# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

## 202799Orig1s000

## <u>MEDICAL REVIEW(S)</u>

M E M O R A N D U M        DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date:        February 29, 2012

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Subject:     Medical Team Leader Secondary Clinical Review
             NDA 202799, letter date 5/23/2011; received 5/27/2011
             Omontys (peginesatide injection) for the treatment of anemia associated with
             chronic renal failure (CRF) in adult patients on dialysis

To:          NDA 202799

Omontys (peginesatide injection) is an erythropoiesis stimulating agent (ESA) developed for
treatment of anemia in patients with chronic renal failure (CRF). In this application the sponsor
is seeking approval of peginesatide for treatment of anemia associated with CRF in adult patients
on dialysis.

**Background:**
In patients with chronic kidney disease (CKD) the prevalence of anemia is strongly associated
with worsening renal failure, due largely to deficiency of endogenous erythropoietin.
Consequently, patients with CRF on dialysis are anemic and require exogenous erythropoiesis
stimulation to maintain a hematocrit sufficient to avoid requirement for red blood cell (RBC)
transfusion.  Erythropoiesis stimulating agents, including Epogen/Procrit (epoetin alfa), Aranesp
(darbepoetin alfa) and Mircera (pegylated epoetin alfa) are approved for reducing need for RBC
transfusions in patients with CRF on dialysis and not on dialysis.  Currently only Epogen/Procrit
and Aranesp are marketed in the U.S.  All three of these ESAs are recombinant proteins
administered three times a week (Epogen/Procrit), once weekly or once every two weeks
(Aranesp), or once every two weeks or monthly [maintenance] (Mircera). In the current
application the sponsor proposes introduction of peginesatide as another ESA for use in adult
patients with CRF on dialysis.  The intended starting dose is 0.04 to 0.08 mg/kg as a single
monthly dose for patients not currently receiving an ESA or is to be based on the total weekly
dose of current ESA for patients being converted from another ESA.  Peginesatide is to be
administered intravenously (IV) or subcutaneously (SC) and the maximum human dose,
regardless of route of administration, is 0.35 mg/kg.

Peginesatide (AF37702) is a synthetic, pegylated dimeric peptide comprised of two identical, covalently-linked 21 amino acid chains and having a molecular weight of about ▓▓▓ (b) (4) It is water-soluble with an unbuffered pH of 7.1 to 8.5. Structurally, the amino acid sequence of peginesatide is not related to that of endogenous erythropoietin. Based on the sponsor's reports, peginesatide binds to and activates the human erythropoietin receptor and stimulates human RBC precursors to undergo proliferation and differentiation similar to other ESAs. (b) (4) ▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓ he sponsor states that the data suggest that peginesatide is a functional agonist of the human EPOr and that the presence of the peg (polyethylene glycol) moiety, ▓▓▓▓▓▓▓▓▓▓▓▓▓▓ (b) (4), does not decrease the magnitude of *in vitro* activation or signal transduction compared to recombinant human erythropoietin (rHuEPO), darbepoetin alfa, ▓▓▓▓▓▓▓▓▓▓▓▓▓ (b) (4), although the kinetics appeared slightly delayed and potency was generally lower.

**Studies Submitted:**
In support of the application the sponsor has submitted two active-controlled, open-label studies in adult patients with chronic renal failure (CRF) [chronic kidney disease (CKD)] on hemodialysis and currently treated with and ESA (Studies AFX01-12 and AFX01-14). [Note: In this review I will generally use the term CKD for consistency with terminology in currently approved ESA labels]. These two studies were designed with the primary objectives of demonstrating the safety and efficacy of peginesatide in the maintenance treatment of anemia in hemodialysis patients and to demonstrate the non-inferiority of peginesatide injection to epoetin alfa in the maintenance treatment of anemia in these patients. The primary efficacy endpoint of this study is the mean change in hemoglobin (Hgb) between Baseline and the Evaluation Period. The baseline Hgb value is defined as the mean of five Hgb values: the four most recent Hgb values taken prior to the day of randomization and the value obtained on the day of randomization. The mean Hgb during the Evaluation Period for each patient is calculated as the mean of the available Hgb values during Study Weeks 29 through 36. The composite safety endpoint includes the following events as adjudicated by the Event Review Committee (ERC): death (all causes), stroke, myocardial infarction, congestive heart failure (CHF) that meets the definition of a serious adverse event (SAE) in the protocol, unstable angina that meets the definition of an SAE in the protocol, and arrhythmia that meets the definition of an SAE in the protocol.

The sponsor has also submitted two active-controlled, open-label studies conducted in adult patients with CKD not on dialysis and not currently receiving ESA treatment (Studies AFX01-11 and AFX01-13). These studies had a similar design to the studies in patients on dialysis. Though peginesatide has been studied in patients with CKD not on dialysis, the sponsor does not propose to market peginesatide for use in these patients with chronic kidney disease who are not on dialysis, likely due to adverse findings for the cardiovascular safety endpoint in the non-dialysis studies as presented under Safety discussion below.

Major features of the design and conduct of these four studies in patients with CKD on dialysis and not on dialysis are summarized in the following table:

**Clinical Efficacy and Safety Studies of Peginesatide in Patients with Chronic Kidney Disease (CKD) On Dialysis and Not On Dialysis:  Summary of Study Design**

| Study Identifier: Study Title [country(ies)] | Study design and type of control; primary endpoints | Population and Number of Subjects | Number of subjects, treatments, Dosage regimens and administration, Route of administration | Comments |
|---|---|---|---|---|
| AFX01-12 Conducted from 9/29/07-1/22/10; US | R (2:1), AC, OL, MC study; randomization stratified by: screening Hgb values (10.0-11.4 and 11.5-12.0 g/dL) and New York Heart Association CHF Class (0 or no heart disease-1 or II-IV); 4-week screening period when pts continue to receive current ESA treatment as per SOC (up to 3 screening efforts allowed per patient); titration period of 28 weeks on treatment following randomizaion; evaluation period of 8 weeks on continued study treatment (weeks 29 to 36); continued followup for an additional 16 weeks (to give total of at least 52 weeks total study followup).<br><br>Primary efficacy endpoint was change from baseline hemoglobin (Hgb) during the Evaluation Period (Wks 29 to 36), with between group difference (peginesatide minus epoetin) calculated using an ANOVA model and and non-inferiority was declared as a lower limit of the 2-sided 95% confidence interval $\geq$-1.0g/dL. Primary safety endpoint was the | Pts $\geq$18 yrs of age with CRF on hemodialysis for at least 3 months and currently on ESA with stable dose (stability defined as $\leq$ 50% change from the maximum prescribed weekly dose (i.e., [max-min]/max $\leq$ 0.5) with no change in prescribed frequency during the last 4 weeks prior to randomization) to maintain Hgb $\geq$ 10.0 and $\leq$ 12.0 g/dL.  Pts must be iron replete and not vitamin B12 or folate deficient. | 420, peginesatide Q4W IV; 210, epoetin alfa IV 1-3 x per wk<br><br>Starting dose of peginesatide based on prescribed total weekly epoetin alfa dose during the last week of the Screening Period as follows:<br><br>**AF37702 Injection Starting Doses**<br><br>| Screening Epoetin alfa Dose (U/kg/week) | AF37702 Injection (mg/kg/Q4W) |<br>|---|---|<br>| <100 | 0.04 |<br>| 100 to 199 | 0.08 |<br>| 200 to 299 | 0.12 |<br>| $\geq$ 300 | 0.16 |<br><br>Dose was adjusted during the titration and evaluation periods to maintain Hgb in range 10.0-12.0g/dL and $\pm$1.5g/dL within baseline value.  Note: for Hgb $\geq$12.0g/dL, adjustment directions were different for peginesatide and control groups as follows:<br><br>|  | pegniesatide | Epoetin |<br>|---|---|---|<br>| Reduce dose by 25% | If Hgb is 12.5-12.9 | If Hgb is 12.0-12.4 |<br>| Delay and reduce dose by 25% | If Hgb is $\geq$13.0 | If Hgb is $\geq$12.5 | | Protocol amendments* **11/07** (increase enrollment to improve chances of meeting safety endpoint numbers); **5/08** (increase duration of screening period from 4 wks to 6 wks; liberalized definition of stable epoetin dose allowed for study entry; allowed for pts to resume study treatment after premature study termination based on investigator's judgment); **10/08** (mainly clarifications; clarified duration of followup; clarification of definition of baseline Hgb to be the mean of "the 4 most recent values prior to randomization and the value on day of randomization" and definition of mean Hgb during evaluation period to be "the mean of the available Hgb values during Study Weeks 29 through 36"; some changes in endpoints based on EMA request; |

| | | | | |
|---|---|---|---|---|
| | time to occurrence of the composite safety endpoint (CSE)[which consisted of death, stroke, myocardial infarction and serious adverse events of congestive heart failure, unstable angina and arrhythmia]. Events were adjudicated by an independent review committee. | | | **6/09** mainly clarifications; modified [broadened scope of] definition of CHF and arrhythmia for composite safety endpoint to align with definition of SAE; modified some secondary endpoints; per-protocol analysis permitted no missing doses between Wks 21 and 35, no RBC transfusions within 12 wks prior to randomization); extended duration of followup to approx closure of other 3 studies). |
| AFX01-14 Conducted from 10/19/07-1/22/10; US, Spain, UK, Germany , Italy, France, Bulgaria, Poland, Romania | Same as AFX01-12 except: Additional stratification factors: geographical region (US, Western European Union (EU), Central EU), and route of administration (IV or SQ). | Same as AFX01-12 | Same as AFX01-12 except: Peginesatide and epoetin administration could be IV or SQ and epoetin alfa or beta could be used | Protocol amendments*: Essentially same as AFX01-12 |
| AFX01-11 Conducted from 10/19/07-2/3/10; US | R (1:1:1), AC, OL, MC study; randomization stratified by: screening Hgb values (8.0-10.4 and 10.5-10.9g/dL) and New York Heart Association CHF Class (0 or no heart disease-1 or II-IV); 4-week screening period; correction period of 24 weeks on treatment following randomization; evaluation period of 8 weeks on continued study treatment (weeks 25 to 36); continued followup for an additional 16 weeks (to give | Pts $\geq$18 yrs of age with CRF with GFR<60 mL/min/1.73m$^2$ not expected to start dialysis for at least 12 wks, not on ESA during prior 12 wks, not known intolerant to ESA; Hgb $\geq$ 8.0 and <11.0 g/dL. Pts must be iron replete and not vitamin B12 or folate deficient. | 150, peginesatide starting dose 0.025mg/kg Q4W SC; 150, peginesatide starting dose 0.04mg/kg Q4W SC; 150, darbepoetin alfa 0.75mcg/kg SC Q2W

Dose was adjusted during the study to reach and maintain Hgb in range 11.0-12.0g/dL. Adjustment directions were the same for all treatment groups. | Protocol amendments* **11/07** (allowed entry/continuation of pts post-transplant if not on chronic dialysis); **10/08** (mainly clarifications; modified [broadened scope of] definition of CHF and arrhythmia for composite safety endpoint to align with definition of SAE; modified some secondary endpoints; per-protocol analysis permitted no missing |

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|---|---|---|---|---|
| | total of at least 52 weeks total study followup).<br><br>The primary efficacy and safety endpoints were the same as for the dialysis studies | | | doses between Wks 21 and 35, no RBC transfusions within 12 wks prior to randomization); 6/**09** (extended duration of followup to approx closure of other 3 studies; some clarifications |
| AFX01-13 Conducted from 11/20/07-12/31/09; U.S., Bulgaria, Hungary, Romania, Poland, Czech Republic, Germany, UK, Italy | Same as AFX01-11 except: Additional stratification factor-- geographical region (US, Western Europe, Central Europe) | Same as AFX01-11 | Same as AFX01-11 | Protocol amendments*: Essentially same as for AFX01-11 |

R=randomized; AC=active-controlled; OL=open-label; MC=multicenter; SOC-standard of care; Hgb=hemoglobin; *=most significant changes; EMA=European Medicines Agency

**Study Results:**

Studies AFX01-12 and AFX01-14 in Patients with Chronic Kidney Disease on Hemodialysis:
The major results for each of the studies are presented and discussed below. For detailed study
description and presentation of analyses and results of the two studies combined, see the Medical
Officer's Review by Dr. A. Dmytrijuk (final signature February 7, 2012).

*Disposition and Population Characteristics for the Dialysis Studies (AFX01-12 and AFX01-14):*
Disposition of patients in the Studies AFX01-12 and AFX01-14 is summarized in the following table:

**Dialysis Studies (AFX01-12 and AFX01-14): Disposition of Patients\***

| | AFX01-12 | | AFX01-14 | |
|---|---|---|---|---|
| | Peginesatide IV Q4W (N=532) | Epoetin alfa IV 1-3 times per wk (N=271) | Peginesatide IV or SQ Q4W (N=549) | Epoetin alfa/beta IV or SQ 1-3 times per wk (N=274) |
| Randomized | 532 (100%) | 271 (100%) | 549 (100%) | 274 (100%) |
| Received at least 1 dose of study drug | 524 (98.5%) | 269 (95.9%) | 542 (98.7%) | 273 (99.6%) |
| Permanently Prematurely discontinued study drug | 190 (35.7%)[a] | 73 (26.9%)[b] | 139 (25.3%)[c] | 71 (25.9%)[d] |
| Prematurely terminated from study | 166 (31.2%) | 69 (25.5%) | 128 (23.3%) | 63 (23.0%) |
| Completed study on drug | 334 (62.7%) | 196 (72.3%) | 403 (73.4%) | 202 (73.7%) |

\* all randomized patients

[a] major reasons: death, 43 [7.8%]; dosing consent withdrawn, 24 [4.5%]; adverse events, 34 [6.4%]; renal transplant, 18 [3.4%]; other, 57 [10.7%]

[b] major reasons: death, 27 [10.0%]; dosing consent withdrawn, 8 [3.0%]; adverse events, 4 [1.5%]; renal transplant, 12 [4.4%]; other 22 [8.1%]

[c] major reasons: death, 46 [8.4%]; dosing consent withdrawn, 40 [7.3%]; adverse events, 13 [2.4%]; renal transplant, 16 [2.9%]; other, 21 [3.9%]

[d] major reasons: death, 26 [9.5%]; dosing consent withdrawn, 11 [4.0%]; adverse events, 8 [2.9%]; renal transplant, 12 [4.4%]; other 10 [3.6%]

reviewer's table based on data in sponsor's tables

In Study AFX01-12 a total of 1496 patients were screened, 693 (46%) failed screening and 803 (54%)
were randomized. In Study AFX01-14 a total of 1309 patients were screened, 823 (63%) were
randomized, and 486 (37.1%) failed screening. In both studies the major reason for screening failure
($\geq$79% of screen failures) was failure to satisfy one or more inclusion criteria (e.g., not meeting
stability of hemoglobin range requirement in half of the cases). In Study AFX01-12 of the screen
failures 95 (13.7%) had not been on stable epoetin dose for $\geq$8 weeks prior to randomization; in Study
AFX01-14 this number was 63 (13%) patients.

During the studies the leading reason for permanently prematurely discontinuing study drug in both
studies was death (7.8%-10.0% of patients in each treatment group). The great majority of patients
who discontinued study drug prematurely also were terminated from the study.

Demographic, baseline and medical history characteristics of the enrolled and treated patients are
summarized in the following table:

**Dialysis Studies (AFX01-12 and AFX01-14): Demographic, Baseline and Medical History Characteristics of Patients\***

|  | AFX01-12 | | AFX01-14 | |
|---|---|---|---|---|
|  | Peginesatide IV Q4W (N=524) | Epoetin alfa IV 1-3 times per wk (N=269) | Peginesatide IV or SQ Q4W (N=542) | Epoetin alfa/beta IV or SQ 1-3 times per wk (N=273) |
| Age (yrs) |  |  |  |  |
| Mean | 57.3 | 57.5 | 58.8 | 58.6 |
| Median | 58 | 57 | 59 | 59 |
| range | 20-91 | 22-90 | 22-93 | 22-97 |
| Age, N (%) |  |  |  |  |
| <65 yrs | 370 (70.6%) | 190 (70.6%) | 350 (64.6%) | 173 (63.4%) |
| ≥65 to <75 yrs | 97 (18.5%) | 44 (16.4%) | 110 (20.3%) | 67 (24.5%) |
| ≥75 yrs | 57 (10.9%) | 35 (13.0%) | 82 (15.1%) | 33 (12.1%) |
| Gender, N (%) |  |  |  |  |
| Male | 293 (55.9%) | 144 (53.5%) | 331 (61.1%) | 153 (56.0%) |
| female | 231 (44.1%) | 125 (46.5%) | 211 (38.9%) | 120 (44.0%) |
| Race, N (%) |  |  |  |  |
| Asian | 16 (3.1%) | 9 (3.3%) | 17 (3.1%) | 12 (4.4%) |
| Black | 234 (44.7%) | 136 (50.6%) | 165 (30.4%) | 75 (27.5%) |
| White | 263 (50.2%) | 116 (43.1%) | 354 (65.3%) | 183 (67.0%) |
| Other | 10 (1.9%) | 8 (3.0%) | 6 (1.1%) | 3 (1.1%) |
| Missing | 1 (0.2%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Ethnicity, N (%) |  |  |  |  |
| Hispanic or Latino | 135 (25.8%) | 69 (25.7%) | 95 (17.5%) | 52 (19.0%) |
| Non-Hispanic or non-Latino | 388 (74.0%) | 200 (74.3%) | 447 (82.5%) | 221 (81.0%) |
| Missing | 1 (0.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Geographic Area, N (%)[#] |  |  |  |  |
| US | 524 (100%) | 269 (100%) | 335 (61.0%) | 167 (60.9%) |
| West Europe | 0 | 0 | 68 (12.4%) | 33 (12.0%) |
| Central Europe | 0 | 0 | 146 (26.6%) | 74 (27.0%) |
| Weight (kg) |  |  |  |  |
| Mean | 85.15 | 83.55 | 79.65 | 78.74 |
| Median | 80.0 | 80.5 | 76.0 | 76.0 |
| Range | 40.0-227.0 | 42.1-158.5 | 38.0-187.5 | 43.5-163.0 |
| Baseline Hgb (g/dL) |  |  |  |  |
| Mean | 11.30 | 11.32 | 11.20 | 11.21 |
| Median | 11.4 | 11.4 | 11.2 | 11.3 |
| Range | 9.9-12.4 | 10.0-12.3 | 10.0-13.0 | 9.3-12.2 |
| Baseline Hgb (g/dL), N (%) |  |  |  |  |
| ≤11.4 g/dL | 290 (55.3%) | 146 (54.3%) | 336 (62.0%) | 178 (65.2%) |
| >11.5 g/dL | 234 (44.7%) | 123 (45.7%) | 206 (38.0%) | 95 (34.8%) |
| Ferritin (ng/mL)[+] |  |  |  |  |
| Mean | 697.6 | 657.0 | 767.1 | 778.5 |
| Median | 666 | 609 | 668 | 668 |
| Range | 44-2245 | 47-1913 | 87-7329 | 58-3026 |
| TSAT (%)[++] |  |  |  |  |
| Mean | 30.9 | 29.1 | 30.4 | 31.0 |

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|---|---|---|---|---|
| Median | 29 | 28 | 29 | 28 |
| range | 11-82 | 9-83 | 11-85 | 9-84 |
| Time on dialysis | | | | |
| ≤1 yr | 49 (9.4%) | 32 (11.9%) | 82 (15.1%) | 40 (14.7%) |
| >1 yr | 475 (90.6%) | 237 (88.1%) | 460 (84.9%) | 233 (85.3%) |
| Current Kt/V | | | | |
| N | 478 | 247 | 404 | 204 |
| Mean | 1.65 | 1.63 | 1.62 | 1.60 |
| Median | 1.6 | 1.6 | 1.6 | 1.6 |
| range | 0.5-4.9 | 0.7-2.8 | 0.8-7.7 | 0.6-3.3 |
| Urea reduction ratio (URR)(%) | | | | |
| N | 473 | 236 | 343 | 168 |
| Mean | 73.7 | 73.6 | 71.3 | 71.9 |
| Median | 74 | 75 | 73 | 74 |
| range | 47-97 | 7-90 | 10-94 | 0-97 |
| Primary causes of chronic renal failure, N (%): | | | | |
| Diabetes | 222 (42.4%) | 118 (43.9%) | 174 (32.1%) | 96 (35.2%) |
| Hypertension | 184 (35.1%) | 97 (36.1%) | 155 (28.6%) | 57 (20.9%) |
| Autoimmune disease | 13 (2.5%) | 10 (3.7%) | 17 (3.1%) | 14 (5.1%) |
| Polycystic kidney disease | 11 (2.1%) | 6 (2.2%) | 29 (5.4%) | 15 (5.5%) |
| Pyelonephritis | 1 (0.2%) | 1 (0.4%) | 34 (6.3%) | 26 (9.5%) |
| Interstitial nephritis | 5 (1.0%) | 1 (0.4%) | 15 (2.8%) | 7 (2.6%) |
| Urologic | 4 (0.8%) | 1 (0.4%) | 11 (2.0%) | 7 (2.6%) |
| Unknown | 21 (4.0%) | 6 (2.2%) | 31 (5.7%) | 11 (4.0%) |
| Other | 63 (12.0%) | 29 (10.8%) | 76 (14.0%) | 40 (14.7%) |
| Cigarette use, N (%) | | | | |
| Yes | 210 (40.1%) | 96 (35.7%) | 147 (27.1%) | 75 (27.5%) |
| No | 314 (59.9%) | 172 (63.9%) | 394 (72.7%) | 198 (72.5%) |
| Missing | 0 (0.0%) | 1 (0.4%) | 1 (0.4%) | 0 (0.0%) |
| Cardiovascular (CV) risk history, N (%): | 519 (99.0%) | 268 (99.6%) | 534 (98.5%) | 270 (98.9%) |
| At least one CV risk without hypertension | 491 (93.7%) | 258 (95.9%) | 448 (82.7%) | 227 (83.2%) |
| Hypertension | 517 (98.7%) | 266 (98.9%) | 522 (96.3%) | 266 (97.4%) |
| Diabetes | 298 (56.9%) | 151 (56.1%) | 238 (43.9%) | 124 (45.4%) |
| Coronary artery disease (CAD) | 238 (45.4%) | 100 (37.2%) | 209 (38.6%) | 91 (33.3%) |
| Myocardial infarction (MI) | 88 (16.8%) | 30 (11.2%) | 78 (14.4%) | 29 (10.6%) |
| Angina | 108 (20.6%) | 49 (18.2%) | 94 (17.3%) | 43 (15.8%) |
| Coronary artery bypass graft | 64 (12.2%) | 26 (9.7%) | 51 (9.4%) | 19 (7.0%) |
| PCI or coronary stent placement | 73 (13.9%) | 32 (11.9%) | 60 (11.1%) | 25 (9.2%) |
| Arrhythmia | 102 (19.5%) | 65 (24.2%) | 122 (22.5%) | 40 (14.7%) |
| AF, flutter, or SVT | 66 (12.6%) | 35 (13.0%) | 77 (14.2%) | 28 (10.3%) |
| VT or fibrillation | 18 (3.4%) | 13 (4.8%) | 14 (2.6%) | 4 (1.5%) |
| Cerebrovascular disease (CVD) | 99 (18.9%) | 54 (20.1%) | 88 (16.2%) | 45 (16.5%) |
| Stroke | 70 (13.4%) | 35 (13.0%) | 58 (10.7%) | 36 (13.2%) |
| TIA | 27 (5.2%) | 10 (3.7%) | 22 (4.1%) | 6 (2.2%) |
| Peripheral vascular disease | 145 (27.7%) | 70 (26.0%) | 112 (20.7%) | 49 (17.9%) |
| Hyperlipidemia | 353 (67.4%) | 190 (70.6%) | 276 (50.9%) | 126 (46.2%) |
| Congestive heart failure | | | | |
| Yes | 238 (45.4%) | 127 (47.2%) | 208 (38.4%) | 93 (34.1%) |

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| | 286 (54.6%) | 142 (52.8%) | 334 (61.6%) | 180 (65.9%) |
|---|---|---|---|---|
| No | 286 (54.6%) | 142 (52.8%) | 334 (61.6%) | 180 (65.9%) |
| NYHA CHF Class | | | | |
| No CHF | 286 (54.6%) | 144 (53.5% | 335 (61.8%) | 180 (65.9%) |
| Class I | 128 (24.4%) | 65 (24.2%) | 97 (17.9%) | 44 (16.1%) |
| Class II | 87 (16.6%) | 50 (18.6%) | 82 (15.1%) | 38 (13.9%) |
| Class III | 22 (4.2%) | 10 (3.7%) | 27 (5.0%) | 11 (4.0%) |
| Class IV | 1 (0.2%) | 0 (0.0%) | 1 (0.2%) | 0 (0.0%) |

* all randomized patients who received one dose of study drug;  + normal range: female, 10-291; male 22-322;  ++ transferrin saturation (TSAT) normal range:  20-55

# for geographic area in Study AFX01-14 numbers represent randomized patients

reviewer's table, based on data in sponsor's tables in study reports

Treatment groups were generally well-balanced for baseline demographic and other characteristics in both studies.  Dialysis parameters at baseline for the subjects were similar across all treatment arms in the studies.  About 98% of enrolled patients were receiving dialysis 3 times weekly.  Diabetes and hypertension were the two primary causes of chronic renal failure in both studies (in about 79% of patients in AFX01-12 and 60% of patients in AFX01-14).  'Other' causes of CRF included HIV nephropathy, complications of transplanted kidney, focal glomerulosclerosis, renal artery stenosis among other reasons.  Proportion of patients with CHF was somewhat greater in Study AFX01-12 than in AFX01-14; however, the prevalence was similar between treatment groups in both studies and more than three-fourths of patients in both studies had NYHA Class I or less CHF.

*Efficacy Results for Dialysis Studies (AFX01-12 and AFX01-14):*   Results of the primary efficacy analyses for each of these studies in patients on dialysis are shown in the following table.  The analysis population for the primary efficacy analysis was the "full analysis population" which consisted of all randomized patients who received at least one dose of study drug.  For both studies the results for the primary efficacy analysis of hemoglobin change from baseline to the evaluation period (Week 29 through 36) satisfied the sponsor's pre-specified criterion for non-inferiority of peginesatide to epoetin, which was that the lower limit of the 95% confidence interval (CI) for peginesatide injection mean minus epoetin mean was $\geq$-1.0g/dL.

