via i.p. injection on Days 1, 3 and 5)
 Group 3 M/F 0.1 mg/kg/dose
 Group 4 M/F 0.25 mg/kg/dose
 Group 5 M/F 0.5 mg/kg/dose

Note: Values represent the number of animals affected / the number of animals started on the study.

3.1.2. Tumor data analysis

Tumor data from the mouse study were also analyzed by the sponsor using the same statistical methodologies that were used to analyze the tumor data from the rat study.

Sponsor's findings:

The following table is copied from sponsor's table which summarizes the tumor incidence:

Text Table 6: Summary of Tumor Incidence

Tumor Type	Dose Group (mg/kg)									
	Males ¹					Females ¹				
	0	1000 ²	0.1	0.25	0.5	0	1000 ²	0.1	0.25	0.5
Spleen										
Hemangiosarcoma	0	23	1	6	4	1	22	4	3	4
Salivary gland										
Hemangiosarcoma	0	0	0	0	0	0	0	0	1	0
Bone marrow										
Hemangiosarcoma	0	0	0	0	1	0	0	0	0	0
Stomach										
Hemangiosarcoma	0	0	0	0	0	0	0	1	0	0
Subcutis³										
Hemangiosarcoma	0	0	0	0	0	0	0	1	0	0
Ileum										
Hemangioma	0	0	0	0	0	0	0	0	1	0
Liver										
Adenoma	0	0	0	0	0	0	0	0	0	1
Harderian gland										
Adenoma	0	0	4	1	1	0	0	2	2	1
Carcinoma	0	0	0	0	0	0	0	1	0	0
Uterus										
Sarcoma	-	-	-	-	-	0	0	1	0	0
Lung										
Hemangiosarcoma	0	3	0	0	0	0	1	0	0	0
Adenoma, single	2	0	4	8	3	1	0	0	1	0
Adenoma, multiple	1	24	0	0	1	1	25	0	2	0
Carcinoma	0	10	0	0	0	1	14	1	0	0
Lymphoid Tissue										
Multicentric lymphoma	0	1	1	0	0	0	0	0	0	0
¹ N = 25/sex/group										
² Positive control (urethane), bone marrow, ileum, liver, salivary glands, stomach, uterus and Harderian gland not evaluated for any PC animal										
³ Subcutis was evaluated in only a single Group 4 female.										

In the male mice administered AF37702, there was a statistically significant increase ($p \leq 0.01$) in splenic hemangiosarcomas in Group 4 compared to the vehicle control and a significant increase in hemangiosarcomas in multiple organs in Groups 4 and 5 ($p \leq 0.01$ and ≤ 0.05 , respectively). There was a corresponding positive trend for both splenic hemangiosarcomas and hemangiosarcomas in multiple organs ($p = 0.009$ and 0.0037 , respectively). In the female mice administered AF37702, there was a significant increase ($p \leq 0.05$) in hemangiosarcomas in multiple organs in Group 3 females and a significant increase in hemangiomas/hemangiosarcomas in multiple organs in Group 3 and 4 females.

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for males and females, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for males and females, respectively.

Reviewer's findings: The tests showed statistically significant pair-wise differences between low dose group and the vehicle control group, between medium dose group and the vehicle control group in survivals in females. There were few differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pair-wise comparisons of the vehicle control group and treated groups are given in Table 6A and 6B in the appendix for males and females, respectively.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship or pair-wise comparisons between control and each of individual treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons

Sex	Organ Name	Tumor Name	Cont 0mg N=25	Low 50mg N=25	Med 250mg N=25	High 400mg N=25	P_Value Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male	spleen	hemangiosarcoma	0	1	6	4	0.023	0.490	0.010	0.055

Using 0.05 level of significance, the incidence of hemangiosarcoma in spleen in male mice was considered to have a statistically significant positive dose response relationship. Also based on the criteria of Haseman, the pair-wise comparison of hemangiosarcoma in spleen between the medium dose group and the vehicle control was considered to be statistically significant in male mice for increased tumor incidence.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in Tg.rasH2 mice. The purpose of rat study was to evaluate AF37702 for carcinogenesis when administered to Sprague-Dawley rats via intravenous injection, once every third week for a period of 2 years. A 26-Week carcinogenicity study was performed using hemizygous Tg.rasH2 mice that were administered AF37702 via intravenous (IV) tail vein injection every three weeks up to 26 weeks, for a total of 10 doses.