**Dialysis Studies (AFX01-12 and AFX01-14):  Primary Efficacy Endpoint: Summary of Hgb and Change in Hgb from Baseline to the Evaluation Period (Full Analysis Population)**

**Study AFX01-12:**

| Hgb (g/dL) | Statistic | AF37702 Inj. IV Q4W (N=524) | Epoetin IV 1-3 Times per Week (N=269) | Total (N=793) |
|---|---|---|---|---|
| Baseline | 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 |
| Evaluation Period | N | 445 | 248 | 693 |
| | Mean (SD) | 11.06 (0.932) | 11.25 (0.846) | 11.13 (0.906) |
| | Median | 11.0 | 11.3 | 11.1 |
| | Q1 - Q3 | 10.4 - 11.6 | 10.8 - 11.8 | 10.5 - 11.7 |
| | Min - Max | 8.5 - 14.2 | 8.6 - 13.5 | 8.5 - 14.2 |

| Change from Baseline | N | 445 | 248 | 693 |
|---|---|---|---|---|
| | Mean (SD) | -0.24 (0.956) | -0.09 (0.922) | -0.19 (0.946) |
| | SE | 0.045 | 0.059 | 0.036 |
| | Median | -0.3 | -0.1 | -0.2 |
| | Q1 - Q3 | -0.9 - 0.4 | -0.6 - 0.5 | -0.8 - 0.4 |
| | Min - Max | -3.0 - 2.5 | -3.2 - 2.3 | -3.2 - 2.5 |
| Difference from Epoetin [1][2] | LS Mean (SE) | -0.15 (0.072) | | |
| | 2-Sided 95% CI | (-0.30, -0.01) | | |

[1] An ANOVA cell means model was used to estimate the mean Hgb change from baseline to the Evaluation Period.
[2] Difference from Epoetin = AF37702 Injection treatment group - Epoetin group.

**Study AFX01-14:**

| Hgb (g/dL) | 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 | 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 |
| Evaluation Period | N | 488 | 237 | 725 |
| | Mean (SD) | 11.13 (1.018) | 11.05 (0.958) | 11.10 (0.999) |
| | Median | 11.1 | 11.1 | 11.1 |
| | Q1 - Q3 | 10.5 - 11.8 | 10.6 - 11.7 | 10.5 - 11.8 |
| | Min – Max | 5.5 - 15.2 | 6.8 - 14.2 | 5.5 - 15.2 |
| Change from Baseline | N | 488 | 237 | 725 |
| | Mean (SD) | -0.07 (1.009) | -0.17 (1.000) | -0.10 (1.006) |
| | SE | 0.046 | 0.065 | 0.037 |
| | Median | -0.1 | -0.2 | -0.1 |
| | Q1 - Q3 | -0.8 - 0.6 | -0.8 - 0.5 | -0.8 - 0.6 |
| | Min – Max | -4.9 - 3.1 | -4.1 - 2.9 | -4.9 - 3.1 |
| Difference from Epoetin alfa/beta[1][2] | LS Mean (SE) | 0.10 (0.078) | | |
| | 2-Sided 95% CI | (-0.05, 0.26) | | |

[1] An ANOVA cell means model was used to estimate the mean Hgb change from Baseline to the Evaluation Period.
[2] Difference from Epoetin alfa/beta = AF37702 Injection treatment group - Epoetin alfa/beta group.

from sponsor's tables

Results of Per-Protocol population analyses were consistent with the primary efficacy analysis. A non-parametric analysis (generalized CMH procedure) also gave similar results to the ANOVA analysis. Six sites which enrolled a total of 71 patients were either closed due to poor documentation or had good clinical practice issues, and sensitivity analyses excluding efficacy data from these patients did not change the efficacy results. Sensitivity analyses evaluating the impact of red blood cell (RBC) transfusions and renal transplant on the study results did not change the study outcome. Sensitivity analyses using various methods of imputing values for missing data gave efficacy results consistent with the primary efficacy analysis. Analysis of the primary efficacy endpoint results by

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pre-specified average screening hemoglobin, NYHA CHF Class, age, geographic region, and route of administration did not reveal any impact of these factors on the overall results.  Results for evaluation by randomization stratification factors of mean screening hemoglobin and NYHA CHF Class and other factors are summarized in the following table:

**Dialysis Studies (AFX01-12 and AFX01-14):  Summary of Hgb and Change in Hgb from Baseline to the Evaluation Period for Pre-Specified Strata (Average Screening Hgb, NYHA CHF Class, Geographic Region) and Other Important Factors (Full Analysis Population)**

| | AFX01-12 | | AFX01-14 | |
|---|---|---|---|---|
| | Peginesatide IV Q4W (N=524) | Epoetin alfa IV 1-3 times per wk (N=269) | Peginesatide IV or SQ Q4W (N=542) | Epoetin alfa/beta IV or SQ 1-3 times per wk (N=273) |
| Average screening Hgb values ≤11.4 g/dL: | | | | |
| Baseline | | | | |
|   N | 302 | 154 | 352 | 180 |
|   Mean | 10.96 | 11.01 | 10.90 | 10.94 |
|   Median | 11.0 | 11.1 | 11.0 | 11.0 |
|   Range | 9.9-12.0 | 10.0 – 12.3 | 10.0-11.7 | 9.3 – 11.7 |
| Evaluation Period | | | | |
|   N | 257 | 139 | 317 | 156 |
|   Mean | 10.9 | 11.21 | 10.95 | 10.99 |
|   Median | 10.9 | 11.3 | 10.9 | 11.0 |
|   Range | 8.5-13.2 | 8.9 – 13.2 | 55-13.8 | 6.8 – 14.2 |
| Change from baseline | | | | |
|   N | 257 | 139 | 317 | 156 |
|   Mean | -0.06 | 0.18 | 0.05 | 0.05 |
|   Median | 0.0 | 0.2 | 0.0 | 0.079 |
|   Range | -3.0 – 2.5 | -2.2 – 2.3 | -4.9 – 3.0 | -3.7 – 2.9 |
| Average screening Hgb values ≥11.5 g/dL: | | | | |
| Baseline | | | | |
|   N | 222 | 115 | 190 | 115 |
|   Mean | 11.77 | 11.75 | 11.76 | 11.75 |
|   Median | 11.8 | 11.7 | 11.8 | 11.7 |
|   Range | 10.9-12.4 | 11.3 – 12.3 | 10.9-13.0 | 11.3 – 12.3 |
| Evaluation Period | | | | |
|   N | 188 | 109 | 171 | 109 |
|   Mean | 11.27 | 11.31 | 11.46 | 11.31 |
|   Median | 11.3 | 11.3 | 11.5 | 11.3 |
|   Range | 8.8 -14.2 | 8.6 – 13.5 | 8.3 -15.2 | 8.6 – 13.5 |
| Change from baseline | | | | |
|   N | 188 | 109 | 171 | 109 |
|   Mean | -0.49 | 0.081 | -0.30 | 0.081 |
|   Median | -0.5 | -0.4 | -0.3 | -0.4 |
|   Range | -2.7 – 2.5 | -3.2 – 2.1 | -3.5 – 3.1 | -3.2 – 2.1 |
| NYHA CHF Class 0-I: | | | | |
| Baseline | | | | |
|   N | 426 | 217 | 438 | 217 |
|   Mean | 11.30 | 11.30 | 11.22 | 11.30 |
|   Median | 11.4 | 11.4 | 11.3 | 11.4 |
|   Range | 9.9-12.4 | 10.0 – 12.3 | 10.0 – 13.0 | 10.0 – 12.3 |
| Evaluation Period | | | | |

| | | | | |
|---|---|---|---|---|
| N | 363 | 198 | 393 | 198 |
| Mean | 11.11 | 11.23 | 11.19 | 11.23 |
| Median | 11.1 | 11.3 | 11.2 | 11.3 |
| Range | 8.5-14.2 | 8.8 – 13.5 | 7.9 – 15.2 | 8.8 – 13.5 |
| Change from baseline | | | | |
| N | 363 | 198 | 393 | 198 |
| Mean | -0.18 | -0.08 | -0.02 | -0.08 |
| Median | -0.2 | -0.1 | -0.0 | -0.1 |
| Range | -3.0 – 2.5 | -3.0 – 2.3 | -3.5 – 3.1 | -3.0 – 2.3 |
| NYHA CHF Class II-IV: | | | | |
| Baseline | | | | |
| N | 98 | 52 | 104 | 50 |
| Mean | 11.32 | 11.42 | 11.13 | 11.12 |
| Median | 11.5 | 11.5 | 11.2 | 11.2 |
| Range | 10.0 - 12 .2 | 10.2 – 12.3 | 10.0 - 12 .2 | 9.9 – 12.2 |
| Evaluation Period | | | | |
| N | 82 | 50 | 95 | 39 |
| Mean | 10.81 | 11.31 | 10.87 | 10.98 |
| Median | 10.9 | 11.5 | 10.8 | 11.0 |
| Range | 8.8-12.9 | 8.6 – 13.5 | 5.5-13.5 | 8.9 – 13.4 |
| Change from baseline | | | | |
| N | 82 | 50 | 95 | 39 |
| Mean | -0.51 | -0.14 | -0.27 | -0.13 |
| Median | -0.5 | -0.2 | -0.4 | 0.0 |
| Range | -2.7 – 1.3 | -3.2 – 1.9 | -4.9 – 1.9 | -2.1 – 2.8 |
| Geographic Region= U.S.: | | | | |
| Baseline | Same as total | Same as total | | |
| N | | | 329 | 167 |
| Mean | | | 11.26 | 11.31 |
| Median | | | 11.4 | 11.4 |
| Range | | | 10.0 – 12.5 | 9.8 – 12.2 |
| Evaluation Period | Same as total | Same as total | | |
| N | | | 287 | 147 |
| Mean | | | 11.12 | 11.18 |
| Median | | | 11.1 | 11.3 |
| Range | | | 5.5 – 15.2 | 7.5 – 13.4 |
| Change from baseline | Same as total | Same as total | | |
| N | | | 287 | 147 |
| Mean | | | -0.15 | -0.15 |
| Median | | | -0.1 | -0.2 |
| Range | | | -4.9 – 3.1 | -4.1 – 2.8 |
| Geographic Region = non-U.S. [EU]: | | | | |
| Baseline | NA | NA | | |
| N | | | 213 | 106 |
| Mean | | | 11.11 | 11.06 |
| Median | | | 11.1 | 11.1 |
| Range | | | 10.0 – 13.02 | 9.3 – 12.2 |
| Evaluation Period | NA | NA | | |
| N | | | 201 | 90 |
| Mean | | | 11.15 | 10.84 |
| Median | | | 11.1 | 10.9 |
| Range | | | 8.3-14.1 | 6.8 – 14.2 |
| Change from baseline | NA | NA | | |
| N | | | 201 | 90 |
| Mean | | | -0.04 | -0.20 |

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| | | | | |
|---|---|---|---|---|
| Median | | | 0.0 | -0.1 |
| Range | | | -3.5 – 2.5 | -3.7 – 2.9 |
| **Route of Administration=IV:** | | | | |
| Baseline | Same as total | Same as total | | |
| N | | | 434 | 219 |
| Mean | | | 11.21 | 11.23 |
| Median | | | 11.3 | 11.3 |
| Range | | | 10.0 – 13.0 | 9.3 – 12.2 |
| Evaluation Period | Same as total | Same as total | | |
| N | | | 390 | 195 |
| Mean | | | 11.15 | 11.07 |
| Median | | | 11.2 | 11.1 |
| Range | | | 5.5 – 15.2 | 6.8 – 14.2 |
| Change from baseline | Same as total | Same as total | | |
| N | | | 390 | 195 |
| Mean | | | -0.07 | -0.16 |
| Median | | | -0.1 | -0.1 |
| Range | | | -4.9 – 3.1 | -4.1 – 2.9 |
| **Route of Administration=SC:** | | | | |
| Baseline | NA | NA | | |
| N | | | 108 | 167 |
| Mean | | | 11.16 | 11.31 |
| Median | | | 11.2 | 11.4 |
| Range | | | 10.0 – 12.2 | 9.8 – 12.2 |
| Evaluation Period | NA | NA | | |
| N | | | 98 | 147 |
| Mean | | | 11.06 | 11.18 |
| Median | | | 11.1 | 11.3 |
| Range | | | 8.3 – 13.0 | 7.5 – 13.4 |
| Change from baseline | NA | NA | | |
| N | | | 98 | 42 |
| Mean | | | -0.10 | -0.22 |
| Median | | | -0.1 | -0.2 |
| Range | | | -3.5 – 2.4 | -2.1 – 1.1 |

from data in sponsor's tables

Results for some of these factors are displayed graphically in the following sponsor's figures:

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**Study AFX01-12:**

Figure 3: Primary Efficacy Endpoint Summarized by Randomization Stratification Factors (Full Analysis Population)



A= AF37702 Injection Q4W IV
B= Epoetin alfa 1–3 times per week IV
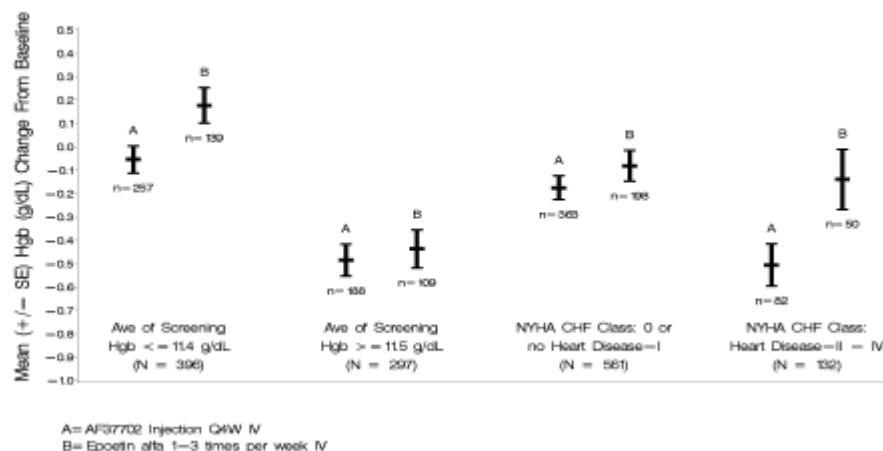
**Study AFX01-14:**

Figure 3: Primary Efficacy Endpoint Summarized by Randomization Stratification Factors (Full Analysis Population)



A= AF37702 Injection Q4W IV or SC
B= Epoetin alfa/beta 1–3 times per week IV or SC
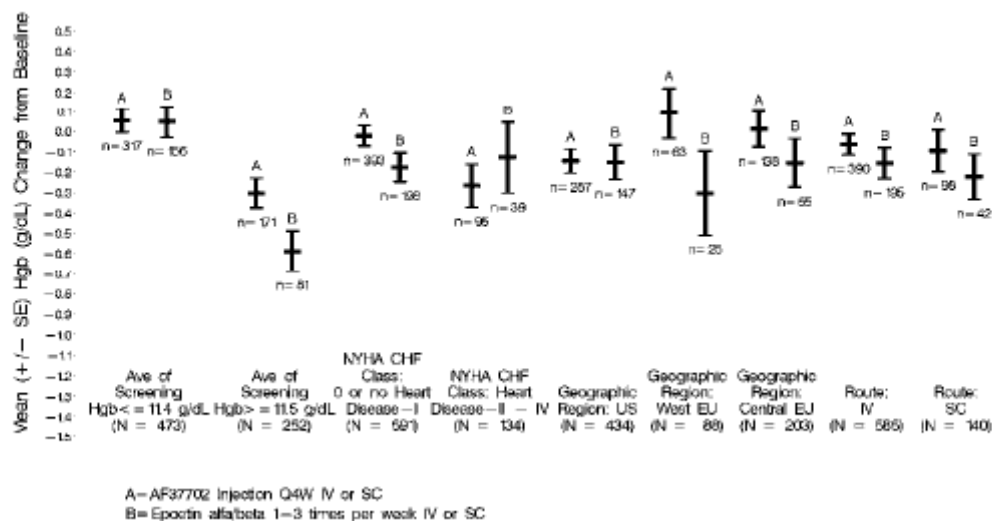
Post-hoc subgroup analyses for study subgroups (post-hoc) based on age, gender, race, and ethnicity also gave results similar to those for the primary efficacy analysis.

Secondary efficacy analyses evaluated the proportion of patients receiving transfusions (RBC or whole blood) during the study, proportion of patients whose mean hemoglobin level during the evaluation period was within the target range (10.0-12.0 g/dL) and other endpoints. These are summarized in the following table:

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**Dialysis Studies (AFX01-12 and AFX01-14):  Patients Receiving RBC Transfusions During Study and Proportion of Patients Achieving Hemoglobin Response (Full Analysis Population)**

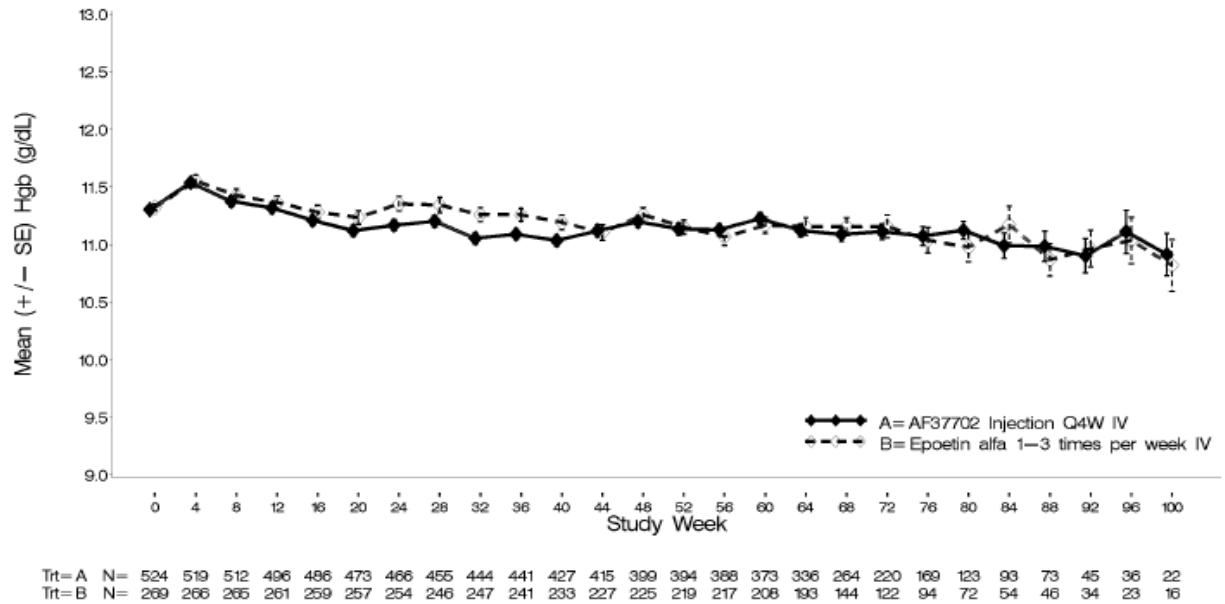| | AFX01-12 | | AFX01-14 | |
|---|---|---|---|---|
| | Peginesatide IV Q4W (N=524) | Epoetin alfa IV 1-3 times per wk (N=269) | Peginesatide IV or SQ Q4W (N=542) | Epoetin alfa/beta IV or SQ 1-3 times per wk (N=273) |
| Patients who received ≥1 transfusion during the titration and/or evaluation periods, N (%) | 54/524 (10.3%) | 23/269 (8.6%) | 42/542 (7.7%) | 27/273 (9.9%) |
| Patients who received ≥1 transfusion during the titration period, N (%) | 45/524 (8.6%) | 19/269 (7.1%) | 35/542 (6.5%) | 20/273 (7.3%) |
| Patients who received ≥1 transfusion during the evaluation period, N (%) | 9/468 (1.9%) | 5/252 (2.0%) | 14/500 (2.8%) | 10/244 (4.1%) |
| Patients whose mean Hgb during evaluation period is within target range of 10.0-12.0 g/dL, N (%) | 330/524 (63.0%) | 193/269 (71.7%) | 344/542 (63.5%) | 180/273 (65.9%) |

Based on data in sponsor's tables

During any 4-week interval, among patients who entered that period on treatment approximately 60 to 75% of patients maintained Hgb with the target range of 10.0-12.0 g/dL, and in general, a greater proportion of patients in the epoetin groups were within the target range compared to the peginesatide group in Study AFX01-12 while the proportions were similar between groups in AFX01-14.

The mean hemoglobin values over time on study drug in these two studies are displayed in the following two sponsor's figures:

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## Study AFT01-12:

**Figure 4:** Mean (± SE) Hemoglobin Values over Time, By 4-Week Intervals (Full Analysis Population)
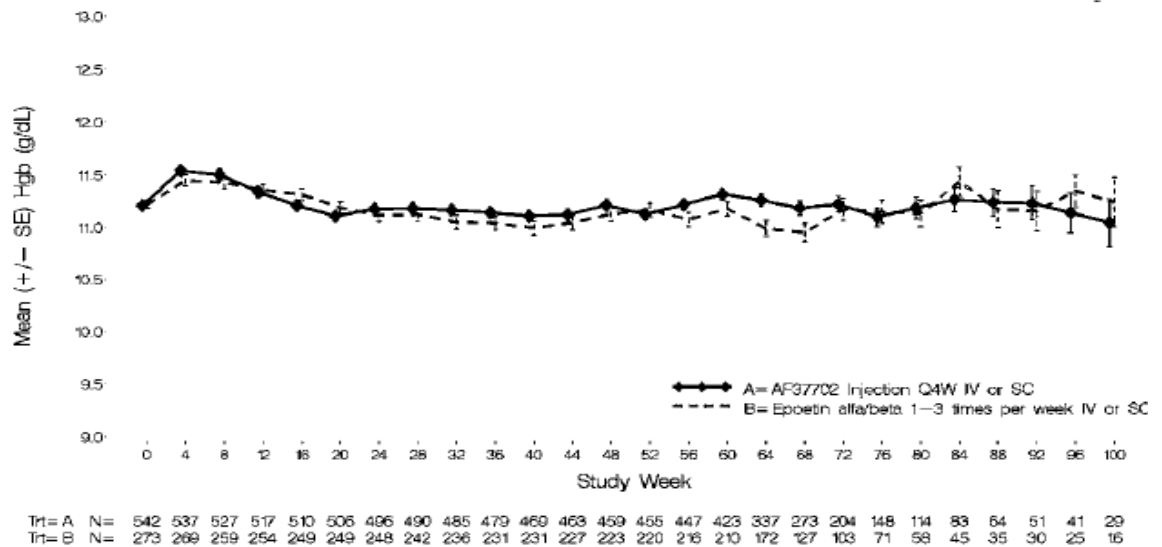


## AFX01-14:

**Figure 4:** Mean (± SE) Hemoglobin Values over Time, by 4-Week Intervals (Full Analysis Population)

Hemoglobin levels were similar between the treatment arms during the study. After an initial slight hemoglobin increase (about 0.2-0.3 g/dL) over the first 4 weeks of treatment, the hemoglobin values in both treatment arms in both studies stabilized with very little change over the duration of the study.

Most patients in both studies received one or more doses of iron supplementation during the study. In In the AFX01-12 study 467/524 (89.1%) of peginesatide-treated patients and 250/269 (92.9%) of epoetin-treated patients received iron supplementation. In the AFX01-14 study 491/542 (90.6%) of peginesatide-treated patients and 245/273 (89.7%) of epoetin-treated patients received iron supplementation. In both studies virtually all of these received one or more doses of IV iron during the study. Iron supplementation by route of iron administration is summarized in the following table.

**Dialysis Studies (AFX01-12 and AFX01-14): Patients Receiving Iron Supplementation (Full Analysis Population)**

| | AFX01-12 | | AFX01-14 | |
|---|---|---|---|---|
| | Peginesatide IV Q4W (N=524) | Epoetin alfa IV 1-3 times per wk (N=269) | Peginesatide IV or SQ Q4W (N=542) | Epoetin alfa/beta IV or SQ 1-3 times per wk (N=273) |
| Patients receiving one or more doses of iron during Screening, N (%): | | | | |
| Total | 288 (55.0%) | 146 (54.3%) | 337 (62.2%) | 177 (64.8%) |
|   Oral | 20 (3.8%) | 10 (3.7%) | 13 (2.4%) | 5 (1.8%) |
|   IV | 273 (52.1%) | 139 (51.7%) | 331 (61.1%) | 174 (63.7%) |
|   Other | 1 (0.2%) | 1 (0.4%) | 0 (0.0%) | 0 (0.0%) |
| Patients receiving one or more doses of iron during Study, N (%): | | | | |
| Total | 467 (89.1%) | 250 (92.9%) | 491 (90.6%) | 245 (89.7%) |
|   Oral | 29 (5.5%) | 16 (5.9%) | 24 (4.4%) | 12 (4.4%) |
|   IV | 464 (88.5%) | 248 (92.2%) | 489 (90.2%) | 245 (89.7%) |
|   Other | 1 (0.2%) | 1 (0.4%) | 0 (0.0%) | 1 (0.4%) |

Based on data in sponsor's tables

*Safety Results for Dialysis Studies (AFX01-12 and AFX01-14):*
A major objective of these studies was to evaluate the safety of peginesatide with regard to cardiovascular safety. This safety concern results from safety data that have accrued mainly from several large published studies (CHOIR, CREATE, Normal Hematocrit and TREAT Studies) of marketed ESAs over the past decade. Major features, results and references for these studies are summarized in the Discussion section of this review.

In the studies in patients on dialysis a total of 1066 patients were treated with peginesatide (524 in AFX01-12 and 542 in AFX01-14) and 542 patients were treated with epoetin (269 in AFX01-12 and 273 in AFX01-14). The following table summarizes the dosing of study drug during the dialysis studies:

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**Dialysis Studies (AFX01-12 and AFX01-14): Summary of Study Drug Dose During the Study (Full Analysis Population)**

| | AFX01-12 | | AFX01-14 | |
|---|---|---|---|---|
| | Peginesatide IV Q4W (N=524) | Epoetin alfa IV 1-3 times per wk (N=269) | Peginesatide IV or SQ Q4W (N=542) | Epoetin alfa/beta IV or SQ 1-3 times per wk (N=273) |
| Units for dose | mg | U per week | mg | U per week |
| First dose | | | | |
| N | 524 | 268 | 542 | 269 |
| Mean | 6.84 | 15581.1 | 5.61 | 10963.0 |
| Median | 5.9 | 10500 | 4.6 | 6600 |
| Range | 1.8 – 22.4 | 600 - 84000 | 1.7 -20.8 | 600 - 88000 |
| Last dose during titration | | | | |
| N | 524 | 268 | 542 | 269 |
| Mean | 8.00 | 15035.1 | 6.53 | 10247.4 |
| Median | 5.6 | 9000 | 4.7 | 6000 |
| Range | 0.5 - 81.0 | 200 - 90000 | 0.6 – 69.0 | 380 -102000 |
| Mean dose during evaluation period | | | | |
| N | 435 | 243 | 481 | 234 |
| Mean | 8.31 | 15045.7 | 7.02 | 10270.9 |
| Median | 5.7 | 9900 | 4.8 | 68059 |
| Range | 0.4 – 101.0 | 300 - 90000 | 0.4 – 97.0 | 210 -83783 |

Based on data in sponsor's tables

The mean mean weekly weight-based epoetin dose during the evaluation period in the studies was 182.6 U/kg per week (median, 125 U/kg per week) in Study AFX01-12 and 134.6 U/kg per week (median, 91 U/kg per week) in Study AFX01-14, which was somewhat less than the doses in the labeled studies for Epogen in dialysis patients (mean, 225 U/kg per week). The mean duration of exposure to study drug was 59.71 weeks in the peginesatide group and 65.16 weeks in the epoetin group in Study AFX01-12 and 61.29 weeks in the peginesatide group and 60.50 weeks in the epoetin group in AFX01-14 with 80.7% of patients in the peginesatide group and 87.4% of patients in the epoetin group in AFX01-12 and 86.5% of patients in the peginesatide group and 83.9% of patients in the epoetin group in AFX01-14 receiving study drug through the evaluation period.

In Study AFX01-12 the mean duration of treatment exposure was 59.71 weeks (median, 64.0 wks; range, 2.0-116.0 wks) in the peginesatide group and 65.16 weeks (median, 67.0; range 0.7-116.4 wks) in the epoetin group. In Study AFX01-14 the mean duration of treatment exposure was 61.29 weeks (median, 64.0 wks; range, 1.9-109.0 wks) in the peginesatide group and 60.50 weeks (median, 62.9; range 0.4-107.1 wks) in the epoetin group. In Study AFX01-14 the average patient treatment exposure in Europe (1.05 patient exposure years (PEY)/patient) was lower than in the U.S. (1.25 PEY/patient), due in part to later study start in Europe.

The following tables summarize the occurrence of adverse events during each of the studies.

## Study AFX01-12:

**Table 24:     Summary of Adverse Events**

| | AF37702 Injection N = 524 | Epoetin N = 269 | Source Table |
|---|---|---|---|
| Total number of TEAEs | 6255 | 3551 | 14.3.5 |
| Number of patients reporting at least one TEAE | 511 (97.5%) | 257 (95.5%) | |
| Total number of Grade 3, 4, or 5 TEAEs | 1082 | 620 | 14.3.8.2 |
| Number of patients with at least one Grade 3, 4, or 5 TEAE | 291 (55.5%) | 158 (58.7%) | |
| Total number of study drug-related TEAEs | 65 | 8 | 14.3.9 |
| Number of patients with at least one study drug-related TEAE | 44 (8.4%) | 8 (3.0%) | |
| Total number of TESAEs | 1100 | 642 | 14.3.10 |
| Number of patients with at least one TESAE | 304 (58.0%) | 168 (62.5%) | |
| Number of patients who died through 28 days after study termination (On-Study) | 58 (11.1%) | 30 (11.2%) | 14.3.11 |
| Total number of TEAEs leading to discontinuation | 97 | 33 | 14.3.7 |
| Number of patients reporting at least one TEAE leading to treatment discontinuation | 78 (14.9%) | 31 (11.5%) | |
| Total number of patients with at least one CSE event | 128 (24.4%) | 68 (25.3%) | See CSE report |

Sponsor's table

## Study AFX01-14:

**Table 28:     Summary of Adverse Events**

| | AF37702 Injection N=542 | Epoetin N=273 | Source Table |
|---|---|---|---|
| Total number of TEAEs | 6889 | 3557 | 14.3.5 |
| No. of patients reporting ≥1 TEAE | 497 (91.7%) | 247 (90.5%) | |
| Total number of Grade 3, 4, or 5 TEAEs | 879 | 532 | 14.3.8.2 |
| No. of patients with ≥1 Grade 3, 4, or 5 TEAE | 258 (47.6%) | 128 (46.9%) | |
| Total number of study drug-related TEAEs | 46 | 21 | 14.3.9 |
| No. of patients with ≥1 study drug-related TEAE | 38 (7.0%) | 13 (4.8%) | |
| Total number of TESAEs | 834 | 452 | 14.3.10 |
| No. of patients with any TESAE | 268 (49.4%) | 141 (51.6%) | |
| No. of patients who died through 28 days after study termination (On-Study) | 57 (10.5%) | 34 (12.5%) | 14.3.11 |
| Total number of TEAEs leading to treatment discontinuation | 60 | 37 | 14.3.7 |
| No. of patients reporting any TEAE leading to treatment discontinuation | 58 (10.7%) | 34 (12.5%) | |
| Total number of patients with ≥1 CSE event | 115 (21.2%) | 64 (23.4%) | CSE Technical Report Table 4.1 |

Sponsor's table

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The vast majority of patients in both studies had one or more treatment-emergent adverse events (TEAE) with a slightly greater percentage of TEAE leading to discontinuation of study drug in the peginesatide arm than in the epoetin arm in Study AFX01-12, and a slightly greater percentage of these events leading to study drug discontinuation in the epoetin arm than in the peginesatide arm in Study AFX01-14. Approximately half of patients in Study AFX01-14 (50.2%) and somewhat more patients in Study AFX01-12 (59.5%) had serious treatment-emergent adverse events (TESAE).

The most common serious TEAE events (TESAES) in Studies AFX01-12 and AFX01-14 are summarized in the following table.

**Dialysis Studies (AFX01-12 and AFX01-14): Most Common\* Treatment-Emergent Serious Adverse Events Terms, [Number (%) of Patients] (Safety Population)**

| | AFX01-12 | | AFX01-14 | |
|---|---|---|---|---|
| | Peginesatide IV Q4W (N=524) | Epoetin alfa IV 1-3 times per wk (N=269) | Peginesatide IV or SQ Q4W (N=542) | Epoetin alfa/beta IV or SQ 1-3 times per wk (N=273) |
| Any TESAE | 304 (58.0%) | 168 (62.5%) | 268 (49.4%) | 141 (51.6%) |
| | | | | |
| Cardiac failure congestive | 37 (7.1%) | 20 (7.4%) | 24 (4.4%) | 17 (6.2%) |
| Atrial fibrillation | 15 (2.9%) | 6 (2.2%) | 8 (1.5%) | 8 (2.9%) |
| Myocardial infarction | 13 (2.5%) | 9 (3.3%) | 10 (1.8%) | 4 (1.5%) |
| Acute myocardial infarction | 19 (3.6%) | 9 (3.3%) | 11 (2.0%) | 9 (3.3%) |
| Cardiac arrest | 16 (3.1%) | 5 (1.9%) | 8 (1.5%) | 9 (3.3%) |
| Coronary artery disease | 16 (3.1%) | 5 (1.9%) | 8 (1.5%) | 7 (2.6%) |
| Angina pectoris | 12 (2.3%) | 7 (2.6%) | 7 (1.3%) | 2 (0.7%) |
| Cardio-respiratory arrest | 11 (2.1%) | 4 (1.5%) | 4 (0.7%) | 3 (1.1%) |
| Gastrointestinal hemorrhage | 9 (1.7%) | 5 (1.9%) | 9 (1.7%) | 4 (1.5%) |
| Non-cardiac chest pain | 13 (2.5%) | 8 (3.0%) | 10 (1.8%) | 4 (1.5%) |
| Chest pain | 14 (2.7%) | 4 (1.5%) | 8 (1.5%) | 5 (1.8%) |
| Pneumonia | 37 (7.1%) | 19 (7.1%) | 31 (5.7%) | 12 (4.4%) |
| Urinary tract infection | 11 (2.1%) | 2 (0.7%) | 7 (1.3%) | 1 (0.4%) |
| Cellulitis | 15 (2.9%) | 10 (3.7%) | 19 (3.5%) | 5 (1.8%) |
| Sepsis | 15 (2.9%) | 13 (4.8%) | 20 (3.7%) | 13 (4.8%) |
| Gangrene | 8 (1.5%) | 5 (1.9%) | 4 (0.7%) | 2 (0.7%) |
| Gastroenteritis | 8 (1.5%) | 5 (1.9%) | 6 (1.1%) | 4 (1.5%) |
| Staphylococcal bacteremia | 6 (1.1%) | 7 (2.6%) | 2 (0.4%) | 1 (0.4%) |
| Arteriovenous graft thrombosis | 6 (1.1%) | 8 (3.0%) | 3 (0.6%) | 3 (1.1%) |
| Arteriovenous fistula thrombosis | 6 (1.1%) | 5 (1.9%) | 10 (1.8%) | 6 (2.2%) |
| Fluid overload | 21 (4.0%) | 18 (6.7%) | 20 (3.7%) | 9 (3.3%) |
| Hyperkalemia | 24 (4.6%) | 15 (5.6%) | 25 (4.6%) | 8 (2.9%) |
| Hypoglycemia | 8 (1.5%) | 7 (2.6%) | 8 (1.5%) | 6 (2.2%) |
| Cerebrovascular accident | 8 (1.5%) | 8 (3.0%) | 11 (2.0%) | 4 (1.5%) |
| Syncope | 6 (1.1%) | 8 (3.0%) | 5 (0.9%) | 2 (0.7%) |
| Convulsion | 12 (2.3%) | 1 (0.4%) | 3 (0.6%) | 3 (1.1%) |
| Mental status changes | 8 (1.5%) | 8 (3.0%) | 5 (0.9%) | 3 (1.1%) |
| Respiratory failure | 16 (3.1%) | 5 (1.9%) | 16 (3.0%) | 7 (2.6%) |
| Pulmonary edema | 15 (2.9%) | 5 (1.9%) | 8 (1.5%) | 9 (3.3%) |
| Chronic obstructive pulmonary disease | 8 (1.5%) | 6 (2.2%) | 3 (0.6%) | 3 (1.1%) |

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| | | | | |
|---|---|---|---|---|
| Dyspnea | 10 (1.9%) | 4 (1.5%) | 1 (0.2%) | 0 (0.0%) |
| Hypotension | 19 (3.6%) | 7 (2.6%) | 11 (2.0%) | 3 (1.1%) |
| Hypertension | 12 (2.3%) | 5 (1.9%) | 3 (0.6%) | 3 (1.1%) |
| Hypertensive crisis | 7 (1.3%) | 7 (2.6%) | 8 (1.5%) | 4 (1.5%) |

Events occurring in 1.5% or more of patients in either study

Data from sponsor's tables

For most TESAE events the rates of occurrence were similar or numerically slightly lower in the peginesatide treatment group.

In both studies the System Organ Class (SOC) contributing most TESAE were 'Infestions and Infestations' and 'Cardiac Disorders' terms followed by others as shown in the table below:

**Dialysis Studies (AFX01-12 and AFX01-14): System Organ Classes with Most Treatment-Emergent Serious Adverse Events * [Number and % of Patients] (Safety Population)**

| | AFX01-12 | | AFX01-14 | |
|---|---|---|---|---|
| | Peginesatide IV Q4W (N=524) | Epoetin alfa IV 1-3 times per wk (N=269) | Peginesatide IV or SQ Q4W (N=542) | Epoetin alfa/beta IV or SQ 1-3 times per wk (N=273) |
| Any TESAE | 304 (58.0%) | 168 (62.5%) | 268 (49.4%) | 141 (51.6%) |
| | | | | |
| Infections and infestations[a] | 123 (23.5%) | 87 (32.3%) | 111 (20.5%) | 64 (23.4%) |
| Cardiac disorders | 114 (21.8%) | 57 (21.2%) | 85 (15.7%) | 56 (20.5%) |
| metabolism and nutrition disorders[b] | 72 (13.7%) | 45 (16.7%) | 57 (10.5%) | 26 (9.5%) |
| respiratory/thoracic/mediastinal disorders | 72 (13.7%) | 28 (10.4%) | 48 (8.9%) | 29 (10.6%) |
| Injury, poisoning and procedural complications | 56 (10.7%) | 36 (13.4%) | 63 (11.6%) | 28 (10.3%) |
| Gastrointestinal disorders | 58 (11.1%) | 33 (12.3%) | 46 (8.5%) | 20 (7.3%) |
| vascular | 54 (10.3%) | 30 (11.2%) | 47 (8.7%) | 16 (5.9%) |
| Nervous system disorders | 53 (10.1%) | 29 (10.8%) | 40 (7.4%) | 21 (7.7%) |
| General disorders and administration site conditions | 42 (8.0%) | 22 (8.2%) | 30 (5.5%) | 23 (8.4%) |

[a] mostly pneumonia, cellulitis and sepsis; [b] mostly fluid overload and hyperkalemia;
* Includes only System Organ Classes having 4% or more of patients with TESAE in either study

Data from sponsor's tables

In Study AFX01-12, 26.3% of peginesatide-treated patients and 32.0% of epoetin-treated patients had thromboembolic events. In Study AFX01-14 28.6% of peginesatide-treated patients and 30.0% of epoetin-treated patients had thromboembolic events. There was one TESAE of thrombocytopenia and one serious case of pancytopenia which occurred in patients in the peginesatide treatment arm in Study AFX01-14. In Study AFX01-12 six patients exposed to peginesatide developed binding antibodies to the drug (4 binding only; 2 neutralizing). Both patients with neutralizing antibodies also showed declining hemoglobin levels despite continued or increased peginesatide. In study AFX01-14 six patients treated with peginesatide developed binding antibodies to the drug that were also neutralizing (one in a patient for whom antibody testing had been requested due to lack of response), but none of

the six developed antibodies to endogenous erythropoietin. There were no instances of allergic or anaphylactic reactions temporally related to peginesatide administration.

In these studies the major safety endpoint was composite safety event (CSE) comprised of death [all causes], stroke, myocardial infarction, and serious events of congestive heart failure, unstable angina and arrhythmia. All events were adjudicated. The analysis results for the CSE and subcategories are shown in the following tables.

**Study AFX01-12: Summary of Composite Safety Endpoint Events: On-Study**

| Composite Safety Endpoint Events | Statistic | AF37702 Inj. IV Q4W (N=524) | Epoetin alfa IV 1-3 Times per Week (N=269) | Total (N=793) |
|---|---|---|---|---|
| Time to First Event (Days)[1] | | | | |
| | Num Events | 128 | 68 | 196 |
| | Num Censored | 396 | 201 | 597 |
| | Median | NE | NE | NE |
| | (95% CI) | NE- NE | NE- NE | NE- NE |
| | Q1 - Q3 | 504.0- NE | 500.0- NE | 500.0- NE |
| | | | | |
| Hazard Ratio [2] Relative to Epoetin alfa | | | | |
| | HR | 1.0122 | | |
| | 90% CI | (0.7905, 1.2962) | | |
| | | | | |
| Chi-Square Test for Time to First Event Between Treatment Groups [3] | | | | |
| | p-value | | | 0.9355 |

[1] Kaplan-Meier method. Time to First Event =Date of First Composite Safety Endpoint Event - Date of Randomization + 1.
Num Censored= No. of patients who did not have composite safety endpoint events during the study.
[2] Parameter estimates were obtained from the Cox proportional hazards model stratified for treatment group and the randomization stratification factors.
[3] Chi-Square Test (as produced by the Cox regression model) compared hazard ratio for the treatment groups, stratified by the randomization stratification factors.
Note: Deaths that occurred through 28 days post study termination were included in the analysis.
NE = Not Estimable

| Composite Safety Endpoint Events | Statistic | AF37702 Inj. IV Q4W (N=524) | Epoetin alfa IV 1-3 Times per Week (N=269) | Total (N=793) |
|---|---|---|---|---|
| No. of Patients with >= 1 ERC Adjudicated Composite Safety Endpoint Events | | | | |
| | N (%) | 128 (24.4) | 68 (25.3) | 196 (24.7) |
| No. of Patients with Following ERC Adjudicated Events*: | | | | |
| Death (All Causes) | N (%) | 58 (11.1) | 30 (11.2) | 88 (11.1) |
| Stroke | N (%) | 12 (2.3) | 12 (4.5) | 24 (3.0) |
| MI | N (%) | 25 (4.8) | 16 (5.9) | 41 (5.2) |
| Unstable Angina | N (%) | 14 (2.7) | 7 (2.6) | 21 (2.6) |
| CHF | N (%) | 59 (11.3) | 26 (9.7) | 85 (10.7) |
| Arrhythmia | N (%) | 36 (6.9) | 18 (6.7) | 54 (6.8) |

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**Study AFX01-14:  Summary of Composite Safety Endpoint Events:  On-Study**

| Composite Safety Endpoint Events | 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) |
|---|---|---|---|---|
| Time to First Event (Days) [1] | | | | |
| | Num Events | 115 | 64 | 179 |
| | Num Censored | 427 | 209 | 636 |
| | Median | NE | NE | NE |
| | (95% CI) | NE- NE | NE- NE | NE- NE |
| | Q1 - Q3 | 557.0- NE | 508.0- NE | 532.0- NE |
| Hazard Ratio [2] Relative to Epoetin alfa | | | | |
| | HR | 0.8856 | | |
| | 90% CI | (0.6851, 1.1446) | | |
| Chi-Square Test for Time to First Event Between Treatment Groups [3] | | | | |
| | p-value | | | 0.4359 |

[1] Kaplan-Meier method. Time to First Event =Date of First Composite Safety Endpoint Event - Date of Randomization + 1.
Num Censored= No. of patients who did not have composite safety endpoint events during the study.
[2] Parameter estimates were obtained from the Cox proportional hazards model stratified for treatment group and the randomization stratification factors.
[3] Chi-Square Test (as produced by the Cox regression model) compared hazard ratio for the treatment groups, stratified by the randomization stratification factors.
Note: Deaths that occurred through 28 days post study termination were included in the analysis.
NE = Not Estimable

| Composite Safety Endpoint Events | 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 with >= 1 ERC Adjudicated Composite Safety Endpoint Events | | | | |
| | N (%) | 115 (21.2) | 64 (23.4) | 179 (22.0) |
| No. of Patients with Following ERC Adjudicated Events*: | | | | |
| Death (All Causes) | N (%) | 57 (10.5) | 34 (12.5) | 91 (11.2) |
| Stroke | N (%) | 14 (2.6) | 8 (2.9) | 22 (2.7) |
| MI | N (%) | 24 (4.4) | 13 (4.8) | 37 (4.5) |
| Unstable Angina | N (%) | 10 (1.8) | 5 (1.8) | 15 (1.8) |
| CHF | N (%) | 44 (8.1) | 23 (8.4) | 67 (8.2) |
| Arrhythmia | N (%) | 27 (5.0) | 17 (6.2) | 44 (5.4) |

From sponsor's tables

In both studies the occurrences of the CSE and its component events during the entire study were similar in the two treatment groups in both studies and death was the most frequent of the component events occurring in approximately half of patients experiencing CSE events recorded in the study.  The time to first CSE event analysis did not suggest an increased risk for patients in the peginesatide group as compared to the epoetin group in either study.

For the dialysis studies, in terms of total deaths in the study database, the percentages of patients who died were similar in the peginesatide and epoetin treatment arms and across studies.  The following table summarizes deaths during the studies.

**Dialysis Studies (AFX01-12 and AFX01-14):  Deaths (Safety Population)**

| | AFX01-12 | | AFX01-14 | |
|---|---|---|---|---|
| | Peginesatide IV Q4W (N=524) | Epoetin alfa IV 1-3 times per wk (N=269) | Peginesatide IV or SQ Q4W (N=542) | Epoetin alfa/beta IV or SQ 1-3 times per wk (N=273) |
| Total Deaths in study database | 65 (12.4%) | 34 (12.6%) | 71 (13.1%) | 34 (12.5%) |
| Total Deaths During Study (through 28 days after study termination)[a] | 58 (11.1%) | 30 (11.2%) | 57 (10.5%) | 34 (12.5%) |
| MI | 5 (1.0%) | 2 (0.7%) | 5 (0.9%) | 1 (0.4%) |
| Stroke | 2 (0.4%) | 1 (0.4%) | 4 (0.7%) | 5 (1.8%) |
| CHF | 1 (0.2%) | 0 (0.0%) | 2 (0.4%) | 2 (0.7%) |
| Arrhythmia | 2 (0.4%) | 1 (0.4% | 3 (0.6%) | 2 (0.7%) |
| Infection | 9 (1.7%) | 6 (2.2%) | 9 (1.7%) | 5 (1.8%) |
| Cardiac arrest | 11 (2.1%) | 3 (1.1%) | 5 (0.9%) | 8 (2.9%) |
| Cardiorespiratory arrest | 6 (1.1%) | 3 (1.1%) | 2 (0.4%) | 1 (0.4%) |
| CRF | 5 (1.0%) | 1 (0.2%) | 2 (0.4%) | 0 (0.0%) |
| Respiratory failure/acute respiratory failure | 4 (0.8%) | 0 (0.0%) | 4 (0.8%) | 0 (0.0%) |
| Cancer | 1 (0.4%) | 1 (0.4%) | 3 (0.6%) | 1 (0.4%) |
| Sudden death | 2 (0.4%) | 0 (0.0%) | 2 (0.4%) | 0 (0.0%) |
| Unknown | 0 (0.0%) | 0 (0.0%) | 1 (0.2%) | 0 (0.0%) |
| Timing of deaths during study[b] | | | | |
| During titration period | 17/524 (3.2%) | 7/269 (2.6%) | 4/542 (0.7%) | 5/273 (1.8%) |
| During evaluation period | 1/468 (0.2%) | 7/252 (2.8%) | 5/500 (1.0%) | 1/244 (0.4%) |
| During long-term safety eval | 37/458 (8.1%) | 15/240 (6.3%) | 34/490 (6.9%) | 14/239 (5.9%) |

[a]includes deaths occurring during followup after study drug discontinuation; includes information from Death Report forms; causes listed do not include all primary causes of death, only most frequent and most relevant
[b] through 28 days after study drug discontinuation, excluding patients who were started on another ESA or who had renal transplant
Based on data in sponsor's tables

Generally, death rates and causes were similar between treatment arms and across studies in the dialysis studies.  Considering the numbers for total deaths in the database and deaths during the study (up to 28 days after study drug discontinuation) in each treatment arm, 80% to 100% of deaths in the database for both studies occurred during the study (including followup).  In both studies, for both treatment arms most deaths occurred during the long-term safety evaluation period.

Studies AFX01-11 and AFX01-13 in Patients with Chronic Kidney Disease Not on Dialysis:
The major results for each of these studies are presented and discussed below.  For presentation of analyses and results of the two studies combined, see the Medical Officer's Review by Dr. A. Dmytrijuk (final signature, February 7, 2012).  As presented in the **Studies submitted** section above, the non-dialysis studies utilized darbepoetin as comparator rather than epoetin which was used in the dialysis studies.  Also, dosing in the non-dialysis studies was exclusively SC while in dialysis Study AFX01-12 dosing was IV and in Study AFX01-14 dosing via either IV or SC route could be used.

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*Disposition and Population Characteristics for the Non-Dialysis Studies (AFX01-11 and AFX01-13):*
For Study AFX01-11 a total of 797 patients were screened and 490 (61%) were randomized.  For Study AFX01-13 a total of 790 patients were screened and 493 (62%) were randomized.  The major reasons for screen failure were failure to satisfy one or more inclusion criteria ($\geq$66% of cases) (e.g., not meeting stability of hemoglobin range requirement in 46% of the cases in AFX01-11 and 52% of the cases in AFX01-13; failure to have one TSAT$\geq$20% or one ferritin level$\geq$100 ng/mL within 4 weeks prior to randomization (16% of the cases in AFX01-11 and 11% of the cases in AFX01-13)), informed consent withdrawn (13%-15% of cases), and other reason not specified (10%-13% of cases).  In both studies all randomized patients received at least one dose of study drug.

Disposition of patients in Studies AFX01-11 and AFX01-13 is summarized in the following table:

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**Non-Dialysis Studies (AFX01-11 and AFX01-13):  Disposition of Patients\***

| | AFX01-11 | | | AFX01-13 | | |
|---|---|---|---|---|---|---|
| | Peginesatide SC starting dose 0.025mg/kg Q4W (N=161) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=165) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=164) | Peginesatide SC starting dose 0.025mg/kg Q4W (N=167) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=163) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=163) |
| Randomized | 161 (100%) | 165 (100%) | 164 (100%) | 167 (100%) | 163 (100%) | 163 (100%) |
| US | 161 (100%) | 165 (100%) | 164 (100%) | 139 (83.2%) | 135 (82.8%) | 139 (85.3%) |
| EU | NA | NA | NA | 28 (16.8%) | 28 (17.2%) | 24 (14.7%) |
| Received at least 1 dose of study drug | 161 (100%) | 165 (100%) | 164 (100%) | 167 (100%) | 163 (100%) | 163 (100%) |
| Permanently Prematurely discontinued study drug | 49 (30.4%)[a] | 46 (27.9%)[b] | 46 (28.0%)[c] | 47 (28.1%)[d] | 46 (28.2%)[e] | 31 (19.0%)[f] |
| Prematurely terminated from study | 41 (25.5%) | 38 (23.0%) | 39 (23.8%) | 43 (25.75%) | 39 (23.9%) | 24 (14.7%) |
| Completed study on drug | 112 (69.6%) | 119 (72.1%) | 118 (72.0%) | 119 (71.3%) | 117 (71.8%) | 132 (81.0%) |

[*]  all randomized patients

[a]  major reasons:  adverse events, 18 [11.2%]; death, 3 [1.9%]; other, 10 [6.2%]; dosing consent withdrawn, 11 [6.8%]; lost to followup, 5 [3.1%]

[b]  major reasons:  adverse events, 13 [7.9%]; death, 9 [5.5%]; other, 13 [7.9%]; dosing consent withdrawn, 8 [4.8%]; lost to followup, 3 [1.8%]

[c]  major reasons:  adverse events, 10 [6.1%]; death, 8 [4.9%]; other, 15 [9.1%]; dosing consent withdrawn, 8 [4.9%]; lost to followup, 3 [1.8%]

[d] major reasons:  adverse events, 9 [5.4%]; death, 15 [9.0%]; other, 6 [3.6%]; dosing consent withdrawn, 13 [7.8%]; lost to followup, 3 [1.8%]

[e] major reasons:  adverse events, 8 [4.9%]; death, 9 [5.5%]; other, 13 [8.0%]; dosing consent withdrawn, 13 [8.0%]; lost to followup, 2 [1.2%]

[f] major reasons:  adverse events, 6 [3.7%]; death, 9 [5.5%]; other, 5 [3.1%]; dosing consent withdrawn, 9 [5.5%]; lost to followup, 2 [1.2%]

reviewer's table based on data in sponsor's tables

About 70% of patients in both studies completed the study on drug. Major reasons for permanently discontinuing study drug were adverse events, withdrawal of consent, death and 'other reasons'. Most of the patients who prematurely discontinued study drug also were terminated from the study.