Rat Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group and one saline control group. Five hundred and ninety-six naive Sprague-Dawley rats were randomly assigned to either the control groups or one

of three treatment groups. Males and females received either the vehicle control or saline control group or AF37702 at dose levels of 0.01, 0.1, and 0.25 mg/kg for Groups 3, 4 and 5, respectively. The tests showed statistically significant dose-response relationship and statistically significant pair-wise difference between high dose group and the vehicle control group in survivals in male rats. Tests showed in the incidence of lymphoma in hemolymphoreticular and c-cell adenoma in thyroid gland in females.

Mouse Study: A 26-Week carcinogenicity study was performed using hemizygous Tg.rasH2 mice that were administered AF37702 via intravenous (IV) tail vein injection every three weeks up to 26 weeks, for a total of 10 doses. The study consisted of one vehicle control group (Group 1), one Positive Control group (Group 2) and three test article groups (Groups 3-5) consisting of 25 male and 25 female mice per group. The mice were treated with either the vehicle (20mM phosphate and 0.003% Tween 20 in 4.7% sorbitol, pH 6.0, Group 1), the Positive Control (urethane in saline administered via 3 separate intraperitoneal (IP) injections on Days 1, 3 and 5) or AF37702 delivered in vehicle via iv injection on Days 1,22,43, 64,85,106, 127, 148, 169 and 190. Dose levels for the test article groups were 0.1, 0.25 and 0.5 mg/kg/dose (Groups 3-5, respectively). Test article and vehicle were administered in a dose volume of 5 mL/kg body weight and the Positive Control was administered in a dose volume of 10 mL/kg body weight. The tests showed a statistically significant difference in pair-wise comparisons between low dose group and the vehicle control group, between medium dose group and the vehicle control group in survivals in females. Tests showed statistically significant positive dose response relationship in the incidence of hemangiosarcoma in spleen in male mice, the statistically significant difference in pair-wise comparisons of hemangiosarcoma in spleen between medium dose group and the vehicle control in males.

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5. Appendix

**Table 1A: Intercurrent Mortality Rate
Male Rats**

Week	CONTROL		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-52	2	3.8%	.	.	4	7.6%	5	9.4%
53-78	11	24.5%	11	20.8%	11	28.3%	17	41.5%
79-92	10	43.4%	14	47.2%	17	60.4%	14	67.9%
92-97	2	47.2%	3	52.8%	7	73.6%	2	71.7%
Term. Sac.	28	100.0%	25	100.0%	14	100.0%	15	100.0%

**Table 1B: Intercurrent Mortality Rate
Female Rats**

Week	CONTROL		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-52	1	1.9%	1	1.9%	1	1.9%	5	9.4%
53-78	11	22.6%	9	18.9%	7	15.1%	2	13.2%
79-92	7	35.9%	8	34.0%	7	28.3%	12	35.9%
93-100	9	52.8%	5	43.4%	9	45.3%	8	50.9%
Term. Sac.	25	100.0%	30	100.0%	29	100.0%	26	100.0%

**Table 2A: Intercurrent Mortality Comparison
Male Rats**

Test	P-Value (across four groups)	P-Value (control vs low)	P-Value (control vs medium)	P-Value (control vs high)
Dose Response	0.0141	0.7683	0.0557	0.0365
Homogeneity	0.0067	0.6747	0.0139	0.0065

**Table 2B: Intercurrent Mortality Comparison
Female Rats**

Test	P-Value (across four groups)	P-Value (control vs low)	P-Value (control vs medium)	P-Value (control vs high)
Dose Response	0.6296	0.4914	0.5179	0.9387
Homogeneity	0.6221	0.4595	0.4726	0.7669

**Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats**

Organ Name	Tumor Name	0 mg	0.01 mg	0.1 mg	0.25 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=53	Low N=53	Med N=53	High N=53	Dos Resp	C vs. L	C vs. M	C vs. H
ADRENAL CORTEX	Adenoma	1	0	1	0	0.707	1.000	0.721	1.000
ADRENAL MEDULLA	Pheochromocytoma	17	18	10	12	0.829	0.536	0.943	0.812
	Pheochromocytoma, Co	2	0	0	0	1.000	1.000	1.000	1.000
ALL_SITES	Lymphoma	1	2	1	3	0.128	0.500	0.721	0.232
BONE MARROW, ST	Hemangioma	0	0	0	1	0.219	.	.	0.446
BRAIN	Astrocytoma	0	0	0	1	0.219	.	.	0.446
DUODENUM	Carcinoma	0	0	1	0	0.461	.	0.474	.
HEART	Schwannoma	0	1	0	1	0.276	0.506	.	0.453
HEMOLYMPHORETIC	Histiocytic Sarcoma	0	0	0	1	0.219	.	.	0.446
	Lymphoma	1	1	1	3	0.080	0.747	0.721	0.232
JEJUNUM	Sarcoma	0	1	0	0	0.729	0.500	.	.
KIDNEY	Carcinoma	0	0	1	0	0.457	.	0.468	.
LIVER	Hepatocellular Carci	0	1	0	0	0.729	0.500	.	.
	Histiocytic Sarcoma	1	0	0	0	1.000	1.000	1.000	1.000
LUNG WITH BRONC	Bronchiolo-Alveolar	1	1	0	0	0.928	0.753	1.000	1.000
MAMMARY GLAND	Fibroadenoma	1	0	1	0	0.707	1.000	0.721	1.000
PANCREAS	Adenoma	0	2	2	1	0.360	0.253	0.222	0.446
	Carcinoma	1	2	0	0	0.919	0.500	1.000	1.000
PARATHYROID GLA	Adenoma	0	1	1	2	0.086	0.500	0.468	0.196
PITUITARY GLAND	Adenoma	4	11	12	9	0.125	0.048	0.014	0.057
	Schwannoma	1	0	0	0	1.000	1.000	1.000	1.000

Table 3A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Rats

Organ Name	Tumor Name	0 mg	0.01 mg	0.1 mg	0.25 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=53	Low N=53	Med N=53	High N=53	Dos Resp	C vs. L	C vs. M	C vs. H
RECTUM	Lymphoma	0	1	0	0	0.730	0.506	.	.
SKIN, OTHER	Basal Cell Tumor	0	0	1	0	0.457	.	0.468	.
	Fibroma	6	3	1	1	0.956	0.917	0.989	0.985
	Keratoacanthoma	6	1	2	1	0.886	0.993	0.950	0.985
	Papilloma	1	1	1	0	0.787	0.753	0.721	1.000
	Sarcoma	0	1	0	0	0.730	0.506	.	.
	Trichoepithelioma	0	0	1	0	0.457	.	0.468	.
TESTIS	Interstitial Cell Ad	2	0	1	1	0.494	1.000	0.854	0.836
THYROID	CCELL_ADENOMA+CARCIN	14	9	7	3	0.990	0.920	0.950	0.998
	FOLLICULAR_ADENOMA+C	2	2	1	3	0.223	0.683	0.849	0.399
THYROID GLAND	C-Cell Adenoma	14	7	7	2	0.994	0.975	0.950	1.000
	C-Cell Carcinoma	0	2	0	1	0.391	0.247	.	0.446
	Follicular Cell Aden	2	1	1	3	0.153	0.875	0.849	0.399
	Follicular Cell Carc	0	1	0	0	0.729	0.500	.	.

**Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Rats**

Organ Name	Tumor Name	0 mg	0.01 mg	0.1 mg	0.25 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=53	Low N=53	Med N=53	High N=53	Dos Resp	C vs. L	C vs. M	C vs. H
ABDOMINAL CAVIT	Neural Crest Tumor	0	1	0	0	0.755	0.506	.	.
ADRENAL CORTEX	Adenoma	2	2	1	2	0.512	0.701	0.888	0.692
ADRENAL MEDULLA	Pheochromocytoma	3	5	3	3	0.652	0.384	0.685	0.662
ALL_SITES	LYMPHOMA	2	1	0	0	0.986	0.884	1.000	1.000
BRAIN	Astrocytoma	0	0	0	1	0.246	.	.	0.500
	Oligodendroglioma	1	0	0	0	1.000	1.000	1.000	1.000
CERVIX	Carcinoma	0	1	0	0	0.755	0.506	.	.
	Papilloma	0	1	0	1	0.311	0.506	.	0.500
CLITORAL GLAND	Carcinoma	0	0	1	0	0.503	.	0.512	.
HEART	Fibroma	0	1	0	0	0.755	0.506	.	.
HEMOLYMPHORETIC	Histiocytic Sarcoma	0	1	0	0	0.755	0.506	.	.
	Lymphoma	0	0	2	3	0.023	.	0.265	0.120
ILEUM	Leiomyosarcoma	0	1	0	0	0.755	0.506	.	.
INJECTION SITE	Papilloma	0	0	0	1	0.246	.	.	0.500
JEJUNUM	Leiomyoma	0	0	1	0	0.503	.	0.512	.
KIDNEY	Nephroblastoma	0	0	0	1	0.250	.	.	0.506
LIVER	Hepatocellular Adeno	0	0	0	1	0.246	.	.	0.500
LUNG WITH BRONC	Bronchiolo-Alveolar	0	0	0	1	0.246	.	.	0.500
MAMMARY GLAND	Adenoma	0	4	0	1	0.743	0.061	.	0.500
	Carcinoma	6	5	2	6	0.484	0.754	0.975	0.655
	Fibroadenoma	28	25	31	23	0.679	0.761	0.386	0.818
OVARY	Carcinoma	1	0	0	0	1.000	1.000	1.000	1.000
	Granulosa Cell Tumor	0	0	1	0	0.503	.	0.512	.
	Sertoli Cell Adenoma	0	0	0	1	0.246	.	.	0.500
PANCREAS	Adenoma	2	0	0	2	0.269	1.000	1.000	0.692
	Carcinoma	0	1	1	1	0.295	0.506	0.512	0.500
PARATHYROID GLA	Adenoma	0	0	0	2	0.059	.	.	0.24