Demographic, baseline and medical history characteristics of the patients enrolled and treated in the non-dialysis studies are summarized in the following table:

**Non-Dialysis Studies (AFX01-11 and AFX01-13):  Demographic, Baseline and Medical History Characteristics of Patients\***

| | AFX01-11 | | | AFX01-13 | | |
|---|---|---|---|---|---|---|
| | Peginesatide SC starting dose 0.025mg/kg Q4W (N=161) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=165) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=164) | Peginesatide SC starting dose 0.025mg/kg Q4W (N=167) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=163) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=163) |
| **Age (yrs)** | | | | | | |
| Mean | 67.1 | 67.1 | 66.4 | 68.1 | 68.3 | 67.2 |
| Median | 67 | 67 | 69 | 70 | 70 | 70 |
| Range | 22 -- 96 | 27 – 94 | 20 -  95 | 27 – 90 | 19 – 92 | 25 – 92 |
| **Age, N (%)** | | | | | | |
| <65 yrs | 70 (43.5%) | 63 (38.2%) | 65 (39.6%) | 63 (37.7%) | 57 (35.0%) | 62 (38.0%) |
| ≥65 to <75 yrs | 35 (21.7%) | 48 (29.1%) | 49 (29.9%) | 42 (25.1%) | 43 (26.4%) | 40 (24.5%) |
| ≥75 yrs | 56 (34.8%) | 54 (32.7%) | 50 (30.5%) | 62 (37.1%) | 63 (38.7%) | 61 (37.4%) |
| **Gender, N (%)** | | | | | | |
| Male | 68 (42.2%) | 81 (49.1%) | 62 (37.8%) | 74 (44.3%) | 67 (41.1%) | 64 (39.3%) |
| Female | 93 (57.8%) | 84 (50.9%) | 102 (62.2%) | 93 (55.7%) | 96 (58.9%) | 99 (60.7%) |
| **Race, N (%)** | | | | | | |
| Asian | 6 (3.7%) | 4 (2.4%) | 8 (4.9%) | 4 (2.4%) | 3 (1.8%) | 3 (1.8%) |
| Black | 38 (23.6%) | 36 (21.8%) | 41 (25.0%) | 34 (20.4%) | 34 (20.9%) | 37 (22.7%) |
| White | 112 (69.6%) | 120 (72.7%) | 109 (66.5%) | 126 (75.4%) | 124 (76.1%) | 122 (74.8) |
| Other | 5 (3.1%) | 5 (3.1%) | 5 (3.1%) | 3 (1.8%) | 2 (1.2%) | 1 (0.6%) |
| **Ethnicity, N (%)** | | | | | | |
| Hispanic or Latino | 41 (25.5%) | 40 (24.2%) | 62 (37.8%) | 26 (15.6%) | 26 (16.0%) | 31 (19.0%) |
| Non-Hispanic or non-Latino | 120 (74.5%) | 125 (75.8%) | 102 (62.2%) | 141 (84.4%) | 137 (84.0%) | 132 (81.0%) |
| **Geographic Area, N (%)** | | | | | | |
| US | 161 (100.0%) | 165 (100.0%) | 164 (100.0%) | 139 (83.2%) | 135 (82.8%) | 139 (85.3%) |
| Western Europe | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 10 (6.0%) | 8 (4.9%) | 8 (4.9%) |
| Central Europe | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 18 (10.8%) | 20 (12.3) | 16 (9.8%) |
| **Weight (kg)** | | | | | | |
| Mean | 86.74 | 86.66 | 82.70 | 82.52 | 83.94 | 82.60 |
| Median | 84.5 | 83.5 | 78.0 | 80.0 | 78.6 | 78.9 |
| Range | 41.3 – 154.3 | 39.0-182.2 | 45.0-172.4 | 38.5 – 161.0 | 44.5 – 258.5 | 42.6-158.3 |
| **Baseline Hgb (g/dL)** | | | | | | |
| Mean | 10.05 | 9.95 | 10.05 | 10.02 | 10.03 | 10.03 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Median | 10.2 | 10.1 | 10.2 | 10.1 | 10.2 | 10.2 |
| Range | 8.1 – 11.1 | 8.3 – 11.1 | 8.1-11.3 | 8.1 – 11.3 | 8.2 – 11.1 | 7.9 – 11.6 |
| Baseline Hgb (g/dL), N (%) | | | | | | |
| ≤10.4 g/dL | 106 (65.8%) | 120 (72.7%) | 113 (68.9) | 119 (71.3%) | 116 (71.2%) | 114 (69.9%) |
| >10.5 g/dL | 55 (34.2%) | 45 (27.3%) | 51 (31.1%) | 48 (28.7%) | 47 (28.8%) | 49 (30.1%) |
| Ferritin (ng/mL)[+] | | | | | | |
| Mean | 235.2 | 261.6 | 240.4 | 231.7 | 281.3 | 258.6 |
| Median | 167 | 171 | 161 | 171 | 199 | 183 |
| Range | 21 - 1605 | 17 – 1536 | 18-1581 | 13 - 1365 | 10 - 1473 | 10 - 3165 |
| TSAT (%)[++] | | | | | | |
| Mean | 25.5 | 27.2 | 25.4 | 25.7 | 28.8 | 27.8 |
| Median | 25 | 25 | 23 | 24 | 25 | 25 |
| Range | 7 - 79 | 8 – 74 | 8 - 75 | 7 - 98 | 7 - 100 | 9 - 100 |
| Estimated GFR (mL/min/1.73m$^2$) | | | | | | |
| Mean | 27.2 | 30.3 | 29.1 | 28.5 | 29.6 | 28.1 |
| Median | 25 | 30 | 286 | 28 | 25 | 27 |
| Range | 6 - 62 | 8 – 70 | 9 - 65 | 8 - 66 | 7 - 76 | 6 - 70 |
| Primary causes of chronic renal failure, N (%): | | | | | | |
| Diabetes | 86 (53.4%) | 93 (56.4%) | 81 (49.4%) | 78 (46.7%) | 83 (50.9%) | 66 (40.5%) |
| Hypertension | 51 (31.7%) | 150 (30.3%) | 59 (36.0%) | 54 (32.3%) | 48 (29.4%) | 56 (34.4%) |
| Autoimmune disease | 2 (1.2%) | 4 (2.4%) | 2 (1.2%) | 5 (3.0%) | 5 (3.1%) | 3 (1.8%) |
| Polycystic kidney disease | 2 (1.2%) | 1 (0.6%) | 4 (2.4%) | 5 (3.0%) | 0 (0.0%) | 4 (2.5%) |
| Pyelonephritis | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (1.8%) | 3 (1.8%) | 1 (0.6%) |
| Interstitial nephritis | 2 (1.2%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 4 (2.5%) | 2 (1.2%) |
| Urologic | 0 (0.0%) | 0 (0.0%) | 2 (1.2%) | 1 (0.6%) | 3 (1.8%) | 1 (0.6%) |
| Unknown | 1 (0.6%) | 4 (2.4%) | 7 (4.3%) | 7 (4.2%) | 2 (1.2%) | 7 (4.3%) |
| Other | 17 (10.6%) | 13 ( 7.0%) | 8 (4.9%) | 14 (8.4%) | 15 (9.2%) | 23 (14.1%) |
| Cigarette use, N (%) | | | | | | |
| Yes | 19 (11.8%) | 17 (10.3%) | 12 (7.3%) | 20 (12.0%) | 16 (9.8%) | 15 (9.2%) |
| No | 142 (88.2%) | 148 (89.7%) | 152 (92.7%) | 146 (87.4%) | 147 (90.2%) | 148 (90.8%) |
| Missing | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) |
| Cardiovascular (CV) risk history, N (%): | 161 (100.0%) | 163 (98.8%) | 161 (98.2%) | 167 (100.0%) | 163 (100.0%) | 160 (98.2%) |
| At least one CV risk without hypertension | 153 (95.0%) | 158 (95.8%) | 145 (88.4%) | 152 (91.0%) | 154 (94.5%) | 150 (92.0%) |
| Hypertension | 159 (98.8%) | 161 (97.6%) | 160 (97.6%) | 164 (98.2%) | 155 (95.1%) | 156 (95.7%) |
| Diabetes | 105 (65.2%) | 121 (73.3%) | 109 (66.5%) | 109 (65.3%) | 109 (66.9%) | 88 (54.0%) |
| Coronary artery disease (CAD) | 73 (45.3%) | 67 (40.6%) | 65 (39.6%) | 54 (32.3%) | 70 (42.9%) | 60 (36.8%) |
| Myocardial infarction (MI) | 26 (16.1%) | 29 (17.6%) | 15 (9.1%) | 22 (13.2%) | 22 (13.5%) | 17 (10.4%) |
| Angina | 33 (20.5%) | 26 (15.8%) | 28 (17.1%) | 23 (13.8%) | 30 (18.4%) | 27 (16.6%) |

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| | | | | | | |
|---|---|---|---|---|---|---|
| Coronary artery bypass graft | 29 (18.0%) | 23 (13.9%) | 26 (15.9%) | 21 (12.6%) | 22 (13.5%) | 13 (8.0%) |
| PCI or coronary stent placement | 24 (14.9%) | 21 (12.7%) | 21 (12.8%) | 18 (10.8%) | 22 (13.5%) | 23 (14.1%) |
| | | | | | | |
| Arrhythmia | 24 (14.9%) | 26 (15.8%) | 22 (13.4%) | 28 (16.8%) | 26 (16.0%) | 21 (12.9%) |
| AF, flutter, or SVT | 18 (11.2%) | 18 (10.9%) | 15 (9.1%) | 18 (10.9%) | 17 (10.4%) | 15 (9.2%) |
| VT or fibrillation | 6 (3.7%) | 5 (3.0%) | 0 (0.0%) | 5 (3.0%) | 5 (3.0%) | 5 (3.1%) |
| | | | | | | |
| Cerebrovascular disease (CVD) | 29 (18.0%) | 32 (19.4%) | 31 (18.9%) | 28 (16.8%) | 33 (20.2%) | 28 (17.2%) |
| Stroke | 14 (8.7%) | 18 (10.9%) | 17 (10.4%) | 17 (10.4%) | 17 (10.4%) | 16 (9.8%) |
| TIA | 9 (5.6%) | 14 (8.5%) | 9 (5.5%) | 10 (6.0%) | 9 (5.5%) | 10 (6.1%) |
| | | | | | | |
| Peripheral vascular disease | 46 (28.6%) | 42 (25.5%) | 25 (15.2%) | 45 (26.9%) | 46 (28.2%) | 40 (24.5%) |
| | | | | | | |
| Hyperlipidemia | 133 (82.6%) | 135 (81.8%) | 124 (75.6%) | 128 (76.6%) | 117 (71.8%) | 118 (72.4%) |
| Congestive heart failure, N (%) | | | | | | |
| Yes | 36 (22.4%) | 42 (25.5%) | 34 (20.7%) | 48 (28.7%) | 56 (34.4%) | 43 (26.4%) |
| No | 125 (77.6%) | 123 (74.5%) | 130 (79.3%) | 119 (71.3%) | 107 (65.6%) | 120 (73.6%) |
| NYHA CHF Class, N (%) | | | | | | |
| No CHF | 125 (77.6%) | 123 (74.5%) | 130 (79.3% | 119 (71.3%) | 107 (65.6%) | 120 (73.6%) |
| Class I | 15 (9.3%) | 16 (9.7%) | 16 (9.8%) | 13 (7.8%) | 20 (12.3%) | 13 (8.0%) |
| Class II | 13 (8.1%) | 16 (9.7%) | 15 (9.1%) | 26 (15.6%) | 29 (17.8%) | 23 (14.1%) |
| Class III | 8 (5.0%) | 8 (4.8%) | 3 (1.8%) | 9 (5.4%) | 7 (4.3%) | 7 (4.3%) |
| Class IV | 0 (0.0%) | 2 (1.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

* all randomized patients who received one dose of study drug;  + normal range: female, 10-291; male 22-322;  ++ transferrin saturation (TSAT) normal range:  20-55

reviewer's table, based on data in sponsor's tables in study report

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Similar to the dialysis studies, diabetes and hypertension were the two primary causes of chronic renal failure in both non-dialysis studies. The study population characteristics for the two non-dialysis studies were similar.

*Efficacy Results for Non-Dialysis Studies (AFX01-11 and AFX01-13):* Results of the primary efficacy analyses for each of these studies in patients not on dialysis are shown in the following tables. The analysis population for the primary efficacy analysis was the "full analysis population", which consisted of all randomized patients who received at least one dose of study drug. For both non-dialysis studies the results for the primary efficacy analysis of hemoglobin change from baseline to the evaluation period (Week 29 through 36) satisfied the sponsor's pre-specified criterion for non-inferiority of peginesatide to darbepoetin, which was that the lower limit of the 97.5% confidence interval (CI) for each peginesatide injection group mean minus the darbepoetin group mean was $\geq$-1.0g/dL.

**Non-Dialysis Studies (AFX01-11 and AFX01-13): Primary Efficacy Endpoint: Summary of Hgb and Change in Hgb from Baseline to the Evaluation Period (Full Analysis Population)**

**Study AFX01-11:**

| | Statistic | AF37702 Inj. SC Starting Dose 0.025 mg/kg Q4W (N=161) | AF37702 Inj. SC Starting Dose 0.04 mg/kg Q4W (N=165) | AF37702 Inj. SC Starting Dose (0.025+0.04) (N=326) | Darbepoetin alfa SC Starting Dose 0.75 mcg/kg Q2W (N=164) | Total (N=490) |
|---|---|---|---|---|---|---|
| Baseline | N | 161 | 165 | 326 | 164 | 490 |
| | Mean (SD) | 10.05 (0.623) | 9.95 (0.685) | 10.00 (0.656) | 10.05 (0.638) | 10.02 (0.650) |
| | Median | 10.2 | 10.1 | 10.2 | 10.2 | 10.2 |
| | Q1 - Q3 | 9.7 - 10.5 | 9.5 - 10.5 | 9.6 - 10.5 | 9.6 - 10.5 | 9.6 - 10.5 |
| | Min - Max | 8.1 - 11.1 | 8.3 - 11.1 | 8.1 - 11.1 | 8.1 - 11.3 | 8.1 - 11.3 |
| Evaluation Period | N | 141 | 151 | 292 | 151 | 443 |
| | Mean (SD) | 11.47 (0.731) | 11.61 (0.856) | 11.54 (0.800) | 11.47 (0.747) | 11.52 (0.782) |
| | Median | 11.5 | 11.8 | 11.6 | 11.5 | 11.6 |
| | Q1 - Q3 | 11.1 - 12.0 | 11.1 - 12.2 | 11.1 - 12.1 | 11.1 - 11.9 | 11.1 - 12.0 |
| | Min - Max | 9.0 - 13.2 | 8.8 - 13.3 | 8.8 - 13.3 | 9.7 - 14.9 | 8.8 - 14.9 |
| Change from Baseline | N | 141 | 151 | 292 | 151 | 443 |
| | Mean (SD) | 1.39 (0.866) | 1.64 (0.965) | 1.52 (0.925) | 1.37 (0.861) | 1.47 (0.906) |
| | SE | 0.073 | 0.079 | 0.054 | 0.070 | 0.043 |
| | Median | 1.4 | 1.7 | 1.5 | 1.3 | 1.5 |
| | Q1 - Q3 | 0.9 - 1.9 | 1.0 - 2.2 | 0.9 - 2.1 | 0.8 - 1.9 | 0.9 - 2.1 |
| | Min - Max | -1.3 - 4.5 | -1.1 - 4.3 | -1.3 - 4.5 | -1.3 - 5.2 | -1.3 - 5.2 |
| Difference from Darbepoetin alfa[1][2] | LS Mean (SE) | 0.03(0.099) | 0.26(0.098) | 0.15(0.085) | | |
| | 2-Sided CI(%*) | (-0.19,0.26) (97.5%) | (0.04,0.48) (97.5%) | (-0.02,0.32) (95%) | | |
| Difference from AF37702 Inj. Starting Dose 0.025 mg/kg [1][3] | LS Mean (SE) | | 0.23(0.099) | | | |
| | 2-Sided CI(%*) | | (0.04,0.43) (95%) | | | |

[1] An ANOVA cell means model was used to estimate the mean Hgb change from Baseline to the Evaluation Period.
[2] Difference from Darbepoetin alfa = AF37702 Injection group - Darbepoetin alfa group.
[3] Difference from AF37702 Inj. Starting Dose 0.025 mg/kg = AF37702 Inj. Starting Dose 0.04 mg/kg - AF37702 Inj. Starting Dose 0.025 mg/kg.
* Confidence level of given confidence interval.

**Study AFX01-13:**

| Hgb (g/dL) | Statistic | AF37702 Inj. SC Starting Dose 0.025 mg/kg Q4W (N=167) | AF37702 Inj. SC Starting Dose 0.04 mg/kg Q4W (N=163) | AF37702 Inj. SC Starting Dose (0.025+0.04) (N=330) | Darbepoetin alfa SC Starting Dose 0.75 mcg/kg Q2W (N=163) | Total (N=493) |
|---|---|---|---|---|---|---|
| Baseline | N | 167 | 163 | 330 | 163 | 493 |
| | Mean (SD) | 10.02 (0.626) | 10.03 (0.618) | 10.02 (0.621) | 10.03 (0.654) | 10.03 (0.632) |
| | Median | 10.1 | 10.2 | 10.2 | 10.2 | 10.2 |
| | Q1 - Q3 | 9.7 - 10.5 | 9.6 - 10.5 | 9.6 - 10.5 | 9.6 - 10.5 | 9.6 - 10.5 |
| | Min - Max | 8.1 - 11.3 | 8.2 - 11.1 | 8.1 - 11.3 | 7.9 - 11.6 | 7.9 - 11.6 |
| Evaluation Period | N | 151 | 145 | 296 | 150 | 446 |
| | Mean (SD) | 11.55 (0.741) | 11.71 (0.855) | 11.63 (0.802) | 11.40 (0.728) | 11.55 (0.784) |
| | Median | 11.6 | 11.8 | 11.7 | 11.5 | 11.6 |
| | Q1 - Q3 | 11.2 - 12.0 | 11.3 - 12.2 | 11.2 - 12.1 | 11.0 - 11.9 | 11.2 - 12.0 |
| | Min - Max | 9.1 - 13.7 | 8.2 - 15.5 | 8.2 - 15.5 | 9.1 - 13.6 | 8.2 - 15.5 |
| Change from Baseline | N | 151 | 145 | 296 | 150 | 446 |
| | Mean (SD) | 1.50 (0.898) | 1.68 (0.962) | 1.59 (0.933) | 1.35 (1.004) | 1.51 (0.963) |
| | SE | 0.073 | 0.080 | 0.054 | 0.082 | 0.046 |
| | Median | 1.5 | 1.6 | 1.6 | 1.3 | 1.5 |
| | Q1 - Q3 | 0.9 - 2.1 | 1.2 - 2.2 | 1.0 - 2.1 | 0.8 - 2.1 | 1.0 - 2.1 |
| | Min - Max | -0.6 - 4.3 | -2.4 - 4.7 | -2.4 - 4.7 | -1.8 - 3.9 | -2.4 - 4.7 |
| Difference from Darbepoetin alfa [1] [2] | LS Mean (SE) | 0.14 (0.101) | 0.31 (0.102) | 0.23 (0.088) | | |
| | 2-Sided CI (%*) | (-0.09,0.36) (97.5%) | (0.08,0.54) (97.5%) | (0.06,0.40) (95%) | | |
| Difference from AF37702 Inj. Starting Dose 0.025 mg/kg [1] [3] | LS Mean (SE) | | 0.18 (0.102) | | | |
| | 2-Sided CI (%*) | | (-0.02,0.38) (95%) | | | |

[1] An ANOVA cell means model was used to estimate the mean Hgb change from Baseline to the Evaluation Period.
[2] Difference from Darbepoetin alfa = AF37702 Injection group - Darbepoetin alfa group.
[3] Difference from AF37702 Inj. Starting Dose 0.025 mg/kg = AF37702 Inj. Starting Dose 0.04 mg/kg - AF37702 Inj. Starting Dose 0.025 mg/kg.
* Confidence level of given confidence interval.

Results of Per-Protocol population analyses were consistent with the primary efficacy analysis. A non-parametric analysis (generalized CMH procedure) gave similar results to the ANOVA analysis. Sensitivity analyses evaluating the impact of red blood cell transfusions and renal transplant on the study results and using various methods of imputing values for missing data gave similar results.

Results for evaluation by randomization stratification factors of mean screening hemoglobin and NYHA CHF Class and other factors are summarized in the table below. In both studies, within the subgroups the results were similar across treatment arms consistent with the primary efficacy analysis. Patients with baseline hemoglobin ≤10.4 g/dL had a greater rise in hemoglobin during the study than did patients with baseline hemoglobin ≥10.5 g/dL.

**Non-Dialysis Studies (AFX01-11 and AFX01-13):  Summary of Hgb and Change in Hgb from Baseline to the Evaluation Period for Pre-Specified Strata (Average Screening Hgb, NYHA CHF Class, Geographic Region) and Other Important Factors (Full Analysis Population)**

| | AFX01-11 | | | AFX01-13 | | |
|---|---|---|---|---|---|---|
| | Peginesatide SC starting dose 0.025mg/kg Q4W (N=161) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=165) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=164) | Peginesatide SC starting dose 0.025mg/kg Q4W (N=167) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=163) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=163) |
| **Average screening Hgb values ≤10.4 g dL:** | | | | | | |
| **Baseline** | | | | | | |
| N | 114 | 115 | 114 | 125 | 121 | 121 |
| Mean | 9.81 | 9.65 | 9.77 | 9.81 | 9.82 | 9.81 |
| Median | 9.9 | 9.7 | 9.9 | 9.9 | 9.9 | 9.9 |
| Range | 8.1 – 10.6 | 8.3 – 10.6 | 8.1 – 10.7 | 8.1 – 11.3 | 8.2 – 11.0 | 7.9 – 11.3 |
| **Evaluation Period** | | | | | | |
| N | 96 | 105 | 104 | 112 | 107 | 109 |
| Mean | 11.42 | 11.49 | 11.41 | 11.53 | 11.69 | 11.46 |
| Median | 11.5 | 11.7 | 11.4 | 11.6 | 11.8 | 11.5 |
| Range | 9.0 – 13.2 | 8.8 – 13.3 | 9.9 – 14.5 | 9.1 – 13.7 | 9.3 – 15.5 | 9.7 – 12.8 |
| **Change from baseline** | | | | | | |
| N | 96 | 105 | 104 | 112 | 107 | 109 |
| Mean | 1.61 | 1.82 | 1.59 | 1.7 | 1.87 | 1.64 |
| Median | 1.7 | 1.9 | 1.6 | 1.7 | 2.0 | 1.6 |
| Range | -1.3 – 4.5 | -1.1 – 4.3 | -0.3 – 5.2 | -0.6 – 4.3 | -0.6 – 4.7 | -0.6 – 3.9 |
| **Average screening Hgb values ≥10.5 g dL:** | | | | | | |
| **Baseline** | | | | | | |
| N | 47 | 50 | 50 | 42 | 42 | 42 |
| Mean | 10.63 | 10.64 | 10.69 | 10.63 | 10.63 | 10.66 |
| Median | 10.6 | 10.6 | 10.7 | 10.7 | 10.6 | 10.6 |
| Range | 10.4 – 11.1 | 10.4 – 11.1 | 10.2 – 11.3 | 9.4 – 11.2 | 10.0 – 11.1 | 9.4 – 11.6 |
| **Evaluation Period** | | | | | | |
| N | 45 | 46 | 47 | 39 | 38 | 41 |
| Mean | 11.58 | 11.87 | 11.59 | 11.59 | 11.76 | 11.24 |
| Median | 11.6 | 11.9 | 11.6 | 11.7 | 11.9 | 11.4 |
| Range | 10.3 – 12.4 | 10.1 – 12.9 | 9.7 – 14.9 | 10.4 – 12.9 | 8.2 – 12.8 | 9.1 – 13.6 |
| **Change from baseline** | | | | | | |
| N | 45 | 46 | 47 | 39 | 38 | 41 |
| Mean | 0.94 | 1.24 | 0.89 | 0.92 | 1.14 | 0.57 |
| Median | 0.9 | 1.2 | 0.9 | 0.9 | 1.2 | 0.7 |
| Range | -0.3 – 1.9 | -0.5 – 2.2 | -1.3 – 4.1 | -0.2 – 2.2 | -2.4 – 2.5 | -1.8 – 3.0 |

| NYHA CHF Class 0-I: | | | | | | |
|---|---|---|---|---|---|---|
| **Baseline** | | | | | | |
| N | 137 | 139 | 140 | 133 | 129 | 130 |
| Mean | 10.04 | 9.95 | 10.02 | 10.06 | 10.07 | 10.05 |
| Median | 10.2 | 10.1 | 10.1 | 10.2 | 10.2 | 10.2 |
| Range | 8.1 -11.1 | 8.3 – 11.1 | 8.1 – 11.3 | 8.1 – 11.3 | 8.4 – 11.0 | 8.2 – 11.6 |
| **Evaluation Period** | | | | | | |
| N | 120 | 131 | 129 | 121 | 121 | 118 |
| Mean | 11.54 | 11.65 | 11.42 | 11.53 | 11.80 | 11.38 |
| Median | 11.5 | 11.8 | 11.5 | 11.6 | 11.8 | 11.5 |
| Range | 9.1 – 13.2 | 8.8 – 13.3 | 9.7 – 14.5 | 9.1 – 13.3 | 9.6 – 15.5 | 9.1 – 13.6 |
| **Change from baseline** | | | | | | |
| N | 120 | 131 | 129 | 121 | 121 | 118 |
| Mean | 1.46 | 1.67 | 1.35 | 1.44 | 1.72 | 1.31 |
| Median | 1.4 | 1.7 | 1.2 | 1.5 | 1.7 | 1.3 |
| Range | -1.3 – 4.5 | -1.1 – 4.3 | -1.3 – 5.2 | -0.6 – 4.2 | -0.3 – 4.7 | -1.8 – 3.9 |
| NYHA CHF Class II-IV: | | | | | | |
| **Baseline** | | | | | | |
| N | 24 | 26 | 24 | 34 | 34 | 33 |
| Mean | 10.09 | 9.95 | 10.21 | 9.85 | 9.89 | 9.97 |
| Median | 10.3 | 10.2 | 10.3 | 9.9 | 10.1 | 10.3 |
| Range | 8.4 – 10.8 | 8.6 – 10.8 | 9.0 – 11.0 | 8.5 – 10.9 | 8.2 – 11.1 | 7.9 – 11.6 |
| **Evaluation Period** | | | | | | |
| N | 21 | 20 | 22 | 30 | 24 | 32 |
| Mean | 11.11 | 11.35 | 11.74 | 11.62 | 11.23 | 11.47 |
| Median | 11.2 | 11.5 | 11.7 | 11.8 | 11.4 | 11.6 |
| Range | 9.0 – 12.4 | 9.5 -12.7 | 10.2 – 14.9 | 9.5 – 13.7 | 8.2 – 13.5 | 10.4 – 12.8 |
| **Change from baseline** | | | | | | |
| N | 21 | 20 | 22 | 30 | 24 | 32 |
| Mean | 1.00 | 1.43 | 1.50 | 1.73 | 1.48 | 1.50 |
| Median | 1.2 | 1.6 | 1.5 | 1.7 | 1.5 | 1.4 |
| Range | -0.4 – 2.5 | -0.5 – 3.2 | 0.1 – 4.1 | 0.1 – 4.3 | -2.4 – 4.1 | -0.2 – 3.6 |
| Geographic region= US: | | | | | | |
| **Baseline** | | | | | | |
| N | Same as total | Same as total | Same as total | 139 | 135 | 139 |
| Mean | | | | 9.97 | 10.04 | 10.06 |
| Median | | | | 10.0 | 10.2 | 10.2 |
| Range | | | | 8.1 – 11.2 | 8.2 – 11.1 | 8.2 – 11.6 |
| **Evaluation Period** | | | | | | |
| N | Same as total | Same as total | Same as total | 125 | 121 | 126 |
| Mean | | | | 11.52 | 11.71 | 11.38 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Median<br>Range | | | | 11.6<br>9.1 – 13.7 | 11.8<br>8.2 – 15.5 | 11.5<br>9.1 – 13.6 |
| Change from baseline<br>N<br>Mean<br>Median<br>Range | Same as total | Same as total | Same as total | 125<br>1.50<br>1.5<br>-0.6 – 4.3 | 121<br>1.68<br>1.6<br>-2.4 – 4.7 | 126<br>1.30<br>1.3<br>-1.8 – 3.9 |
| Geographic region=non-US: | | | | | | |
| Baseline<br>N<br>Mean<br>Median<br>Range | NA | NA | NA | 28<br>10.22<br>10.3<br>8.7 – 11.3 | 28<br>9.99<br>10.2<br>8.8 – 11.0 | 24<br>9.88<br>9.9<br>7.9 – 10.9 |
| Evaluation Period<br>N<br>Mean<br>Median<br>Range | NA | NA | NA | 26<br>11.68<br>11.8<br>9.7 – 12.9 | 24<br>11.72<br>11.7<br>9.4 – 13.5 | 24<br>11.51<br>11.6<br>9.3 – 12.8 |
| Change from baseline<br>N<br>Mean<br>Median<br>Range | NA | NA | NA | 26<br>1.46<br>1.5<br>-0.3 – 3.1 | 24<br>1.71<br>1.7<br>-0.5 – 4.1 | 24<br>1.63<br>1.8<br>-1.4 – 3.2 |

Based on sponsor's tables

The following sponsor's figures display some of these results graphically.

## Study AFX01-11:

**Figure 3:** Primary Efficacy Endpoint Summarized by Randomization Stratification Factors (Full Analysis Population)



A= AF37702 Injection SC starting dose: 0.025 mg/kg Q4W
B= AF37702 Injection SC starting dose: 0.04 mg/kg Q4W
C= Darbepoetin alfa SC starting dose: 0.75 mcg/kg Q2W
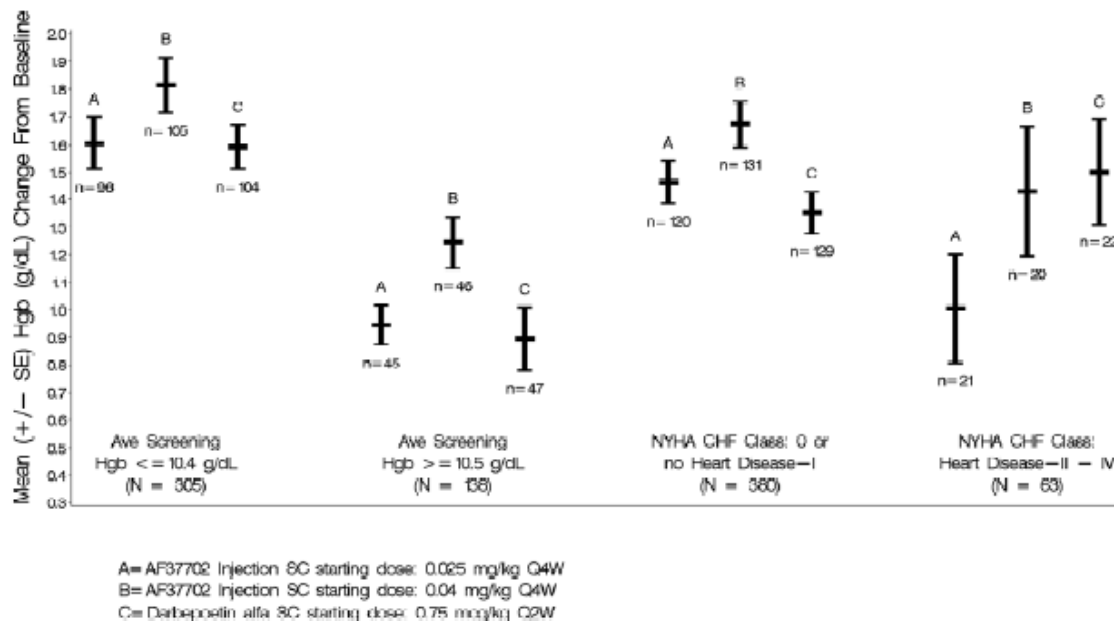
## Study AFX01-13:

**Figure 3:** Primary Efficacy Endpoint Summarized by Randomization Stratification Factors (Full Analysis Population)



A= AF37702 Injection SC starting dose: 0.025 mg/kg Q4W
B= AF37702 Injection SC starting dose: 0.04 mg/kg Q4W
C= Darbepoetin alfa SC starting dose: 0.75 mcg/kg Q2W
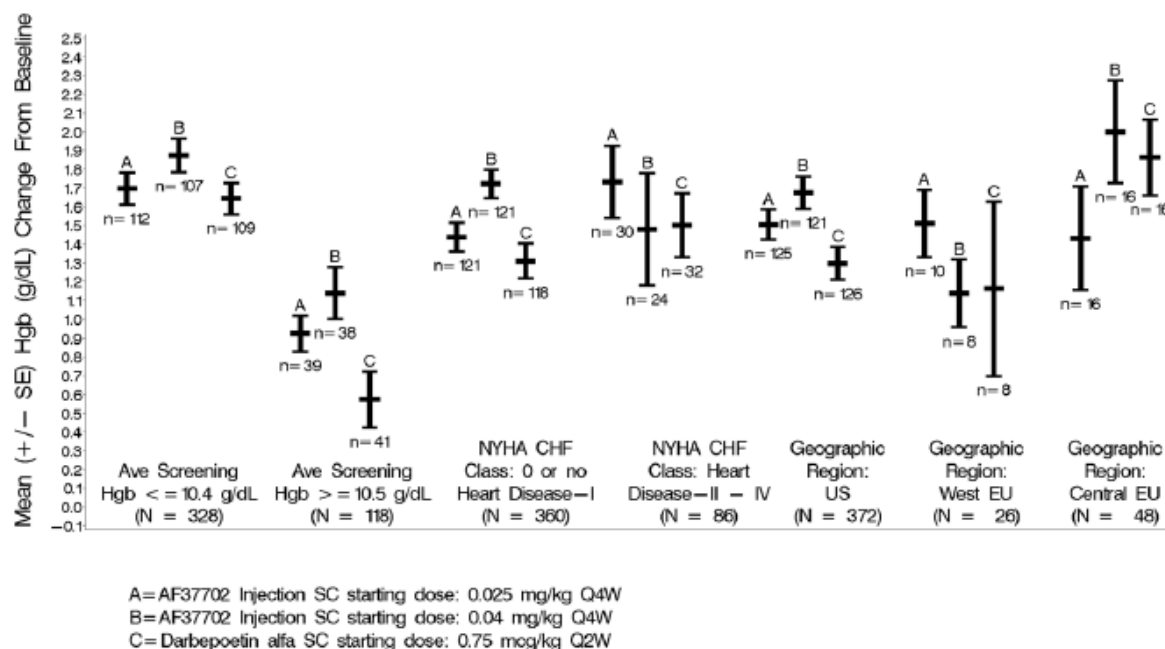
Results of post-hoc subgroup analyses based on age, gender, race, and ethnicity were similar to those for the primary efficacy analysis in both studies.

Secondary analyses evaluated proportions of patients receiving RBC or whole blood transfusions and extent and durability of hemoglobin responses during the studies. Some of these results are displayed in the following table.

**Non-Dialysis Studies (AFX01-11 and AFX01-13): Patients Receiving RBC Transfusions During Study and Proportion of Patients Achieving Hemoglobin Response (Full Analysis Population)**

|  | AFX01-11 | | | AFX01-13 | | |
|---|---|---|---|---|---|---|
|  | Peginesatide SC starting dose 0.025mg/kg Q4W (N=161) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=165) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=164) | Peginesatide SC starting dose 0.025mg/kg Q4W (N=167) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=163) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=163) |
| Patients who received $\geq$1 transfusion during the correction and/or evaluation periods, N (%) | 10/161 (6.2%) | 12/165 (7.3%) | 8/164 (4.9%) | 19/167 (11.4%) | 17/163 (10.4%) | 8/163 (4.9%) |
| Patients who received $\geq$1 transfusion during the correction period, N (%) | 7/161 (4.3%) | 12/165 (7.3%) | 5/164 (3.0%) | 14/167 (8.4%) | 13/162 (8.0%) | 6/163 (3.7%) |
| Patients who received $\geq$1 transfusion during the evaluation period, N (%) | 5/151 (3.3%) | 2/156 (1.3%) | 3/155 (1.9%) | 5 /160 (3.1%) | 4/150 (2.7%) | 2/154 (1.3%) |
| Patients achieving a Hgb response[+], N (%) | 150/161 (93.2%) | 155/165 (93.9%) | 154/164 (93.9%) | 152/167 (91.0%) | 152/163 (93.3%) | 155/163 (95.1%) |

[+] Hgb increase of $\geq$1.0 g/dL above baseline and Hgb$\geq$11.0 g/dL without RBC or whole blood transfusion during the previous 8 wks.
[*] all randomized patients who received one dose of study drug
      data from sponsor's tables

A sustained hemoglobin response (defined as two successive Hgb values within 11.0-12.0 g/dL) during the Evaluation period was achieved for 81.4% (131/161) patients in the peginesatide 0.025 mg/kg group, 83.0% (137/165) of patients in the peginesatide 0.04 mg/kg group and 87.2% (143/164) of patients in the darbepoetin group in Study AFX01-11 and for 80.8 % (135/167) patients in the peginesatide 0.025 mg/kg group, 79.1% (129/163) of patients in the peginesatide 0.04 mg/kg group and 88.3% (144/163) of patients in the darbepoetin group in Study AFX01-13 [excluded values within 28 days of RBC or whole blood transfusion].

The mean hemoglobin values over time on study drug in the treatment arms in these two studies are displayed in the following two sponsor's figures:

**Study AFT01-11:**

Figure 4: Mean (± SD) Hemoglobin over Time, by 4-Week Intervals (Full Analysis Population)
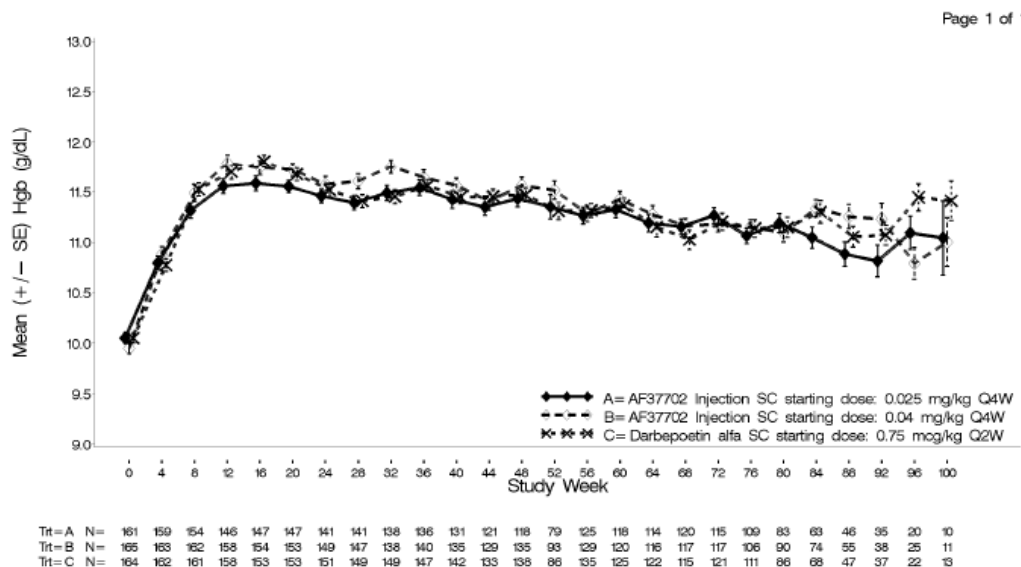


Source: carrd /pub/studies/affymaxu/afx0111/primary/f_mnhgb.sas 08:45 06DEC10

Source: Figure 1.1, Table 14.2.4

**Study AFX01-**

Figure 4: Mean (± SE) Hemoglobin Over Time, By 4-Week Intervals (Full Analysis Population)
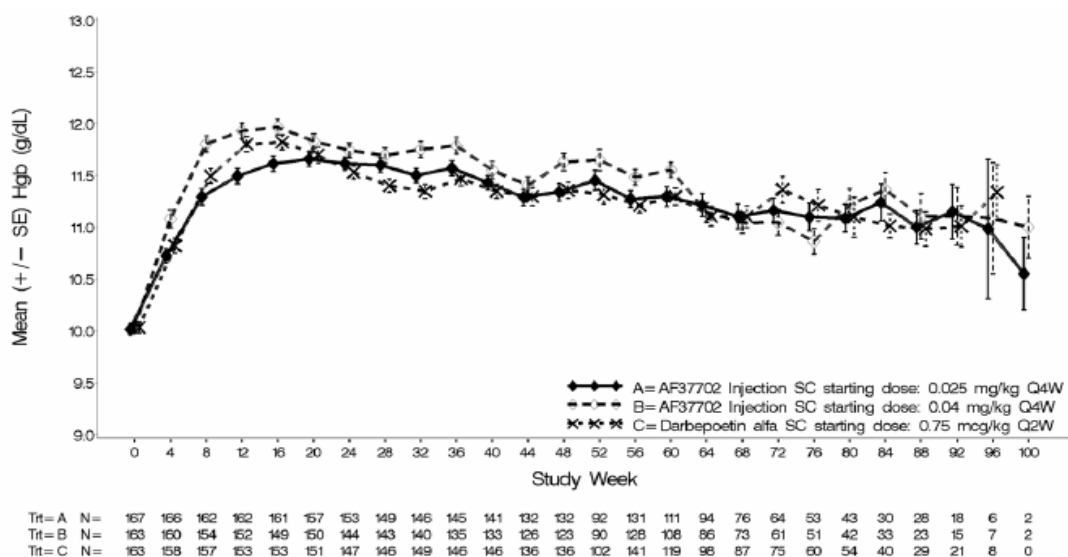


Source: weif /pub/studies/affymaxu/afx0113/primary/f_mnhgb.sas 09:18 13DEC10

**13:**    Source: Figure 1.1, Table 14.2.4

The mean change from baseline in hemoglobin level over time reached a maximum of approximately 1.5 to 1.8 g/dL increase per 4 weeks during the first 8 to 16 weeks (slightly longer in Study AFX01-13) and thereafter was stable or declined slightly to approximately 1.2 g/dL per 4 weeks in all treatment groups. The hemoglobin values and change from baseline was a bit greater in the peginesatide 0.04 mg/kg groups.

Most patients in both studies received one or more doses of iron supplementation during the study. In In the AFX01-11 study 114/161 (70.8%) of patients in the peginesatide 0.025mg/kg group, 112/165 (67.9%) of patients in the peginesatide 0.04mg/kg group and 109/164 (66.5%) of darbepoetin treated patients received iron supplementation. In the AFX01-13 study 114/167 (68.3%) of patients in the peginesatide 0.025mg/kg group, 97/163 (59.5%) of patients in the peginesatide 0.04mg/kg group and 116/163 (71.2%) of darbepoetin treated patients received iron supplementation. Unlike the dialysis studies, among these non-dialysis patients most received only oral iron supplementation. In Study AFX01-11 only 13.9% to 18.6% of patients in any treatment arm received IV iron. In Study AFX01-13, IV iron usage was more common with 26.9% of patients in the peginesatide 0.025 mg/kg group, 22.7% of patients in the peginesatide 0.04 mg/kg treatment group and 36.2% of patients in the darbepoetin treatment group receiving one or more doses of IV iron during the study. Iron supplementation by route of iron administration during these studies is summarized in the following table.

**Non-Dialysis Studies (AFX01-11 and AFX01-13): Patients Receiving Iron Supplementation (Full Analysis Population)**

| | AFX01-11 | | | AFX01-13 | | |
|---|---|---|---|---|---|---|
| | Peginesatide SC starting dose 0.025mg/kg Q4W (N=161) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=165) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=164) | Peginesatide SC starting dose 0.025mg/kg Q4W (N=167) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=163) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=163) |
| Patients receiving one or more doses of iron during Screening, N (%): | | | | | | |
| Total | 85 (52.8%) | 80 (48.5%) | 73 (44.5%) | 71 (42.5%) | 71 (43.6%) | 73 (44.8%) |
| Oral | 83 (51.6%) | 76 (46.1%) | 71 (43.3%) | 61 (36.5%) | 60 (36.8%) | 64 (39.3%) |
| IV | 3 (1.9%) | 5 (3.0%) | 3 (1.8%) | 13 (7.8%) | 17 (10.4%) | 15 (9.2%) |
| Other | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Patients receiving one or more doses of iron during Study[a], N (%): | | | | | | |
| Total | 114 (70.8%) | 112 (67.9%) | 109 (66.5%) | 114 (68.3%) | 97 (59.5%) | 116 (71.2%) |
| Oral | 102 (63.4%) | 103 (62.4%) | 98 (59.8%) | 90 (53.9%) | 78 (47.9%) | 83 (50.9%) |
| IV | 30 (18.6%) | 23 (13.9%) | 26 (15.9%) | 45 (26.9%) | 37 (22.7%) | 59 (36.2%) |
| other | 0 (0.0%) | 1 (0.6%) | 3 (1.8%) | 1 (0.6%) | 0 (0.0%) | 1 (0.6%) |

[a] during correction, evaluation, and/or long terms safety and efficacy period

data from sponsor's tables

*Safety Results for Non-Dialysis Studies (AFX01-11 and AFX01-13):* As was the case for the dialysis studies, the protocol for the non-dialysis studies planned for evaluation of peginesatide with regard to cardiovascular safety. In the non-dialysis studies a total of 656 patients were treated with peginesatide (326 in AFX01-11 and 330 in AFX01-13) and 327 patients were treated with darbepoetin (164 in

AFX01-11 and 163 in AFX01-13).  The following table summarizes study drug dose during the non-dialysis studies.

**Non-Dialysis Studies (AFX01-11 and AFX01-13):  Summary of Study Drug Dose During the Study (Full Analysis Population)**

| | AFX01-11 | | | AFX01-13 | | |
|---|---|---|---|---|---|---|
| | Peginesatide SC starting dose 0.025mg/kg Q4W (N=161) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=165) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=164) | Peginesatide SC starting dose 0.025mg/kg Q4W (N=167) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=163) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=163) |
| Units for dose | mg | mg | mcg | mg | mg | mcg |
| First dose | | | | | | |
| N | 161 | 165 | 164 | 167 | 163 | 163 |
| Mean | 2.17 | 3.46 | 61.7 | 2.06 | 3.33 | 61.5 |
| Median | 2.1 | 3.3 | 59 | 2.0 | 3.1 | 59 |
| Range | 1.0 – 3.9 | 1.6 – 7.3 | 25 - 130 | 1.0 – 4.0 | 1.8 -9.9 | 32 - 109 |
| Last dose during correction: | | | | | | |
| N | 161 | 165 | 164 | 167 | 163 | 163 |
| Mean | 2.59 | 3.37 | 49.5 | 2.46 | 3.14 | 49.9 |
| Median | 1.7 | 2.7 | 35 | 1.9 | 2.3 | 34 |
| Range | 0.4 – 10.6 | 0.2 – 12.8 | 10 - 375 | 0.5 – 8.8 | 0.6 – 13.4 | 11 - 291 |
| Mean dose during evaluation: | | | | | | |
| N | 139 | 147 | 149 | 149 | 140 | 149 |
| Mean | 2.78 | 3.07 | 49.3 | 2.38 | 3.10 | 47.3 |
| Median | 1.7 | 2.3 | 34 | 1.7 | 2.0 | 30 |
| Range | 0.4 – 12.8 | 0.4 – 13.8 | 9 - 496 | 0.3 – 12.5 | 0.4 – 24.4 | 7 - 317 |

Data from sponsor's tables

In Study AFX01-11 the mean duration of treatment exposure was 71.27 weeks (median, 79.1 wks; range, 4.0-107.1 wks) in the peginesatide 0.025 mg/kg group, 72.26 weeks (median, 80.0 wks; range, 7.6-108.9 wks) in the peginesatide 0.04mg/kg group and 72.87 weeks (median, 78.4; range 4.0-107.0 wks) in the darbpoetin group.  In Study AFX01-13 the mean duration of treatment exposure was 63.51 weeks (median, 64.6 wks; range, 4.0-101.0 wks) in the peginesatide 0.025 mg/kg group, 61.69 weeks (median, 64.4 wks; range, 4.0-97.9 wks) in the peginesatide 0.04 mg/kg group and 65.62 weeks (median, 67.6; range 2.0-98.6 wks) in the darbepoetin group.

The sponsor's tables summarizing adverse events occurring in the two studies are shown below:

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**Study AFX01-11:**

Table 23:     Summary of Adverse Events and Location of Source Table

| | AF37702-LS<br>N = 161 | AF37702-HS<br>N = 165 | AF37702<br>Injection<br>Combined<br>N = 326 | Darbepoetin<br>alfa<br>N = 164 | Source<br>Table |
|---|---|---|---|---|---|
| Total number of TEAEs | 1731 | 1591 | 3322 | 1391 | 14.3.5 |
| Number of patients reporting at least one TEAE | 149 (92.5%) | 153 (92.7%) | 302 (92.6%) | 146 (89.0%) | |
| | | | | | |
| Total number of Grade 3, 4, or 5 TEAEs | 250 | 260 | 510 | 242 | 14.3.8.2 |
| Number of patients with at least one Grade 3, 4, or 5 TEAE | 67 (41.6%) | 76 (46.1%) | 143 (43.9%) | 63 (38.4%) | |
| | | | | | |
| Total number of study drug-related TEAEs | 24 | 20 | 44 | 9 | 14.3.9 |
| Number of patients with at least one study drug-related TEAE | 16 (9.9%) | 12 (7.3%) | 28 (8.6%) | 8 (4.9%) | |
| | | | | | |
| Total number of TESAEs | 274 | 254 | 528 | 219 | 14.3.10 |
| Number of patients with at least one TESAE | 77 (47.8%) | 75 (45.5%) | 152 (46.6%) | 71 (43.3%) | |
| | | | | | |
| Number of patients who died through 28 days after study termination (On-Study) | 7 (4.3%) | 16 (9.7%) | 23 (7.1%) | 10 (6.1%) | 14.3.11 |
| | | | | | |
| Total number of TEAEs leading to discontinuation | 30 | 24 | 54 | 24 | 14.3.7 |
| Number of patients reporting at least one TEAE leading to treatment discontinuation | 21 (13.0%) | 22 (13.3%) | 43 (13.2%) | 18 (11.0%) | |
| | | | | | |
| Total number of patients with at least one CSE event | (17.4%) | 35 (21.2%) | 63 (19.3%) | 28 (17.1%) | CSE<br>Technical<br>Report<br>Table 1.1 |

TEAE=treatment emergent adverse event; TESAE= treatment emergent serious adverse event; CSE=composite safety event

Sponsor's table

**Study AFX01-13:**

Table 25: Summary of Adverse Events

| | AF37702-LS N = 167 | AF37702-HS N = 163 | AF37702 Injection Combined N = 330 | Darbepoetin alfa N = 163 | Source Table |
|---|---|---|---|---|---|
| Total Number of TEAEs | 1776 | 1808 | 3584 | 1616 | 14.3.5 |
| Number of patients reporting at least one TEAE | 160 (95.8%) | 152 (93.3%) | 312 (94.5%) | 153 (93.9%) | |
| | | | | | |
| Total number of Grade 3, 4, or 5 TEAEs | 310 | 334 | 644 | 232 | 14.3.8.2 |
| Number of patients with at least one Grade 3, 4, or 5 TEAE | 86 (51.5%) | 82 (50.3%) | 168 (50.9%) | 67 (41.1%) | |
| | | | | | |
| Total number of study drug-related TEAEs | 23 | 26 | 49 | 18 | 14.3.9 |
| Number of patients with at least one study drug-related TEAE | 17 (10.2%) | 13 (8.0%) | 30 (9.1%) | 11 (6.7%) | |
| | | | | | |
| Total number of TESAEs | 236 | 329 | 565 | 176 | 14.3.10 |
| Number of patients with at least one TESAE | 86 (51.5%) | 80 (49.1%) | 166 (50.3%) | 70 (42.9%) | |
| | | | | | |
| Number of patients who died through 28 days after study termination (On-Study) | 22 (13.2%) | 13 (8.0%) | 35 (10.6%) | 12 (7.4%) | 14.3.11 |
| | | | | | |
| Total number of TEAEs leading to discontinuation | 36 | 24 | 60 | 21 | 14.3.7 |
| Number of patients reporting at least one TEAE leading to treatment discontinuation | 25 (15.0%) | 17 (10.4%) | 42 (12.7%) | 16 (9.8%) | |
| | | | | | |
| Total number of patients with at least one CSE event | 40 (24.0%) | 38 (23.3%) | 78 (23.6%) | 28 (17.2%) | CSE Report 3.1 |

TEAE=treatment emergent adverse event; TESAE= treatment emergent serious adverse event; CSE=composite safety event

Sponsor's table

As in the dialysis studies the vast majority of patients reported at least one adverse event during the study. About half of patients in each treatment group in the non-dialysis studies had one or more TESAE, similar to dialysis Study AFX01-14 but slightly less than in dialysis Study AFX01-12. The proportions of patients having TEAEs and TESAES were a bit higher in Study AFX01-13 than in AFX01-11. However, the proportions were similar across treatment arms in each of the studies. In both of the non-dialysis studies, the proportion of patients having TEAE leading to treatment discontinuation was numerically greater in each of the peginesatide groups than in the darbepoetin group. In the non-dialysis studies the proportion of patients who died through 28 days after study termination was numerically greater in the pooled peginesatide groups as compared to the darbepoetin group with this observation being more pronounced in Study AFX01-13.