**Table 3B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Rats**

Organ Name	Tumor Name	0 mg	0.01 mg	0.1 mg	0.25 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=53	Low N=53	Med N=53	High N=53	Dos Resp	C vs. L	C vs. M	C vs. H
PITUITARY GLAND	Adenoma	25	26	21	21	0.776	0.405	0.799	0.733
SKIN, OTHER	Fibroma	0	1	1	1	0.295	0.506	0.512	0.500
	Schwannoma	0	1	0	1	0.311	0.506	.	0.500
THYMUS	Thymoma	0	1	0	0	0.755	0.506	.	.
THYROID GLAND	C-Cell Adenoma	8	6	12	13	0.035	0.822	0.259	0.157
	C-Cell Carcinoma	1	0	2	0	0.688	1.000	0.518	1.000
	Follicular Cell Aden	0	0	1	0	0.506	.	0.518	.
TISSUE NOS	Hibernoma	0	1	0	0	0.755	0.506	.	.
TYROID	CCELL_ADENOMA+CARCIN	9	6	13	13	0.050	0.883	0.270	0.229
UTERUS	ADENOMA+CARCINOMA	1	1	1	1	0.517	0.759	0.765	0.753
	Adenoma	0	0	1	1	0.186	.	0.512	0.500
	Carcinoma	1	1	0	0	0.941	0.759	1.000	1.000
	Endometrial Stromal	0	0	1	0	0.503	.	0.512	.
		11	7	4	3	0.988	0.908	0.991	0.996
	Hemangioma	2	1	0	0	0.986	0.884	1.000	1.000
	Papilloma	0	1	0	0	0.755	0.506	.	.
	Squamous Cell Carcin	0	0	1	0	0.503	.	0.512	.
UTERUS+VAGINA	STROMAL_POLYP	11	7	4	3	0.988	0.908	0.991	0.996
VAGINA	Sarcoma	0	0	1	0	0.506	.	0.518	.
	Schwannoma	0	0	0	1	0.246	.	.	0.500
	Stromal Polyp	1	1	1	0	0.833	0.759	0.765	1.000
ZYMBALS GLAND	Adenoma	0	0	1	0	0.506	.	0.518	.

**Table 4A: Intercurrent Mortality Rate
Male Mice**

Week	Vehicle_CONTROL		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-10	.	.	.	.	.	.	.	.
11-15	.	.	.	.	.	.	.	.
16-20	.	.	1	4.0%	.	.	.	.
21-26	1	4.0%	.	.	1	4.0%	.	.
Term. Sac.	24	100.0%	24	100.0%	24	100.0%	25	100.0%

**Table 4B: Intercurrent Mortality Rate
Female Mice**

Week	Vehicle_CONTROL		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT	NO.OF DEATH	PERCENT
0-10	.	.	.	.	.	.	.	.
11-15	.	.	.	.	.	.	.	.
16-20	.	.	.	.	.	.	.	.
21-26	.	.	1	4.0%	.	.	.	.
Term. Sac.	22	100.0%	24	100.0%	25	100.0%	24	100.0%

**Table 5A: Intercurrent Mortality Comparison
Male Mice**

Test	P-Value (across four groups)	P-Value (control vs low)	P-Value (control vs medium)	P-Value (control vs high)
Dose Response	0.8785	0.9977	0.9977	0.8875
Homogeneity	0.7978	0.9885	0.9885	0.3173

**Table 5B: Intercurrent Mortality Comparison
Female Mice**

Test	P-Value (across four groups)	P-Value (control vs low)	P-Value (control vs medium)	P-Value (control vs high)
Dose Response	0.2505	<.0001	<.0001	1.000
Homogeneity	0.1058	0.1531	.?	.?