The most common serious TEAE events (TESAES) in Studies AFX01-11 and AFX01-13 are summarized in the following table.

**Non-Dialysis Studies (AFX01-11 and AFX01-13): Most Common\* Treatment-Emergent Serious Adverse Events Terms, [Number (%) of Patients] (Safety Population)**

| | AFX01-11 | | | AFX01-13 | | |
|---|---|---|---|---|---|---|
| | Peginesatide SC starting dose 0.025mg/kg Q4W (N=161) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=165) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=164) | Peginesatide SC starting dose 0.025mg/kg Q4W (N=167) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=163) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=163) |
| Any TESAE | 77 (47.8%) | 75 (45.5%) | 71 (43.3%) | 86 (51.5%) | 80 (49.1%) | 70 (42.9%) |
| | | | | | | |
| Anemia | 5 (3.1%) | 5 (3.0%) | 1 (0.6%) | 7 (4.2%) | 6 (3.7%) | 4 (2.5%) |
| Cardiac failure congestive | 15 (9.3%) | 16 (9.7%) | 14 (8.5%) | 7 (4.2%) | 18 (11.0%) | 12 (7.4%) |
| Atrial fibrillation | 3 (1.9%) | 7 (4.2%) | 3 (1.8%) | 1 (0.6%) | 5 (3.1%) | 4 (2.5%) |
| Myocardial infarction | 1 (0.6%) | 6 (3.6%) | 4 (2.4%) | 4 (2.4%) | 2 (1.2%) | 4 (2.5%) |
| Acute myocardial infarction | 4 (2.5%) | 3 (1.8%) | 1 (0.6%) | 5 (3.0%) | 4 (2.5%) | 2 (1.2%) |
| Cardiac arrest | 2 (1.2%) | 2 (1.2%) | 1 (0.6%) | 5 (3.0%) | 2 (1.2%) | 3 (1.8%) |
| Bradycardia | 1 (0.6%) | 2 (1.2%) | 4 (2.4%) | 4 (2.4%) | 5 (3.1%) | 0 (0.0%) |
| Gastrointestinal hemorrhage | 4 (2.5%) | 4 (2.4%) | 0 (0.0%) | 2 (1.2%) | 5 (3.1%) | 2 (1.2%) |
| Pneumonia | 10 (6.2%) | 8 (4.8%) | 9 (5.5%) | 4 (2.4%) | 11 (6.7%) | 5 (3.1%) |
| Urinary tract infection | 5 (3.1%) | 9 (5.5%) | 7 (4.3%) | 5 (3.0%) | 5 (3.1%) | 1 (0.6%) |
| Cellulitis | 6 (3.7%) | 5 (3.0%) | 3 (1.8%) | 4 (2.4%) | 2 (1.2%) | 3 (1.8%) |
| Sepsis | 4 (2.5%) | 1 (0.6%) | 3 (1.8%) | 0 (0.0%) | 3 (1.8%) | 2 (1.2%) |
| Hypokalemia | 4 (2.5%) | 7 (4.2%) | 1 (0.6%) | 6 (3.6%) | 2 (1.2%) | 4 (2.5%) |
| Dehydration | 2 (1.2%) | 4 (2.4%) | 5 (3.0%) | 3 (1.8%) | 4 (2.5%) | 0 (0.0%) |
| Hypoglycemia | 2 (1.2%) | 3 (1.8%) | 5 (3.0%) | 1 (0.6%) | 6 (3.7%) | 6 (3.7%) |
| Renal failure acute | 21 (13.0%) | 13 (7.9%) | 9 (5.5%) | 11 (6.6%) | 11 (6.7%) | 15 (9.2%) |
| Renal failure chronic | 12 (7.5%) | 3 (1.8%) | 8 (4.9%) | 10 (6.0%) | 6 (3.7%) | 8 (4.9%) |
| Azotemia | 4 (2.5%) | 3 (1.8%) | 6 (3.7%) | 2 (1.2%) | 1 (0.6%) | 1 (0.6%) |
| Renal failure | 5 (3.1) | 4 (2.4%) | 4 (2.4%) | 2 (1.2%) | 2 (1.2%) | 1 (0.6%) |
| Hypertension | 3 (1.9%) | 5 (3.0%) | 5 (3.0%) | 2 (1.2%) | 1 (0.6%) | 1 (0.6%) |

\*occurred in 1.5% or more patients in the study

Data from sponsor's tables

TESAE were reported during all study periods (correction, evaluation and long-term safety followup). In Study AFX01-11 the most common TESAE were 'cardiac failure congestive' (9.5% of peginesatide treated patients; 8.5% of darbepoietin-treated patients), 'renal failure acute' (10.4% of peginesatide-treated patients; 5.5% of darbepoetin-treated patients), 'pneumonia' (5.5% of peginesatide-treated patients; 5.5% of darbepoetin-treated patients), 'renal failure chronic' (4.6% of peginesatide-treated patients; 4.9% of darbepoetin-treated patients), 'urinary tract infection'(4.3% of peginesatide-treated patients; 4.3% of darbepoetin-treated patients). In Study AFX01-13 the most common TESAE were 'cardiac failure congestive' (7.6% of peginesatide treated patients; 7.4% of darbepoetin-treated patients), 'renal failure acute' (6.7% of peginesatide-treated patients; 9.2% of darbepoetin-treated patients), 'renal failure chronic' (4.8% of peginesatide-treated patients; 4.9% of darbepoetin-treated patients), 'pneumonia'(4.5% of peginesatide-treated patients; 3.1% of darbepoetin-treated patients). In Study AFX01-11 proportions of patients having onset of TESAE were numerically greater in the

combined peginesatide groups than in the darbepoetin group for all treatment periods with the greatest difference during the correction period (correction period: peginesatide, 68/326 (20.9%), darbepoetin 25/164 (15.2%); evaluation period: peginesatide, 38/307 (12.4%), darbepoetin 17/155 (11.0%); long-term safety period: peginesatide, 99/299 (34.1%), darbepoetin 47/151 (31.1%)). In Study AFX01-13 proportions of patients having onset of TESAE were numerically greater in the combined peginesatide groups than in the darbepoetin group for all treatment periods with the magnitude of difference being similar during all periods but greater than in Study AFX01-11 (correction period: peginesatide, 78/330 (23.6%), darbepoetin 30/163 (18.4%); evaluation period: peginesatide, 50/310 (16.1%), darbepoetin 16/154 (10.4%); long-term safety period: peginesatide, 99/298 (33.2%), darbepoetin 41/153 (26.8%)).

In both studies the System Organ Class (SOC) contributing most TESAE were 'Cardiac Disorders', 'Renal and Urinary Disorders', 'Infections and Infestations' terms followed by others as shown in the following table:

**Non-Dialysis Studies (AFX01-11 and AFX01-13): Summary of Most Common Treatment-Emergent Serious Adverse Events for Most Frequent System Organ Classes\*, [Number (%) of Patients] (Safety Population)**

| | AFX01-11 | | | AFX01-13 | | |
|---|---|---|---|---|---|---|
| | Peginesatide SC starting dose 0.025mg/kg Q4W (N=161) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=165) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=164) | Peginesatide SC starting dose 0.025mg/kg Q4W (N=167) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=163) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=163) |
| Any TESAE | 77 (47.8%) | 75 (45.5%) | 71 (43.3%) | 86 (51.5%) | 80 (49.1%) | 70 (42.9%) |
| | | | | | | |
| Cardiac disorders | 26 (16.1%) | 36 (21.8%) | 29 (17.7%) | 29 (17.4%) | 38 (23.3%) | 23 (14.1%) |
| Renal and urinary disorders | 39 (24.2%) | 23 (13.9%) | 27 (16.5%) | 23 (13.8%) | 20 (12.3%) | 15 (9.2%) |
| Infections and Infestations | 28 (17.4%) | 31 (18.8%) | 27 (16.5%) | 24 (14.4%) | 29 (17.8%) | 18 (11.0%) |
| Metabolism and nutrition disorders | 12 (7.5%) | 18 (10.9%) | 14 (8.5%) | 14 (8.4%) | 16 (9.8%) | 18 (11.0%) |
| Gastrointestinal disorders | 13 (8.1%) | 10 (6.1%) | 13 (7.9%) | 17 (10.2%) | 20 (12.3%) | 12 (7.4%) |
| Respiratory, thoracic and mediastinal disorcers | 12 (7.5%) | 13 (7.9%) | 8 (4.9%) | 12 (7.2%) | 10 (6.1%) | 12 (7.4%) |
| Nervous system disorders | 8 (5.0%) | 6 (3.6%) | 5 (3.0%) | 10 (6.0%) | 14 (8.6%) | 7 (4.3%) |
| Vascular disorders | 13 (8.1%) | 9 (5.5%) | 10 (6.1%) | 15 (9.0%) | 11 (6.7%) | 8 (4.9%) |
| Injury, poison and procedural complications | 12 (7.5%) | 9 (5.5%) | 4 (2.4%) | 3 (1.8%) | 9 (5.5%) | 8 (4.9%) |
| General disorders and administration site conditions | 8 (5.0%) | 6 (3.6%) | 6 (3.7%) | 12 (7.2%) | 10 (6.1%) | 4 (2.5%) |
| Blood and lymphatic system disorders | 6 (3.7%) | 7 (4.2%) | 3 (1.8%) | 9 (5.4%) | 9 (5.5%) | 4 (2.5%) |

\*Includes only System Organ Classes where 4% or more of study patients had TESAE

data from sponsor's tables

In Study AFX01-11, 9.8% of peginesatide-treated patients and 7.9% of darbepoetin-treated patients had thromboembolic events. In Study AFX01-13, 13.0% of peginesatide-treated patients and 8.6% of darbepoetin-treated patients had thromboembolic events. In Study AFX01-11 four patients exposed to peginesatide developed binding antibodies to the drug (1 binding only; 3 neutralizing). Decreased hemoglobin with or without increased peginesatide doses was seen in all 4 patients shortly before or after detection of the antibody. In study AFX01-13 six patients treated with peginesatide developed binding antibodies to the drug (1 binding only, 5 neutralizing). In 5 patients hemoglobin decrease was seen shortly before or after detection of the antibody.

For the major cardiovascular safety endpoint, the sponsor's tables below summarize the Composite Safety Endpoint (CSE) and components thereof and show the statistical analysis for each of the non-dialysis studies. In both studies the proportions of patients who experienced at least one CSE event was numerically higher in each of the peginesatide treatment groups than in the darbepoetin group, with the difference being more marked in Study AFX01-13. CSE component events with a difference of $\geq$2% between any treatment groups were death and unstable angina in Study AFX01-11 and death and arrhythmia in AFX01-13, with higher rates in the peginesatide groups in all cases. The time to first CSE event for the combined peginesatide groups relative to darbepoetin gave a hazard ratio of 1.07 (0.71, 1.61) for Study AFX01-11 and 1.58 (1.05, 2.38) for Study AFX01-13.

**Study AFX01-11:   Summary of Composite Safety Endpoint:  Safety Population and On-Study**

| Composite Safety Endpoint Events | Statistic | AF37702 Inj. SC Starting Dose 0.025 mg/kg Q4W (N=161) | AF37702 Inj. SC Starting Dose 0.04 mg/kg Q4W (N=165) | AF37702 Inj. SC Starting Dose (0.025+0.04) (N=326) | Darbepoetin alfa SC Starting Dose 0.75 mcg/kg Q2W (N=164) | Total (N=490) |
|---|---|---|---|---|---|---|
| Time to First Event (Days) [1] | | | | | | |
| | Num Events | 28 | 35 | 63 | 28 | 91 |
| | Num Censored | 133 | 130 | 263 | 136 | 399 |
| | Median | NE | NE | NE | NE | NE |
| | (95% CI) | NE- NE | NE- NE | NE- NE | NE- NE | NE- NE |
| | Q1 - Q3 | NE- NE | 614.0- NE | NE- NE | NE- NE | NE- NE |
| Hazard Ratio [2] Relative to Darbepoetin alfa | | | | | | |
| | HR | 1.0276 | 1.2436 | 1.1373 | | |
| | 90% CI | (0.6619, 1.5955) | (0.8192, 1.8878) | (0.7825, 1.6529) | | |
| Hazard Ratio [2] Relative to AF37702 Inj. Starting Dose 0.025 mg/kg | | | | | | |
| | HR | | 1.2101 | | | |
| | 90% CI | | (0.7971, 1.8372) | | | |
| Chi-Square Test for Time to First Event Compared to Darbepoetin alfa [3] | | | | | | |
| | p-value | 0.9188 | 0.3904 | 0.5714 | | |
| Chi-Square Test for Time to First Event Among Active Treatment Groups [3] | | | | | | |
| | p-value | | 0.4524 | | | |

[1] Kaplan-Meier method. Time to First Event =Date of First Composite Safety Endpoint Event - Date of Randomization + 1.
Num Censored= No. of patients who did not have composite safety endpoint events during the study.
[2] Parameter estimates were obtained from the Cox proportional hazards model stratified for treatment and the randomization stratification factors.
[3] Chi-Square Test (as produced by the Cox regression model) compared hazard ratio for the treatment groups, stratified by the randomization stratification factors.
Note: Deaths that occurred through 28 days post study termination were included in the analysis.
NE = Not Estimable

| Composite Safety Endpoint Events | Statistic | AF37702 Inj. SC Starting Dose 0.025 mg/kg Q4W (N=161) | AF37702 Inj. SC Starting Dose 0.04 mg/kg Q4W (N=165) | AF37702 Inj. SC Starting Dose (0.025+0.04) (N=326) | Darbepoetin alfa SC Starting Dose 0.75 mcg/kg Q2W (N=164) | Total (N=490) |
|---|---|---|---|---|---|---|
| No. of Patients with >= 1 ERC Adjudicated Composite Safety Endpoint Events | | | | | | |
| | N (%) | 28 (17.4) | 35 (21.2) | 63 (19.3) | 28 (17.1) | 91 (18.6) |
| No. of Patients with Following ERC Adjudicated Events*: | | | | | | |
| Death (All Causes) | N (%) | 7 (4.3) | 16 (9.7) | 23 (7.1) | 10 (6.1) | 33 (6.7) |
| Stroke | N (%) | 1 (0.6) | 1 (0.6) | 2 (0.6) | 1 (0.6) | 3 (0.6) |
| MI | N (%) | 5 (3.1) | 6 (3.6) | 11 (3.4) | 5 (3.0) | 16 (3.3) |
| Unstable Angina | N (%) | 5 (3.1) | 2 (1.2) | 7 (2.1) | 1 (0.6) | 8 (1.6) |
| CHF | N (%) | 13 (8.1) | 16 (9.7) | 29 (8.9) | 13 (7.9) | 42 (8.6) |
| Arrhythmia | N (%) | 8 (5.0) | 10 (6.1) | 18 (5.5) | 7 (4.3) | 25 (5.1) |
| Patient's First ERC Adjudicated Events: | | | | | | |
| ACUTE MI | N (%) | 2 (1.2) | 4 (2.4) | 6 (1.8) | 3 (1.8) | 9 (1.8) |
| ACUTE MI/ARRHYTHMIA | N (%) | 1 (0.6) | 0 | 1 (0.3) | 0 | 1 (0.2) |
| ACUTE MI/CHF | N (%) | 1 (0.6) | 2 (1.2) | 3 (0.9) | 1 (0.6) | 4 (0.8) |
| ARRHYTHMIA | N (%) | 4 (2.5) | 5 (3.0) | 9 (2.8) | 5 (3.0) | 14 (2.9) |
| ARRHYTHMIA/CHF | N (%) | 0 | 2 (1.2) | 2 (0.6) | 0 | 2 (0.4) |
| ARRHYTHMIA/DEATH | N (%) | 1 (0.6) | 0 | 1 (0.3) | 0 | 1 (0.2) |
| CHF | N (%) | 10 (6.2) | 12 (7.3) | 22 (6.7) | 12 (7.3) | 34 (6.9) |
| DEATH | N (%) | 5 (3.1) | 7 (4.2) | 12 (3.7) | 6 (3.7) | 18 (3.7) |
| STROKE | N (%) | 0 | 1 (0.6) | 1 (0.3) | 1 (0.6) | 2 (0.4) |
| UNSTABLE ANGINA | N (%) | 4 (2.5) | 2 (1.2) | 6 (1.8) | 0 | 6 (1.2) |

* Rows are not mutually exclusive.
Note 1 : Deaths that occurred through 28 days post study termination were included in the analysis.
Note 2: Unstable Angina, CHF and Arrhythmia must meet the SAE definition in the protocol.

Data: ADCSE_S, ADCSE_E, ADCSE. Prog: cse/programs/tfl/t-endpoint-correct.sas, 1-1-t-endpoint-11.rtf (23FEB2011:20:08))
Source: CSE Technical Report Table 1.1

| Composite Safety Endpoint Events | Statistic | AF37702 Inj. SC Starting Dose 0.025 mg/kg Q4W (N=161) | AF37702 Inj. SC Starting Dose 0.04 mg/kg Q4W (N=165) | AF37702 Inj. SC Starting Dose (0.025+0.04) (N=326) | Darbepoetin alfa SC Starting Dose 0.75 mcg/kg Q2W (N=164) | Total (N=490) |
|---|---|---|---|---|---|---|
| No. of Patients with >= 1 ERC Adjudicated Composite Safety Endpoint Events Within First 52 Weeks | | | | | | |
| | N (%) | 18 (11.2) | 19 (11.5) | 37 (11.3) | 15 (9.1) | 52 (10.6) |
| Within First 52 Weeks Relative Risk (RR) from Darbepoetin alfa[4][5] | | | | | | |
| | RR | 1.2121 | 1.2419 | 1.2259 | | |
| | 95% CI | (0.6388, 2.3000) | (0.6580, 2.3441) | (0.6979, 2.1535) | | |
| Relative Risk (RR) from AF37702 Inj. Starting Dose 0.025 mg/kg[4][6] | | | | | | |
| | RR | | 0.9817 | | | |
| | 95% CI | | (0.5418, 1.7791) | | | |

[4] Relative risk estimate and CI were obtained from the CMH test including terms for treatment group and the randomization stratification factors.
[5] Relative risk from Darbepoetin alfa = AF37702 Injection group/ Darbepoetin alfa group.
[6] Relative risk from AF37702 Inj. Starting Dose 0.025 mg/kg = AF37702 Inj. Starting Dose 0.04 mg/kg/AF37702 Inj. Starting Dose 0.025 mg/kg.
Note: Deaths that occurred through 28 days post study termination were included in the analysis.

Data: ADCSE_S, ADCSE_E, ADCSE. Prog: cse/programs/tfl/t-endpoint-correct.sas, 1-1-t-endpoint-11.rtf (23FEB2011:20:08)

Source: CSE Technical Report Table 1.1

**Study AFX01-13:  Summary of Composite Safety Endpoint:  Safety Population and On-Study**

| Composite Safety Endpoint Events | Statistic | AF37702 Inj. SC Starting Dose 0.025 mg/kg Q4W (N=167) | AF37702 Inj. SC Starting Dose 0.04 mg/kg Q4W (N=163) | AF37702 Inj. SC Starting Dose (0.025+0.04) (N=330) | Darbepoetin alfa SC Starting Dose 0.75 mcg/kg Q2W (N=163) | Total (N=493) |
|---|---|---|---|---|---|---|
| Time to First Event (Days) [1] | | | | | | |
| | Num Events | 40 | 38 | 78 | 28 | 106 |
| | Num Censored | 127 | 125 | 252 | 135 | 387 |
| | Median | NE | NE | NE | 690.0 | 690.0 |
| | (95% CI) | 651.0- NE | NE- NE | NE- NE | NE- NE | 690.0- NE |
| | Q1 - Q3 | 540.0- NE | 584.0- NE | 540.0- NE | 643.0- 690.0 | 599.0- NE |
| Hazard Ratio [2] Relative to Darbepoetin alfa | | | | | | |
| | HR | 1.5011 | 1.5629 | 1.5303 | | |
| | 90% CI | (0.9995, 2.2544) | (1.0343, 2.3616) | (1.0635, 2.2021) | | |
| Hazard Ratio [2] Relative to AF37702 Inj. Starting Dose 0.025 mg/kg | | | | | | |
| | HR | | 1.0412 | | | |
| | 90% CI | | (0.7147, 1.5167) | | | |
| Chi-Square Test for Time to First Event Compared to Darbepoetin alfa [3] | | | | | | |
| | p-value | 0.1004 | 0.0752 | 0.0545 | | |
| Chi-Square Test for Time to First Event Among Active Treatment Groups [3] | | | | | | |
| | p-value | | 0.8600 | | | |

[1] Kaplan-Meier method. Time to First Event =Date of First Composite Safety Endpoint Event - Date of Randomization + 1.
Num Censored= No. of patients who did not have composite safety endpoint events during the study.
[2] Parameter estimates were obtained from the Cox proportional hazards model stratified for treatment and the randomization stratification factors.
[3] Chi-Square Test (as produced by the Cox regression model) compared hazard ratio for the treatment groups, stratified by the randomization stratification factors.
Note: Deaths that occurred through 28 days post study termination were included in the analysis.
NE = Not Estimable

| Composite Safety Endpoint Events | Statistic | AF37702 Inj. SC Starting Dose 0.025 mg/kg Q4W (N=167) | AF37702 Inj. SC Starting Dose 0.04 mg/kg Q4W (N=163) | AF37702 Inj. SC Starting Dose (0.025+0.04) (N=330) | Darbepoetin alfa SC Starting Dose 0.75 mcg/kg Q2W (N=163) | Total (N=493) |
|---|---|---|---|---|---|---|
| No. of Patients with >= 1 ERC Adjudicated Composite Safety Endpoint Events | | | | | | |
| | N (%) | 40 (24.0) | 38 (23.3) | 78 (23.6) | 28 (17.2) | 106 (21.5) |
| No. of Patients with Following ERC Adjudicated Events*: | | | | | | |
| Death (All Causes) | N (%) | 22 (13.2) | 13 (8.0) | 35 (10.6) | 12 (7.4) | 47 (9.5) |
| Stroke | N (%) | 2 (1.2) | 3 (1.8) | 5 (1.5) | 2 (1.2) | 7 (1.4) |
| MI | N (%) | 7 (4.2) | 6 (3.7) | 13 (3.9) | 6 (3.7) | 19 (3.9) |
| Unstable Angina | N (%) | 4 (2.4) | 5 (3.1) | 9 (2.7) | 2 (1.2) | 11 (2.2) |
| CHF | N (%) | 11 (6.6) | 16 (9.8) | 27 (8.2) | 15 (9.2) | 42 (8.5) |
| Arrhythmia | N (%) | 6 (3.6) | 13 (8.0) | 19 (5.8) | 6 (3.7) | 25 (5.1) |
| Patient's First ERC Adjudicated Events: | | | | | | |
| ACUTE MI | N (%) | 5 (3.0) | 2 (1.2) | 7 (2.1) | 1 (0.6) | 8 (1.6) |
| ACUTE MI/CHF | N (%) | 1 (0.6) | 2 (1.2) | 3 (0.9) | 3 (1.8) | 6 (1.2) |
| ACUTE MI/STROKE | N (%) | 0 | 1 (0.6) | 1 (0.3) | 0 | 1 (0.2) |
| ARRHYTHMIA | N (%) | 5 (3.0) | 10 (6.1) | 15 (4.5) | 3 (1.8) | 18 (3.7) |
| ARRHYTHMIA/CHF | N (%) | 1 (0.6) | 1 (0.6) | 2 (0.6) | 0 | 2 (0.4) |
| CHF | N (%) | 7 (4.2) | 11 (6.7) | 18 (5.5) | 12 (7.4) | 30 (6.1) |
| DEATH | N (%) | 15 (9.0) | 6 (3.7) | 21 (6.4) | 6 (3.7) | 27 (5.5) |
| STROKE | N (%) | 2 (1.2) | 2 (1.2) | 4 (1.2) | 2 (1.2) | 6 (1.2) |
| UNSTABLE ANGINA | N (%) | 4 (2.4) | 3 (1.8) | 7 (2.1) | 1 (0.6) | 8 (1.6) |

* Rows are not mutually exclusive.
Note 1 : Deaths that occurred through 28 days post study termination were included in the analysis.
Note 2: Unstable Angina, CHF and Arrhythmia must meet the SAE definition in the protocol.

Data: ADCSE_S, ADCSE_E, ADCSE. Prog: cse/programs/tfl/t-endpoint-correct.sas, 3-1-t-endpoint-13.rtf (23FEB2011:20:08)

| Composite Safety Endpoint Events | Statistic | AF37702 Inj. SC Starting Dose 0.025 mg/kg Q4W (N=167) | AF37702 Inj. SC Starting Dose 0.04 mg/kg Q4W (N=163) | AF37702 Inj. SC Starting Dose (0.025+0.04) (N=330) | Darbepoetin alfa SC Starting Dose 0.75 mcg/kg Q2W (N=163) | Total (N=493) |
|---|---|---|---|---|---|---|
| No. of Patients with >= 1 ERC Adjudicated Composite Safety Endpoint Events Within First 52 Weeks | | | | | | |
| | N (%) | 25 (15.0) | 31 (19.0) | 56 (17.0) | 20 (12.3) | 76 (15.4) |
| Within First 52 Weeks Relative Risk (RR) from Darbepoetin alfa[4][5] | | | | | | |
| | RR | 1.2234 | 1.5500 | 1.3890 | | |
| | 95% CI | (0.7116, 2.1031) | (0.9278, 2.5894) | (0.8678, 2.2231) | | |
| Relative Risk (RR) from AF37702 Inj. Starting Dose 0.025 mg/kg[4][6] | | | | | | |
| | RR | | 0.7927 | | | |
| | 95% CI | | (0.4911, 1.2796) | | | |

[4] Relative risk estimate and CI were obtained from the CMH test including terms for treatment group and the randomization stratification factors.
[5] Relative risk from Darbepoetin alfa = AF37702 Injection group/ Darbepoetin alfa group.
[6] Relative risk from AF37702 Inj. Starting Dose 0.025 mg/kg = AF37702 Inj. Starting Dose 0.04 mg/kg/AF37702 Inj. Starting Dose 0.025 mg/kg.
Note: Deaths that occurred through 28 days post study termination were included in the analysis.
Data: ADCSE_S, ADCSE_E, ADCSE. Prog: cse/programs/tfl/t-endpoint-correct.sas, 3-1-t-endpoint-13.rtf (23FEB2011:20:08)
Source: CSE Table 3.1

The following table summarizes deaths in the two non-dialysis studies.

**Non-Dialysis Studies (AFX01-11 and AFX01-13):  Deaths (Safety Population)**

| | AFX01-11 | | | AFX01-13 | | |
|---|---|---|---|---|---|---|
| | Peginesatide SC starting dose 0.025mg/kg Q4W (N=161) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=165) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=164) | Peginesatide SC starting dose 0.025mg/kg Q4W (N=167) | Peginesatide SC starting dose 0.04mg/kg Q4W (N=163) | Darbepoetin alfa SC starting dose 0.75mcg/kg Q2W (N=163) |
| Total deaths in study database | 10 (6.2%) | 21 (12.7%) | 12 (7.3%) | 27 (16.2%) | 15 (9.2%) | 12 (7.4%) |
| Total deaths during study (through 28 days after study termination)[a] | 7 (4.3%) | 16 (9.7%) | 10 (6.1%) | 22 (13.2%) | 13 (8.0%) | 12 (7.4%) |
|     MI | 0 (0.0%) | 1 (0.6%) | 1 (0.6%) | 2 (1.2%) | 2 (1.2%) | 1 (0.6%) |
|     Stroke | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (1.2%) | 0 (0.0%) | 0 (0.0%) |
|     CHF | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 2 (1.2%) | 1 (0.6%) | 0 (0.0%) |
|     Arrhythmia | 0 (0.0%) | 2 (1.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.6%) | 1 (0.6%) |
|     Infection | 0 (0.0%) | 1 (0.6%) | 2 (1.2%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) |
|     Cardiac arrest | 2 (1.2%) | 2 (1.2%) | 0 (0.0%) | 3 (1.8%) | 0 (0.0%) | 1 (0.6%) |
|     Cardiorespiratory arrest | 2 (1.2%) | 1 (0.6%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) |
|     CRF | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 2 (1.2%) | 3 (1.8%) | 2 (1.2%) |
|     Respiratory failure/acute respiratory failure | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) |
|     Cancer | 0 (0.0%) | 0 (0.0%) | 2 (1.2%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) |
|     Sudden death | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 2 (1.2%) | 1 (0.6%) | 2 (1.2%) |
|     Unknown | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 0 (0.1%) |
| Timing of deaths during study [b] | | | | | | |
|     During correction period | 2/61 (1.2%) | 3/165 (1.8%) | 2/164 (1.2%) | 3/167 (1.8%) | 3/163 (1.8%) | 4/163 (2.5%) |
|     During evaluation period | 0/151 (0.0%) | 3/156 (1.9%) | 0/155 (0.0%) | 3/160 (1.8%) | 3/150 (2.0%) | 1/154 (0.6%) |
|     During long-term safety eval | 4/144 (2.8%) | 6/146 (4.1%) | 7/151 (4.6%) | 13/154 (8.4%) | 5/144 (3.5%) | 6/153 (3.9%) |

[a] includes deaths occurring during followup after study drug discontinuation; includes information from Death Report forms; causes listed do not include all causes (only most frequent and relevant are listed)
[b] through day 28 after  study drug discontinuation, excluding patients who were started on another ESA or underwent renal transplant

based on sponsor's tables

For the non-dialysis studies, in terms of total deaths in the study database, the percentages of patients who died (while lower in the non-dialysis studies overall and for all treatment arms except the peginesatide 0.025 mg/kg treatment arm in Study AFX01-13 than in the dialysis studies) varied among treatment arms, ranging from 6.2% in the 0.025 mg/kg peginesatide arm in Study AFX01-11 to 16.2% in the 0.025 mg/kg peginesatide arm in Study AFX01-13. Generally, causes of death appeared similar across treatment arms and across studies in the non-dialysis studies; however, these studies were smaller than the dialysis studies (enrolled only about 61% of the number of patients as the dialysis studies) and numbers of events were fewer. Considering the numbers for total deaths in the database and deaths during the study (up to 28 days after study drug discontinuation), while most deaths occurred during the study, the proportions of on study deaths (as percentage of total deaths in database) varied widely from 70% to 100%, however numbers of deaths were small. Overall, more of the deaths occurred during the long-term safety evaluation period than during the correction and evaluation periods; however, numbers were small.

Additional Studies:

One additional multicenter, randomized, controlled, open-label study in patients with CKD on dialysis comparing two doses of peginesatide was conducted by the sponsor in Russia. In this Phase 2 trial (Study AFX01-15) 114 adult patients with CKD who had been on dialysis for at least 2 weeks prior to randomization and who had not received ESA treatment or RBC or whole blood transfusion in the prior 12 weeks and who had hemoglobin values ≥8.0 g/dL and <11.0 g/dL were randomized (1:1:1) to treatment with either peginesatide starting dose of 0.04 mg/kg IV every 4 weeks, peginesatide starting dose 0.08 mg/kg IV every 4 weeks, or epoetin alfa (Eprex) [an ESA that is not approved in the U.S]. It is not known whether any of the enrolled patients were ESA naïve (i.e., not previously treated with and ESA). The study consisted of a 4-week Screening Period followed by a 20-week Correction Period followed by an 8-week Evaluation Period. The primary efficacy endpoint was the mean change in hemoglobin from baseline to the Evaluation period. All patients received at least one dose of study drug and 107 patients completed study treatment. The results for the primary efficacy endpoint are shown below:

**Study AFX01-15: Primary Efficacy Endpoint: Summary of Hemoglobin and Change in Hemoglobin from Baselin to Evaluation Period (Full Analysis Population)**

|  | peginesatide 0.04 mg/kg | peginesatide 0.04 mg/kg | epoetin |
|---|---|---|---|
| Baseline | | | |
| N | 39 | 37 | 38 |
| Mean Hgb (±SD) | 9.3±0.74 | 9.2±0.70 | 9.1±0.74 |
| Evaluation period | | | |
| N | 37 | 37 | 36 |
| Mean Hgb (±SD) | 11.5±1.1 | 11.6±0.94 | 11.5±0.78 |
| Change | | | |
| N | 37 | 37 | 36 |
| Mean Hgb (±SD) | 2.2±1.04 | 2.4±0.97 | 2.4±0.99 |

A total of 18 patients reported 31 TESAEs (peginesatide 0.08 mg/kg group, 8/37 (21.6%) patients; peginesatide 0.04 mg/kg, 6/39 (15.4%) patients; epoetin 4/38 (10.5%) patients). There were no deaths in the study. Seven patients withdrew from the study prematurely (peginesatide 0.04 mg/kg: 2 [1,

withdrew consent; 1, kidney transplant]; peginesatide 0.08 mg/kg [1, noncompliance]; epoetin [4, kidney transplant]).

Pediatric Plan:
No pediatric patients were studied in the drug development program for peginesatide.  The sponsor has requested a waiver for study of peginesatide in patients younger than 12 months of age because of very low prevalence of anemia due to CKD in this age group who are on dialysis and not undergoing kidney transplantation.  The sponsor requests a deferral for studies in patients age >12 months to <18 years.  For these patients the sponsor plans four studies  including:  (1)a phase 2, open-label single-arm uncontrolled study to evaluate safety and efficacy of peginesatide for maintenance treatment of anemia (IV or SC every 4 weeks for 24 weeks) in children from 1 to <18 years with CKD on hemodialysis and already receiving ESA therapy.  Starting dose will be based on patient's current ESA dose and use a conversion factor determined from PK/PD modeling data from adult studies.  The drug will be titrated during Weeks 1-16 and efficacy evaluation will be from week 17-24; (2)an open-label 6-months extension study for patients who have completed the first study to continue on achieved stable dose of peginesatide for an additional 6 months of treatment; (3)a phase 3, randomized, active-control, open-label, parallel groups study to evaluate efficacy and safety of peginesatide for treatment of anemia (IV or SC every 4 weeks for 24 weeks) in children from 1 to <18 years with CKD on hemodialysis and already receiving ESA therapy.  Starting dose will be based on the results of the first study.  The drug will be titrated during Weeks 1-16 and efficacy evaluation will be from week 17-24; (4)an open-label 6-months extension study for patients who have completed the third study to continue on achieved stable dose of peginesatide for an additional 6 months of treatment.  Full protocols for these studies have not yet been submitted.

**Discussion:**
The sponsor is seeking approval of Omontys (peginesatide) for the indication:
> "Omontys is an erythropoiesis-stimulating agenet (ESA) that is indicated for the treatment of anemia associated with chronic renal failure (CRF) in adult patients on dialysis.
>
> Omontys is not indicated for the treatment of anemia in CFR patients not on dialysis or for the treatment of anemia due to cancer chemotherapy [*See Warnings and Precautions (5.1, 5.2)*]."

Efficacy:
The clinical development program included four randomized, controlled, open-label clinical trials in patients with chronic renal failure, with two studies being in patients on dialysis (Studies AFX01-12 and AFX01-14) and two in patients not on dialysis (Studies AFX01-11 and AFX013).  In this review major results are presented for each individual study.  Results of the combined dialysis studies and the combined non-dialysis studies are presented in Dr. Dmytrijuk's Clinical Review (signed 2/09/2012).  For each pair of studies the individual study results were similar.

The efficacy analysis results for the patients on dialysis (Studies AFX01-12 and AFX01-14) were robust and convincing.  There was reasonable consistency between the two studies (one done in the U.S. and one multinational).  The primary efficacy endpoint was mean change in hemoglobin between baseline (the mean of the four most recent hemoglobin values prior to randomization) and the evaluation period (mean hemoglobin from week 29 through week 36).  The primary efficacy analyses

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from the FDA Statistical Review of the individual dialysis studies are shown below (see Statistical Reviews by Q Xu, Ph.D., 2/7/2012):

Study AFX01-12:

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) | | |

Study AFX01-14:

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 | Epotin 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) | | |

For each study the Statistical Review concluded that the primary efficacy endpoint satisfied the protocol-specified criterion for the non-inferiority of efficacy of peginesatide relative to epoetin. The Statistical Review comments that the sponsor has used the full analysis population (98.8% of randomized patients) rather than the intent-to-treat (ITT) population for the analysis of the primary efficacy endpoint; however, because the minor difference between the two populations, this does not significantly impact the analysis results. The review noted some differences between treatments in the baseline and observed characteristics of the two treatment arms. These may be summarized as follows:

- In AFX01-12:
  - 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 (15.6% vs. 8.5%).
  - The proportion of patients terminated from the study prematurely was slightly higher in the peginesatide group compared to the epoetin group (31.2 % vs. 25.5%)
  - There were more white patients in the peginesatide group compared to the epoetin group (50.2% vs. 43.1%)
  - There were fewer black patients in the peginesatide group compared to the epoetin group (44.7% vs 50.6%)

- Mean and median serum ferritin values were higher in the peginesatide group compared to the epoetin group (mean ferritin: 697.6 ng/mL vs 657 ng/mL; median ferritin: 666 ng/mL vs 609 ng/mL)
        - Baseline renal disease characteristics were balanced between the peginesatide and epoetin groups.
        - Baseline cardiovascular disease characteristics were balanced between the peginesatide and epoetin groups.
- In AFX01-14:
    - 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 (60.8% vs 39.2%).
    - The proportion of patients with lower baseline hemoglobin values ($\leq$11.4 g/dL) is lower in the peginesatide group than in the epoetin group (62% vs 65.2%).
    - Baseline cardiovascular disease characteristics were balanced between the peginesatide and epoetin groups.

Change in hemoglobin from baseline, proportion of patients maintained within target hemoglobin range, and rates of RBC and whole blood transfusions were similar between the two treatment groups during the evaluation period in both studies. The primary efficacy endpoint (change in hemoglobin) was an objective well-understood clinical laboratory measurement, so the open-label design of the studies is not a major concern for efficacy. Starting peginesatide dose for each patient was determined based on the patient's prior stable ESA dose using a calculated conversion based on pharmacokinetics. There appeared to be a slight tendency for peginesatide doses to creep upward during the studies while epoetin doses tended to decline slightly. However, generally, the dosing strategy appeared to work well. Mean of the patients' mean epoetin dose during the evaluation period in the epoetin arm was 182.6 U/kg per week (median mean, 125 U/kg per week) in Study AFX01-12 and 134.6 U/kg per week (median mean, 91 U/kg per week) in Study AFX01-14. In the studies leading to labeling approval of Epogen/Procrit for use in CKD patients on dialysis, the median dose to maintain hematocrit between 30% and 36% was approximately 225 units/kg per week. It should be noted that the original approval of Epogen/Procrit (epoetin alfa) for use in patients with CKD on dialysis was based on the demonstration of a reduction in red blood cell transfusions in these patients with epoetin as compared to placebo. In the current peginesatide studies, though there was no placebo arm in either study and there were no meaningful between group differences in hemoglobin levels during the studies, it is reasonable to assume both treatments had a therapeutic effect, because of the well-known decline in hemoglobin with end-stage renal failure due to loss of endogenous erythropoietin production and due to ongoing blood loss from chronic hemodialysis. I think, however, we are less certain about the actual magnitude of the effect of either of the drugs (peginesatide or epoetin) in these current studies. Overall, the results appear adequate to reasonably establish efficacy of peginesatide for the indication being sought.

Though the sponsor is not seeking approval for use of peginesatide in patients with CKD not on dialysis, it is relevant to look at the efficacy results for the non-dialysis population, since the development plan for the drug initially did intend to target the non-dialysis CKD population as well as the on-dialysis CKD population. The sponsor's efficacy analyses for Studies AFX01-11 and AFX01-13 demonstrate efficacy in the non-dialysis CKD population based on pre-specified analyses and assessments parallel to those that were done for the studies in CKD patients on dialysis. FDA statistical review did not focus on efficacy analyses of the non-dialysis studies but showed an analysis of the primary efficacy endpoint for those two studies combined as shown below:

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

For the non-dialysis studies the review concluded the result show that peginesatide can be considered non-inferior to the comparator by the applicant's pre-specified criteria.

Safety:
Because of safety concerns that have emerged for erythropoiesis stimulating agents (ESAs) over the past decade and that have led to major changes in the labeling for these agents for safety, all four of the peginesatide studies included a well-defined, pre-specified cardiovascular safety endpoint, termed 'composite safety endpoint (CSE)' as a primary safety endpoint for analysis. The concern for cardiovascular safety arose partly from three published studies, the CHOIR, CREATE and Normal Hematocrit Studies. These studies compared use of ESAs to target higher as compared to lower hemoglobin levels in patients with chronic kidney disease with the anticipation that higher hemoglobin levels would lead to better clinical outcomes. All of these studies were open-label. The major features (particularly primary endpoints), results and the references for these three studies are shown in the following sponsor's table. An additional multinational study, the TREAT Study [Trial to Reduce Cardiovascular Events with Aranesp Therapy; Pfeffer MA et al. N Eng J Med 2009; 361(11):2019-32] evaluated effect of treatment with darbepoetin alfa versus placebo on cardiovascular outcomes in patients with diabetes and chronic kidney disease not on dialysis. The major findings of the four studies are discussed below. See the FDA Statistical Review by M Rothmann, Ph.D. (signed 2/7/2012) for more detailed discussion of these studies.

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Table 2:     Observed Hazard Ratios (High Hgb Target vs. Low Hgb Target), Statistical Power, and Anticipated Event Rates in CHOIR, CREATE, and Normal Hematocrit Studies

| | CHOIR Study [1] | CREATE Study [2] | Normal Hematocrit Study [3] | CSE of AF37702 Injection Phase 3 Studies |
|---|---|---|---|---|
| Patient Population | ESA-naïve patients not on dialysis. | ESA-naïve patients not on dialysis. | End Stage Renal Disease patients with CHF or ischemic heart disease. | ESA-treated patients on dialysis (62%) and patients not on dialysis who had not received ESA treatment within 12 weeks prior to randomization (38%) (see Section 7.4.1) |
| Primary Endpoint | Composite of: <br> • Death <br> • Stroke <br> • MI <br> • Hospitalization for CHF (without renal replacement therapy) | Composite of: <br> • Sudden death <br> • Stroke <br> • MI <br> • Acute heart failure <br> • TIA <br> • Angina pectoris resulting in hospitalization for ≥24 hours or prolongation of hospitalization <br> • Cardiac arrhythmia resulting in hospitalization for ≥24 hours <br> • Complication of peripheral vascular disease (amputation or necrosis) | Composite of: <br> • Death <br> • Nonfatal myocardial infarction | Composite of: <br> • Death (all causes) <br> • Stroke <br> • MI <br> • CHF (that met the definition of an SAE) <br> • Unstable angina (that met the definition of an SAE) <br> • Arrhythmia (that met the definition of an SAE) <br><br> See Sections 6.2.1 and 6.2.2. |
| Hgb or Hct Target Levels Being Compared | 1) Hgb: 13.5 g/dL <br> 2) Hgb: 11.3 g/dL | 1) Hgb: 13.0–15.0 g/dL <br> 2) Hgb: 10.5–11.5 g/dL | 1) Hct: 42% <br> 2) Hct: 30% | Not applicable: Comparison was of AF37702 Inj. vs. comparators using same Hgb targets (see Table 1). |
| Summary of Statistical Power | 80% power to detect a 25% reduction in the composite endpoint rate over 3 years. | 80% power to detect a 33% reduction in the hazard ratio for the composite endpoint over 4 years. | 90% power to detect a 20% difference in event-free survival after three years (risk ratio of 1.3). | 89% power to exclude a hazard ratio greater than 1.3 for AF37702 Inj. vs. comparators (see Section 7.4.1). |
| Anticipated Event Rates | Anticipated event rate in the low Hgb group: 30% over 3 years. | Anticipated annual event rate in the low Hgb group: 15%. | Not specified. | Anticipated event rate in the comparator group: 17.4% per year (see Section 7.4.1). |
| Observed Hazard or Risk Ratio for High Hgb/Low Hgb (or High Hct/Low Hct) and 95% Confidence Interval: | | | | |
| | 1.34 (1.03, 1.74) | 1.28 (0.88, 1.89)* | 1.3 (0.9, 1.9) | |

* Hazard ratio and CI were presented as low Hgb target/high Hgb target in publication, so reciprocals are presented here for consistency with other studies.

Sponsor's table

References:  CHOIR [Correction of Hemoglobin and Outcomes in Renal Insufficiency] Study: Singh AK et al. N Engl J Med 2006; 355(20):2085-98

CREATE [Cardiovascular Risk Reduction by early Anemia Treatment with Epoetin Beta] Study:  Drueke TB et al, N Eng J Med 2006; 355(20):2071-84

Normal Hematocrit Study:  Besarab A et al, N Eng J Med 1998;339(9):584-90

CHOIR and CREATE were studies in patients with chronic kidney disease not on dialysis and who had not received ESAs prior to the study.  The CHOIR Study was conducted in the U.S. and studied 1432 patients with chronic kidney disease (estimated glomerular filtration rate (GFR) of 15 to 50 mL/min/1.73m$^2$ body surface area) and hematocrit <11.0 g/dL who had not previously received epoetin.  Patients were randomized to a target hemoglobin of 13.0 to 13.5 g/dL (N=715) or 10.5 to 11.0 g/dL (N=717) (modified early in the study to 13.5 and 11.3 g/dL, respectively) with planned treatment duration with epoetin alfa up to 3 years.  About half of patients had diabetes and over 90% had hypertension; one-third had prior MI, stroke, CABG, PCI or lower limb amputation.  The study was terminated prematurely after a median duration of 16 months of epoetin treatment due to increased cardiovascular risk in the higher hemoglobin group.  There were 125 composite events (including 52 deaths, 64 patients with hospitalization for CHF [excluding renal replacement therapy], 18 patients with MI and 12 patients with stroke) among patients in the higher hematocrit group as

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compared to 97 composite events (including 36 deaths, 47 patients with hospitalization for CHF, 20 patients with MI and 12 patients with stroke) in the lower hematocrit group. Mean epoetin alfa dose in the high hemoglobin group was 10,694 units/wk for those who achieved the target and 12,884 units/wk for those who did not achieve the target. In the low hemoglobin group mean epoetin alfa dose was 6057 units/wk for those who achieved the target and 11,098 units/wk for those who did not achieve the target. In the CREATE Study which was a multi-national study (no U.S. centers) 605 non-dialysis patients with an estimated GFR of 15 to 35 mL/min/1.73 m$^2$ body surface area and hemoglobin of 11.0 to 12.5 g/dL were randomized to a target hemoglobin range of either 13.0 to 15.0 g/dL (N=301) or 10.5 to 11.5 g/dL (N=302) with epoetin beta treatment (2 patients excluded because center closed). In this study mean age was about 59 years, 54% were male, one-quarter had diabetes mellitus and about 90% had hypertension. At the conclusion of the study (mean observation time almost 3 years) a first cardiovascular event had occurred in 58 patients (including 31 deaths) in the high hemoglobin group and 47 patients (including 21 deaths) in the low hemoglobin group. The TREAT Study studied 4038 patients (about 58% from U.S.) with diabetes, chronic kidney disease (estimated GFR 20-60 mL/min/1.73 m$^2$ body surface area) and hemoglobin ≤11.0 g/dL randomly assigned to double-blinded treatment with either darbepoetin alfa (N=2012) or placebo (N=2026) to achieve a hemoglobin level of about 13 g/dL. The primary endpoint was the composite of death due to any cause or a cardiovascular event (nonfatal MI, CHF, stroke or hospitalization for myocardial ischemia). The study enrolled and treated patients over about 39 months and went to completion achieving 1203 cardiovascular composite events. The primary endpoint occurred in 632 patients (412 deaths) in the darbepoetin group and in 602 patients (395 deaths) in the placebo group. There was a significantly greater occurrence of stroke in patients in the darbepoetin group (101 patients) as compared to the placebo group (53 patients). The hazard ratio or relative risk (95% CI) in this study was 1.05 (0.94-1.17). During the study patients in the placebo group whose hemoglobin dropped below 9 g/dL received darbepoetin as rescue; consequently 46% of patients in the placebo group received at least one dose of darbepoetin. The median monthly dose of darbepoetin in the darbepoetin group was 176 mcg and 0 mcg in the placebo group.

The Normal Hematocrit Study was conducted in 1233 patients with end-stage renal disease with clinical evidence of congestive heart failure or ischemic heart disease who were undergoing hemodialysis who were randomized to receive epoetin alfa targeted to achieve and maintain a hematocrit of 42% (N=618) versus 30% (N=615) with a planned treatment duration of 3 years after final patient enrolled. About half of patients had diabetes and a quarter had hypertension. After a median ESA treatment duration of 14 months (range 4 days to 30 months), there were 183 deaths and 19 first nonfatal MIs in the higher hematocrit group compared to 150 deaths and 14 first nonfatal MIs in the lower hematocrit group with no notable causes for the imbalance, leading to premature termination of the study. After about 6 months on epoetin treatment mean epoetin dose in the low hematocrit group was about 140-160 units/kg/wk and about 480-500 units/kg/wk in the high hemoglobin group.

Examination of these studies by the Agency, which included presentations and discussion at meetings of the Oncology Drugs Advisory Committee (May 10, 2007) and the Cardiovascular and Renal Drugs Advisory Committee (October 18, 2010), led to major revisions of the safety information in the labels for the ESAs in 2007 and 2011. The revisions reflected the findings, including increased risk for death when higher hemoglobin levels (13 to 14 g/dL) as compared to lower hemoglobin levels (9 to 11.3 g/dL) were targeted in patients with chronic kidney disease. The current labels for the ESAs include:

boxed warnings and text to describe the adverse cardiovascular risk seen in the trials, recommendation to initiate ESA dosing only when hemoglobin is below 10 g/dL, and emphasis on dosing only to a hemoglobin level necessary to avoid red blood cell transfusions. Overall, the labeling changes encourage a more conservative approach to ESA-driven correction of anemia in patients with chronic kidney disease. The factors leading to the increased risk for adverse cardiovascular outcomes in certain patients are not fully understood but may involve ESA dose, intrinsic responsiveness or lack of responsiveness of patients to erythropoiesis stimulation, and concurrent conditions among other factors.

The four major peginesatide trials in this current application were conducted in patients with chronic kidney disease on dialysis (2 studies) and in patients with chronic kidney disease not on dialysis (2 studies). All four major trials utilized an active control, mainly epoetin alfa in the studies of patients on dialysis and darbepoetin in the studies of patients not on dialysis. Though the protocol-defined primary efficacy outcome was achieved in both populations, the applicant is seeking approval of peginesatide only for the patients on dialysis, and not for the chronic kidney disease patients who are not on dialysis. This decision is likely mainly due to an apparent worse outcome for cardiovascular safety for the non-dialysis patients who received peginesatide as compared to those who received the active comparator.

The composite safety endpoint (CSE) was defined as a composite of six events (death, stroke, myocardial infarction (MI), serious events of congestive heart failure (CHF), unstable angina, and arrhythmia), all adjudicated blinded by an independent review committee. The primary CSE analysis included (1)CSE events other than death that occurred through day of termination from the study and (2)death that occurred through 28 days after termination from the study. The FDA Statistical Review (Q Xu, Ph.D., 2/7/2012) states the following for the sizing of the 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).

The FDA statistical review and sponsor's submission also included analyses of an additional post hoc safety endpoint referred to as the MACE composite safety endpoint (where MACE refers to Major Adverse Cardiovascular Event). The MACE composite included death, stroke and MI. These three endpoints are somewhat more objective and have been used in other cardiovascular studies. The analysis was conducted to determine if a hazard ratio of the upper limit of the two-sided 90% CI greater than 1.3 could be excluded. The following table shows the FDA summary of analyses for the CSE, MACE composite, and deaths for both the dialysis studies and the non-dialysis studies.

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) | |

The Statistical review stated the following for the analyses:

*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.*

Sensitivity analyses to adjust for baseline imbalances did not provide evidence that imbalanced baseline factors impacts the overall conclusion of a higher risk in the peginesatide treatment group as compared to the darbepoetin treatment group in the non-dialysis population. On drug sensitivity analysis (i.e., censoring at the time at which patients stopped study drug) gave similar conclusions to the primary safety analyses. Subgroup analyses did not show any striking findings and were deemed only exploratory and suggestive but not conclusive.