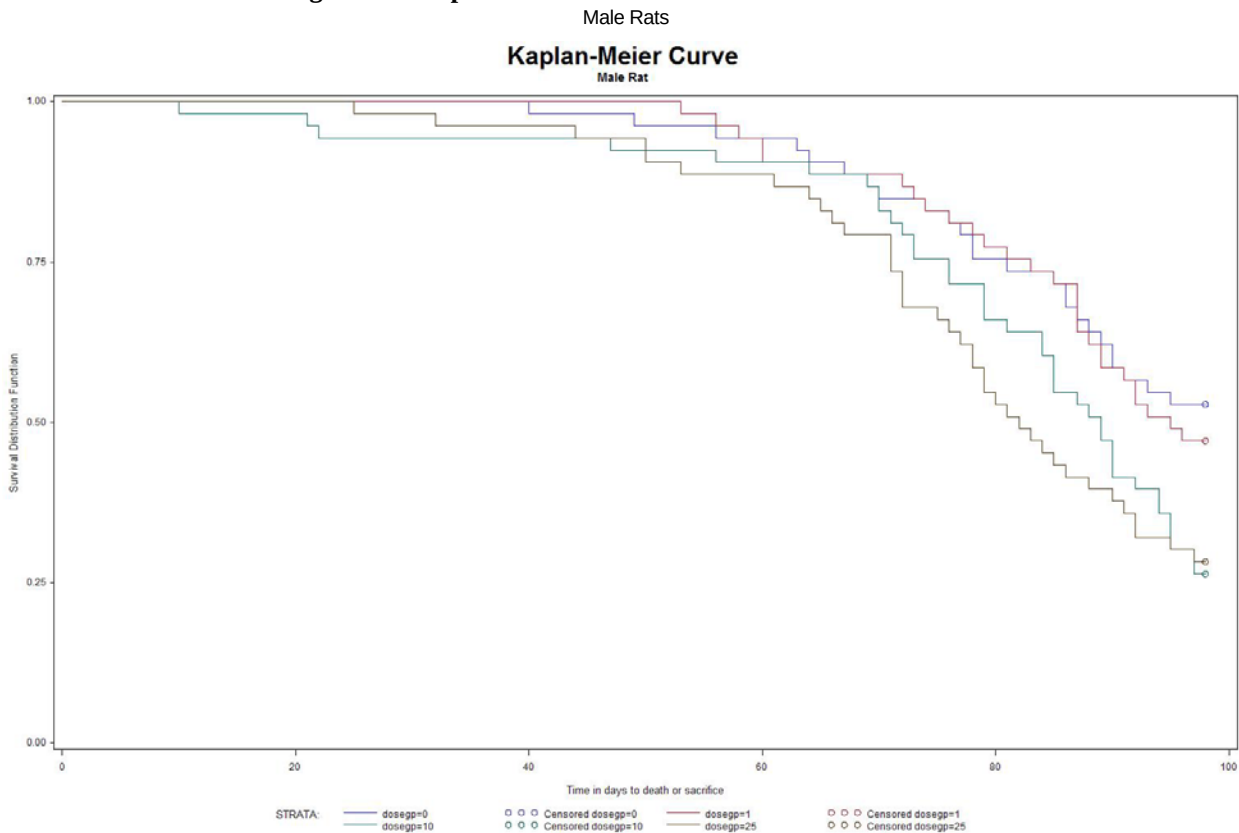
**Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice**

Organ Name	Tumor Name	0 mg	0.1 mg	0.25 mg	0.5 mg	P_Value	P_Value	P_Value	P_Value
		Cont	Low	Med	High				
		N=25	N=25	N=25	N=25	Dos Resp	C vs. L	C vs. M	C vs. H
bone marrow, fe	hemangiosarcoma	0	0	0	1	0.255	.	.	0.500
harderian gland	adenoma	0	4	1	1	0.596	0.050	0.490	0.500
lungs with bron	adenoma	3	4	8	4	0.336	0.476	0.085	0.500
multicentric	lymphoma	0	1	0	0	0.495	0.500	.	.
spleen	hemangiosarcoma	0	1	6	4	0.023	0.490	0.010	0.055

**Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Female Mice**

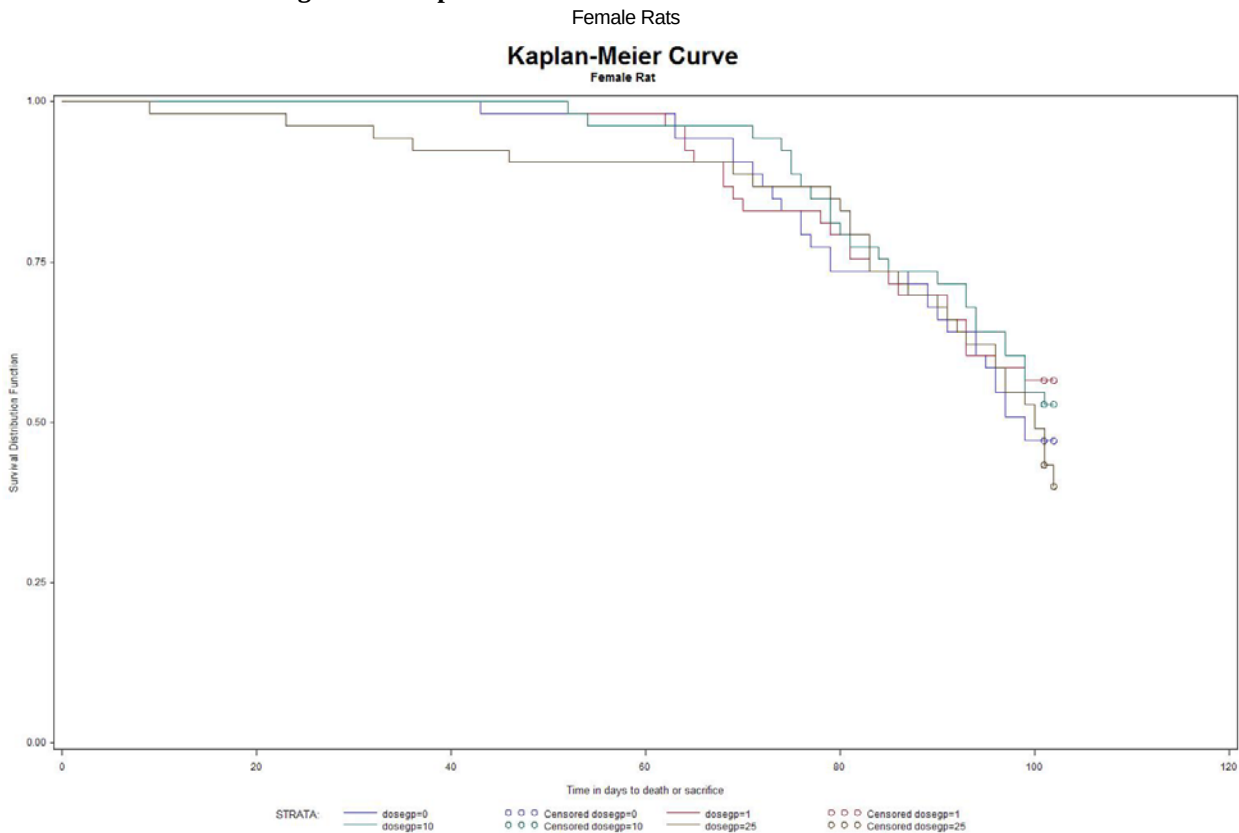
Organ Name	Tumor Name	Cont	Low	Med	High	0 mg	0.1 mg	0.25 mg	0.5 mg
		N=25	N=25	N=25	N=25	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ALL_SITES	HAEMANGIOSARCOMA+HAE	1	5	5	4	0.219	0.086	0.095	0.174
harderian gland	adenoma	0	2	2	1	0.406	0.235	0.245	0.500
	carcinoma	0	1	0	0	0.505	0.490	.	.
intestine, ileu	hemangioma	0	0	1	0	0.505	.	0.500	.
liver	hepatocellular adeno	0	0	0	1	0.253	.	.	0.500
lungs with bron	adenoma	2	0	3	0	0.748	0.745	0.500	0.755
	carcinoma	1	1	0	0	0.815	0.745	0.500	0.500
salivary glands	hemangiosarcoma	0	0	1	0	0.505	.	0.500	.
spleen	hemangiosarcoma	1	4	3	4	0.182	0.162	0.305	0.174
stomach	hemangiosarcoma	0	1	0	0	0.505	0.490	.	.
subcutis	hemangiosarcoma	0	1	0	0	0.505	0.490	.	.
uterus	sarcoma	0	1	0	0	0.505	0.490	.	.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats



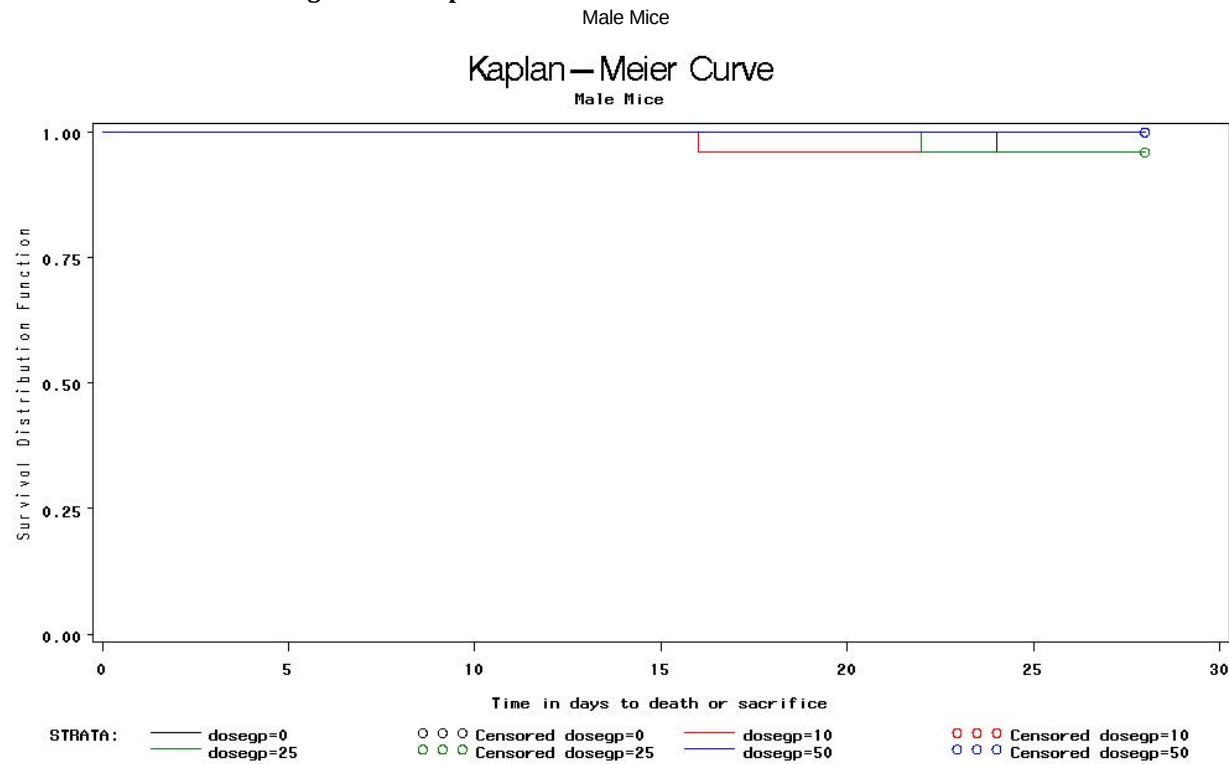
X-Axis: Weeks, Y-Axis: Survival rates

Figure 1B: Kaplan-Meier Survival Functions for Female Rats



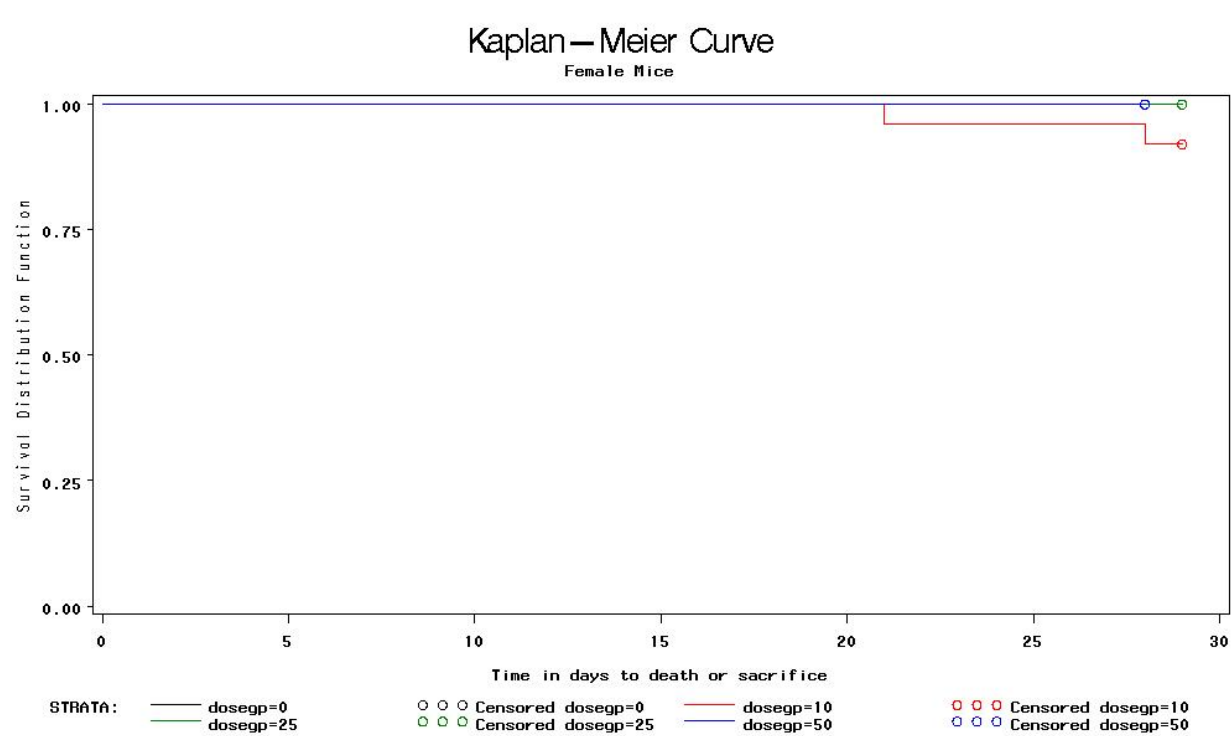
X-Axis: Weeks, Y-Axis: Survival rates

Figure 2A: Kaplan-Meier Survival Functions for Male Mice



X-Axis: Weeks, Y-Axis: Survival rates

Figure 2B: Kaplan-Meier Survival Functions for Female Mice



X-Axis: Weeks, Y-Axis: Survival rates

6. References:

1. Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.
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3. Cox D. R. (1972) "Regression models and life tables", *Journal of the Royal Statistical Society*, B, 34, 187-220.
4. Gehan (1965) "A generalized Wilcoxon test for comparing arbitrarily singly censored samples", *Biometrika*, 52, 203-223.
5. Haseman, J (1983), "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339.
6. Lin, K.K. and Rahman, M.A. (1998), "Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs", *Journal of Biopharmaceutical Statistics*, 8(1), 1-15.
7. Rahman, M.A. and Lin, K.K. (2008), "A comparison of False Positive Rates of Peto and Poly-3 Methods for Long-Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics*, 18:5, 849-858.
8. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J. Wahrendorf (1980), "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva*, 311-426.
9. Tarone RE (1975), "Test for trend in life table analysis", *Biometrika*, 62: 679-82.
10. U.S. Department of Health and Human Services, "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals", Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, 2001.

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/s/

MIN MIN
12/08/2011

KARL K LIN
12/08/2011
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202799

Applicant: Affymax

Stamp Date: 27-May-2011

Drug Name: peginesatide

NDA/BLA Type: NDA

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

x

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.		x		However, a DMC periodically conducted a safety review
Appropriate references for novel statistical methodology (if present) are included.	x			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

Reference ID: 2969006

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			Since little missing data are expected, no imputation was used for patients discontinuing prior to the Evaluation Period. sensitivity analyses in patients discontinuing prior to the Evaluation Period was performed using: (1) a change in Hgb of 0 g/dL and (2) a change in Hgb computed using the last Hgb value recorded.
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Qing Xu	07/01/2011
Reviewing Statistician	Date

Mark Rothmann	07/01/2011
Supervisor/Team Leader	Date

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/s/

QING XU
07/01/2011

MARK D ROTHMANN
07/01/2011