With regard to study drug exposure the Statistical Review made the following comments:
- For both dialysis and non-dialysis studies, the total patients exposure time was lower in the peginesatide group compared to the active control group.
- Dialysis patients received substantially higher doses compared with non-dialysis patients.

Because some publications have suggested a possible association between poor initial hematopoietic response to ESAs and increased risk of cardiovascular events, the FDA Statistical team also conducted

an exploratory analysis of the combined data from AFX01-11 and AFX01-13 to investigate such association. The reviewers concluded the following for that analysis:

> 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.

The Clinical Review (A Dmytrijuk, final signature 2/7/2011) findings for the application are similar to the Statistical conclusions stating:

> *Reviewer comment for section 7: Studies AFX01-12 and AFX01-14 were designed to evaluate the safety and efficacy of peginesatide treatment compared to epoetin treatment in patients with anemia due to CKD who were on dialysis. Studies AFX01-11 and AFX01-13 were designed to evaluate the safety and efficacy of peginesatide treatment compared to darbepoetin treatment in patients with anemia due to CKD who were not on dialysis. In patients on dialysis or not on dialysis, the analyses of these studies showed that peginesatide is non-inferior to epoetin or to darbepoetin, respectively, in its ability to maintain Hgb levels in the protocol target range of 10-12g/dL. Also, in patients with CKD who are on dialysis, peginesatide appeared to show similar safety results when compared to epoetin by both CSE and MACE outcomes.*
>
> *However, in patients with CKD not on dialysis (trials AFX01-11 and AFX01-13), there is an imbalance in safety outcomes that was significantly different by the sponsor's planned analysis of CSE (HR 1.32 (90% CI = 1.02, 1.72), favoring darbepoetin. When assessed by MACE outcomes and with a 95% confidence interval, the difference, was still numerically unfavorable to peginesatide, but was not significantly different in these two trials. There were baseline imbalances unfavorable to peginesatide in the proportion of patients with diabetes, peripheral vascular disease, and coronary heart disease. Exploratory analyses of the imbalances do not identify a treatment interaction.*

Notable is that in the trials for both patients on dialysis and not on dialysis, the hemoglobin range studied (up to 12.0 g/dL), is higher than the current label recommendations for the ESA products. The challenge for interpretation of the safety results of these studies is to determine whether the cardiovascular findings in the non-dialysis population in this application have any bearing on the safety in the dialysis population for which the sponsor is seeking approval. The term "chronic kidney disease" encompasses a broad range of renal impairment ranging from mild impairment of GFR to dialysis dependence; however, it also represents a continuum with patients commonly having progressive renal impairment over time. It seems to me most likely that any negative physiologic impact caused by ESAs would not be different among patients on dialysis and those not on dialysis. It seems more likely that it simply may be easier to detect differences in rates in some populations (i.e., where the 'noise' level is lower for these events of interest, which are not uniquely striking but rather

just increased frequency of common cardiovascular adverse occurrences). An additional factor may be that the active comparator was epoetin in the dialysis studies and darbepoetin in the non-dialysis studies, so with the existing database it is not possible to distinguish between quantitative differences that might be due to population and those that might be due to the particular ESA comparator used. Finally, and perhaps most importantly, since the trials all were open-label it is not certain that other aspects of patient management that may have been applied in a non-random fashion inadvertently in the study could not have affected the study results.

Introduction of ESAs was a major advance in the management of anemia associated with chronic renal failure and these agents have become a mainstay in the care of patients with chronic kidney disease by allowing stabilization of hemoglobin levels and decreasing need for red blood cell transfusions in these patients. Even with the emergent cardiovascular safety concerns there continues to be a favorable benefit risk profile for the judicious use of these products in this clinical setting. In this context, based on the information in the current application, peginesatide has adequately demonstrated efficacy and acceptable safety for use in patients with chronic kidney disease who are on dialysis and have been stabilized on other ESAs prior to their exposure to peginesatide. Use of peginesatide for these patients who are already receiving an ESA does not place additional patients at risk for the adverse effects of this class of drugs. Based on the available data in patients on dialysis peginesatide does not appear to add additional risk to that imposed by currently approved and marketed ESAs for this population. Approval of peginesatide would provide an additional therapeutic option for these patients. Because patients who are dialysis-dependent but have not yet been exposed to or stabilized on an ESA were not enrolled in the studies, it is not known whether those patients would have shown a cardiovascular safety signal. The findings for cardiovascular safety in the trials in chronic kidney disease patients not on dialysis echo the concerning findings in several published studies of ESAs in chronic kidney disease populations discussed above. Considering the uncertainty regarding the extent of the increased safety risk, it would be most prudent to limit approval of peginesatide for the indication in the dialysis population studied, namely to dialysis patients already stabilized on ESAs, and have the sponsor conduct an additional controlled clinical study in patients with CKD on or starting dialysis but who have not yet started or been stabilized on an ESA.

At a presentation of the peginesatide application to the Oncology Drugs Advisory Committee on December 7, 2011, the overwhelming majority of members concluded that the benefit risk profile for peginesatide based on the available data was favorable for the its use in patients with chronic kidney disease on dialysis (yes=15; no=1; abstain=1). However, concerns for safety were also expressed with particular mention of the non-blinded nature of the studies, concern that the dialysis population studied may have been too narrow to detect a safety signal and concern for potential mis-use of peginesatide in the non-dialysis population.

Overall, the Clinical and Statistical reviews have concluded that the data submitted in this application support the applicant's claim of efficacy and safety of peginesatide in dialysis patient who are stable on current ESA treatment.

**Conclusions and Recommendations:**
The sponsor has provided adequate evidence to support use of peginesatide in patients with chronic kidney disease who are on dialysis and have been stabilized on an erythropoiesis stimulating agent. The sponsor should conduct a post-marketing adequate and well-controlled study in dialysis patients

not yet stabilized on an ESA                                                    (b) (4)   The starting
dose of peginesatide should be based on the current ESA dose as was done in the clinical trials.

Because peginesatide is dosed once monthly instead of biweekly to three times a week as for currently
marketed ESA agents, I think there is a strong potential for off-label use of the drug in patients who
are not on dialysis simply due to convenience.  Therefore, a risk management plan such as the sponsor
has proposed to educate prescribers to the use and risks of the drug and restriction of the distribution
of the drug to dialysis centers is appropriate.

The labeling of the drug should carry the Boxed Warning and other class labeling as for the other
ESAs.

Exact wording of the labeling should be negotiated with the sponsor.

Post-marketing studies should be required as follows:
- The sponsor should conduct an adequate and well-controlled study in dialysis patients not yet
  stabilized on an ESA.  The study should be randomized, double-blind (double-dummy, if
  necessary), active controlled with a primary cardiovascular safety endpoint.  The protocol for the
  proposed study should be submitted for FDA review.

- To satisfy PREA requirement the sponsor should conduct studies of peginesatide in pediatric
  patients age 1 year and older with chronic kidney disease on dialysis.  Full protocols should be
  submitted for review prior to study initiation.  A waiver should be granted for patients less than 1
  year of age.

- Because treatment with peginesatide is likely to be life-long upon initiation of treatment, the
  sponsor should plan and conduct a study to gain long-term safety information about use of the
  drug.

- The sponsor should complete and submit the ongoing study AFX01-06 of peginesatide therapy that
  is being conducted in patients with anemia associated with CKD who have a history of anti-
  erythropoietin antibodies.

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

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/s/

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KATHY M ROBIE SUH
03/09/2012

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Submission Number | 202799 |
| Submission Code | N |
| | |
| Letter Date | May 23, 2011 |
| Stamp Date | May 27, 2011 |
| PDUFA Goal Date | March 27, 2012 |
| | |
| Reviewer Name | Andrew Dmytrijuk, M.D. |
| Review Completion Date | January 13, 2011 |
| | |
| | |
| Established Name | Peginesatide |
| (Proposed) Trade Name | None |
| Therapeutic Class | Anti-anemia |
| Applicant | Affymax Inc. |
| | 4001 Miranda Ave. |
| | Palo Alto, CA 94304 |
| | |
| Priority Designation | S |
| | |
| Formulation | Injection |
| Dosing Regimen | 0.4-0.8mg/kg Once Monthly |
| Indication | Treatment of Anemia Associated With Chronic Renal Failure |
| Intended Population | Adult Patients on Dialysis |

Clinical Review
Andrew Dmytrijuk, M.D.
NDA 202799
Peginesatide (Omontys)

# Table of Contents

Clinical Review
Andrew Dmytrijuk, M.D.
NDA 202799
Peginesatide (Omontys)

# 1    Recommendations/Risk Benefit Assessment

## 1.1    Recommendation on Regulatory Action

Peginesatide (Omontys) should be approved for the following indication:

- For the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis in whom previous erythropoiesis-stimulating agent (ESA) therapy has been stable.  The recommended peginesatide starting dose for patients with CKD on dialysis is 0.04 to 0.08 mg/kg administered intravenously (IV) or subcutaneously (SC) once monthly with the initial peginesatide dose based on total weekly epoetin or darbepoetin alfa dose at the time of conversion from another ESA.

The rationale for this approval recommendation is based on the following information.

- The efficacy of the proposed therapy is supported by two trials (AFX01-12 and AFX01-14) conducted in adult patients with anemia associated with CKD who were on dialysis and in two trials (AFX01-11 and AFX01-13) conducted in adult patients with anemia associated with CKD who were not on dialysis.  These were similarly designed, randomized, active control, multi-center, open label studies.  The goal of the studies was to maintain Hgb levels in the protocol's target range of 10-12 g/dL.  Peginesatide, compared to ESA, can be considered non-inferior in terms of efficacy for both groups of patients, i.e., those who were on dialysis and those who were not on dialysis based on the protocol specified efficacy analysis.  The lower limit two-sided 95% or 97.5% confidence interval (CI) difference between the two treatment group's mean changes of hemoglobin (Hgb) from baseline was > -1.0 g/dL as shown below:

- Dialysis Least Squares Mean and 95% CI

    - AFX01-12
        - Peginesatide 0.04 mg/kg starting dose = -0.15 (-0.30,-0.01)
    - AFX01-14
        - Peginesatide 0.04 mg/kg starting dose = 0.10 (-0.05, 0.26)

- Not-on Dialysis Least Squares Mean and 97.5% CI

    - AFX01-11
        - Peginesatide 0.025 mg/kg starting dose = 0.03 (-0.19,0.26)
        - Peginesatide 0.04 mg/kg starting dose = 0.26 (0.04, 0.48)
    - AFX01-13
        - Peginesatide 0.025 mg/kg starting dose = 0.14 (-0.09,0.36)
        - Peginesatide 0.04 mg/kg starting dose = 0.31 (0.08, 0.54)

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- In Studies AFX01-12, AFX01-14, AFX01-11 and AFX01-13 the primary safety objective was to rule out an increase of 30% or more in the risk of a composite safety endpoint

    (CSE) based on a two-sided 90% CI for the CSE hazard ratio. The sponsor's CSE consisted of death, stroke, myocardial infarction (MI), congestive heart failure (CHF), unstable angina and arrhythmia.

    o Similar safety outcomes were observed for peginesatide and epoetin therapy for patients on dialysis in studies AFX01-12 and AFX01-14. These patients had hemoglobin levels which were stabilized with ESA at the time of enrollment. The CSE hazard ratio (HR) and 90% CI = 0.95 (0.79, 1.13). Analysis of the MACE (death, stroke and MI) outcomes show a HR and 95%CI = 0.83 (0.65, 1.07).
    o Greater risks for adverse cardiovascular outcomes with peginesatide compared to darbepoetin were observed for patients in the not-on-dialysis studies AFX01-11 and AFX01-13. In these studies the CSE HR and 90% CI = 1.32 (1.02, 1.72) which was unfavorable to peginesatide. When assessed by MACE outcomes the HR and 95%CI = 1.28 (0.84, 1.94). While numerically unfavorable to peginesatide the MACE outcomes were not significantly different between treatments in these two trials. There were baseline imbalances unfavorable to peginesatide in the proportion of patients with diabetes, peripheral vascular disease, and coronary heart disease. Exploratory analyses of the imbalances do not identify a treatment interaction.

- The additional reviewer proposed wording, "in whom previous erythropoiesis-stimulating agent (ESA) therapy has been stable" should be added to the indication to reflect that patients in the pivotal registration trials (AFX01-12 and AFX01-14) patients were required to have been on dialysis for $\geq 3$ months and were receiving epoetin therapy. Peginesatide has not been studied in patients on dialysis who were naive to ESA treatment.

## 1.2 Risk Benefit Assessment

The sponsor has submitted the results of four trials (two trials in patients with CKD on dialysis and two trials in patients with CKD not on dialysis) to support this NDA. AFX01-12 and AFX01-14 were phase 3 randomized, controlled, open-label, multicenter studies in patients with CKD on dialysis. AFX01-11 and AFX01-13 were phase 3 randomized, controlled, open-label, multicenter studies in patients with CKD not on dialysis.

The primary efficacy analysis for all four trials was a comparison of the mean change in hemoglobin between the baseline and the evaluation period (weeks 29 to 36 for studies AFX01-12 and14 and weeks 25-36 for studies AFX01-11 and 13). Peginesatide would be considered non-inferior to the comparator (epoetin for the on-dialysis trials and darbepoetin for the non-dialysis trials), based on change from baseline hemoglobin, 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 $\geq$ -1.0 g/dL for the on-dialysis trials. Similarly,

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peginesatide would be considered non-inferior to comparator if the lower limit of the two-sided 97.5% CI for the difference between the two treatment groups' mean change of hemoglobin (peginesatide - darbepoetin) from baseline was ≥ -1.0 g/dL for the non-dialysis trials.

For the two "on-dialysis" trials, based on the pre-specified efficacy analysis plan for each trial, peginesatide is non-inferior to epoetin. For the two "not-on-dialysis" trials, based on the pre-specified efficacy analysis plan for each trial, it also appears that peginesatide is non-inferior to darbepoetin.

The major safety concern raised by these trials is the uncertainty regarding cardiovascular safety of peginesatide use in patients with anemia associated with CKD who are not on dialysis. 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. The outcomes were compared using 90% confidence intervals. The composite safety endpoint (CSE), defined as the first occurrence of death, stroke, MI, CHF, unstable angina, or arrhythmia, was the primary protocol specified safety endpoint for the analysis. An additional planned safety analysis was to be performed assessing the MACE (major adverse cardiac events) composite endpoint, defined as the first occurrence of death, stroke or myocardial infarction.

The safety outcomes in both on-dialysis trials (AFX01-12 and AFX01-14) appear similar for both treatment groups for both the CSE and the MACE endpoints. Patients in these studies had hemoglobin levels which were previously stabilized with ESA.

However, in the two non-dialysis trials (AFX01-11 and AFX01-13), there are differences in the safety outcomes for the two treatments, with results unfavorable for peginesatide. Using the applicant's pre-specified primary safety analysis plan and the CSE outcomes, the safety of peginesatide appears to be statistically significantly inferior to darbepoetin. However, the secondary analysis comparing MACE outcomes and using a 95% confidence interval, shows that although the safety outcomes for peginesatide are numerically worse, the outcomes are not statistically significantly different from that of the darbepoetin-treated group.

The benefit risk ratio favors the approval of peginesatide for the treatment of patients with anemia associated with CKD who are on dialysis in whom previous erythropoiesis-stimulating agent (ESA) therapy has been stable.

## 1.3 Recommendations for Postmarketing Risk Management Activities

The sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) which has the following goals:

- (b) (4)

(b) (4)

- 

The REMS would consist of a medication guide and REMS Communication Plan. The REMS communication plan would consist of a Dear Medical Personnel Letter (DMPL). The sponsor proposes that the DMPL would be distributed (b) (4) for two years. The target for the DMPL would be nephrologists. (b) (4)

*Reviewer comment: No other erythropoiesis stimulating agent (ESA) approved drugs have a REMS program for the similar indication of the treatment of anemia associated with CKD. It does not appear that a REMS program is necessary for peginesatide for the proposed indication worded as recommended above.*

## 1.4 Recommendations for other Post Marketing Study Commitments

The sponsor should address the following as postmarketing commitments below:

- The sponsor should undertake the usual postmarketing monitoring and reporting.
- Conduct a prospective randomized, double blind, controlled safety and efficacy study of subcutaneous (SC) peginesatide versus SC darbepoetin in patients with anemia associated with CKD not on dialysis. Study drugs should be administered once monthly. The hemoglobin level should be maintained in the $\geq 10$ g/dL-$\leq 11.0$ g/dL range. Monthly matching placebo should be administered when the hemoglobin is outside the specified range. The major adverse cardiac events (MACE), i.e., death, stroke and myocardial infarction (MI) should be the primary safety outcomes that are evaluated. A blinded independent adjudication panel should evaluate MACE events. Patients should be exposed to the study drugs for a period of no less than one year and followed for safety for an additional year. At the end of the two year period, a study report should be submitted to the NDA that describes the major safety and efficacy findings from the study.
- The sponsor should submit a final study report for study AFX01-06 which is evaluating the safety and efficacy of peginesatide in patients with anti-erythropoietin antibodies.
- The sponsor should be granted the requested waiver and deferral for pediatric studies as discussed in section 7.6.2 Pediatrics and Effects on Growth in this review.

# 2   Introduction and Regulatory Background

## 2.1   Product Information

Peginesatide is an erythropoiesis-stimulating agent (ESA). It is a synthetic, pegylated dimeric erythropoietin receptor activating peptide that, unlike currently approved ESAs, has no homology to erythropoietin. It is comprised of two identical, 21-amino acid chains covalently bonded to a linker derived from iminodiacetic acid and β-alanine.

Peginesatide is administered once monthly. The proposed indication is for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis. The sponsor states that peginesatide is not indicated for the treatment of anemia in patients with CKD not on dialysis or for the treatment of anemia due to cancer chemotherapy.

## 2.2   Table of Currently Available Treatments for Proposed Indications

The currently approved and marketed ESAs in the United States are Epoetin alfa (Epogen and Procrit) and Darbepoetin alfa (Aranesp). Pegylated Epoetin beta (Mircera) is approved but not marketed in the US. Epogen alfa and Darbepoetin alfa share the indication for the treatment of anemia due to CKD, including patients on dialysis and patients not on dialysis. These ESAs are also indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

The table below shows the approved therapies, boxed warnings related to the CKD/anemia indication and dosing information. In addition, red blood cell (RBC) transfusions are used for the treatment of patients with CKD and associated anemia. Epoetin beta (Mircera) is approved but not marketed in the US. Epoetin beta is marketed in Europe.[1]

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**Table 1: Approved Therapies for Anemia Associated with Chronic Kidney Disease**

| Therapy | Complete Indication | Boxed Warning Related to Anemia Associated with CKD Indication | Dose and Administration for Anemia Associated with CKD |
|---|---|---|---|
| **Darbepoetin (Aranesp)** | Aranesp is an erythropoiesis-stimulating agent (ESA) indicated for the treatment of anemia due to:<br>• Chronic Kidney Disease (CKD) in patients on dialysis and patients not on dialysis.<br>• The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy. | In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL.<br>• No trial has identified a hemoglobin target level, Aranesp dose, or dosing strategy that does not increase these risks.<br>• Use the lowest Aranesp dose sufficient to reduce the need for red blood cell (RBC) transfusions. | Recommended starting dose for CKD patients on dialysis:<br>• 0.45 mcg/kg intravenously or subcutaneously weekly, or 0.75 mcg/kg intravenously or subcutaneously every 2 weeks. Intravenous route is recommended for patients on hemodialysis.<br>Recommended starting dose for patients with CKD not on dialysis:<br>• 0.45 mcg/kg intravenously or subcutaneously at 4 week intervals. |
| **Epoetin alfa (Epogen/Procrit)** | Epogen is an ESA indicated for:<br>• Treatment of anemia due to<br>- CKD in patients on dialysis and not on dialysis.<br>- Zidovudine in HIV-infected patients.<br>- The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.<br>• Reduction of allogeneic RBC transfusions in | Same as Darbepoetin | CKD Patients:<br>• Initial dose: 50 to 100 Units/kg 3 times weekly (adults) and 50 Units/kg 3 times weekly (children on dialysis). Individualize maintenance dose. Intravenous route recommended for patients on hemodialysis. |

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| | | | |
|---|---|---|---|
| | patients undergoing elective, noncardiac, nonvascular surgery. | | |
| **Epoetin beta (Mircera)** | Mircera is an ESA indicated for:<br>• Treatment of anemia due to:<br>– CKD in patients on dialysis and not on dialysis. | Mircera is approved but not marketed in the US. The European product label does not contain a boxed warning. | CKD Patients:<br>• Initial dose: 0.6 mcg/kg intravenously or subcutaneously once every two weeks. Individualize maintenance dose to maintain Hgb > 11g/dL and < 12 g/dL. |

## 2.3   Availability of Proposed Active Ingredient in the United States

Peginesatide is not marketed in the USA or elsewhere worldwide.

## 2.4   Important Safety Issues With Consideration to Related Drugs

Since the original approval of epoetin alfa and darbepoetin alfa, 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.  The major trials evaluating the risks were the "Normal Hematocrit Study (NHS)" (Besarab et al. 1998)[2], the "Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)" (Drueke et al. 2006)[3], the "Correction of Hemoglobin Outcomes in Renal Insufficiency (CHOIR)" (Singh et al. 2006)[4], and the "Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT)" (Pfeffer et al. 2009)[5].

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

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The CREATE study was an open-label study that enrolled 603 patients with anemia due to CKD who were not receiving hemodialysis. The baseline hemoglobin levels were ≥ 11 g/dL to 12.5 g/dL. Patients were treated with Epoetin beta and patients were randomized to maintain a hemoglobin (Hgb) target of 13-15 g/dL (higher target level) or 10.5-11.5 g/dL (lower target level). The primary endpoint was the time to first cardiovascular event. Cardiovascular events were defined as death, MI, acute heart failure, stroke, transient ischemic attack, and angina with hospitalization for 24 hours or more, prolongation of hospitalization, complication of peripheral vascular disease or arrhythmia with hospitalization for ≥ 24 hours. In this study there were 58 events in the higher target group and 47 events in the lower target group. The hazard ratio was 0.78 (95% CI = 0.53-1.14) demonstrating no benefit for cardiovascular risk reduction with a higher target Hgb.

The CHOIR trial was an open label study that enrolled 1432 patients with anemia due to CKD not receiving dialysis. The baseline Hgb was < 11 g/dL. These patients were treated with epoetin alfa and randomized to maintain a target Hgb of either 13.5g/dL, i.e., a higher Hgb group or to a target Hgb of 11.3 g/dL, i.e., a lower Hgb group. The primary efficacy endpoint was a composite endpoint of the time to death or time to first event of non-fatal MI, hospitalization for congestive heart failure, or stroke. The trial was terminated prematurely for adverse safety outcomes. There were 125/715 (18%) patients in the high Hgb group compared to 97/717 (14%) in the low Hgb group who experienced the composite endpoint. The hazard ratio for the composite primary endpoint was 1.34 (95% CI =1.03, 1.74), significantly favoring the lower Hgb group.

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

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These studies raised safety concerns regarding ESA therapy for the anemia of CKD. Based on these studies 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 revised 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 > 11 g/dL. The labels recommend that prescribers: individualize dosing for patients with CKD and use the lowest dose sufficient to reduce the need for red blood cell transfusions; to initiate ESA therapy when the Hgb is < 10 g/dL, and to reduce or interrupt the dose if the Hgb approaches or exceeds 10 - 11 g/dL.

In addition, cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with ESAs. PRCA has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment. The product labels for the marketed ESAs state that if severe anemia and low reticulocyte count develop during treatment with ESAs, prescribers are to withhold ESA therapy and evaluate patients for neutralizing antibodies to erythropoietin. ESAs should be permanently discontinued in patients who develop PRCA following treatment with ESAs.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

- Pre - IND meeting: January 22, 2004.
- IND 63257 submission: March 25, 2005.
- Special Protocol Assessment (Carcinogenicity): August 23, 2006. End of Phase 2 meeting: February 23, 2007. During the meeting the Sponsor was advised to evaluate the safety of peginesatide with regard to cardiovascular risks in connection with target Hgb levels as was done in the CHOIR study. 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."
- Pre-NDA meeting: October 21, 2010.
- NDA submission: May 23, 2011.

## 2.6 Other Relevant Background Information

Not applicable.

*Reviewer comment for section 2: It is estimated that more than 20 million people aged 20 years or older in the United States have CKD.[6] In the US, 470,000 have end-stage renal disease (ESRD) requiring dialysis or transplantation. Anemia is commonly found in patients with CKD. When defined as a Hgb concentration < 11.0 g/dL, anemia affects an estimated 840,000 adults*

*with CKD in the US population, rising to 1.6 million adults when anemia is defined as an Hgb concentration less than 12.0 g/dL. The prevalence of CKD associated anemia increases progressively as kidney impairment worsens. The authors estimate that approximately 10–20% of patients with CKD receive ESA therapy before they require dialysis.*

*No trial has identified a Hgb target level, ESA dose, or dosing strategy that does not increase these risks. How far below 10 g/dL may be appropriate for an individual to initiate ESA therapy is not defined in the product labels. Prescribers and patients must weigh the benefits and risks of ESA therapy versus transfusion therapy individually. Also, the product label does not specifically recommend that the goal of therapy is to achieve a Hgb of ≥ 10 g/dL or a specific target level because therapy should be individualized to the patient.*

*PRCA is a rare adverse reaction that can occur with ESA treatment resulting in a life-threatening anemia. The mechanism involves an immune reaction during therapy with administered ESAs in which an anti-ESA antibody cross-reacts with endogenous erythropoietin and blocks erythropoietin function. McKoy et al in 2008 reported that, since 2002, FDA safety databases included reports on 59 new cases of PRCA.[7] Since peginesatide has no homology with ESAs it is unlikely that PRCA would develop in patients treated with this drug. The immunogenicity of peginesatide is further discussed in the Immunogenicity section of this review.*

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

On July 29, 2011 the Division of Scientific Investigations (DSI) was consulted to evaluate 3 study sites that were used in this study. The study sites: 1005, Dr. Brigitte Schiller-Moran, Satellite Healthcare, Inc. enrolled 33 patients in study AFX01-12; 1041, Dr. Edouard Martin, South Florida Research Institute enrolled 60 patients in study AFX01-14; 4002, Dr. Andrey Gurevich, St. Petersburg Medical Academy for Postgraduate Studies enrolled 15 patients in study AFX01-15 and 4003, Dr. Konstatin Gurevich, St. Petersburg Medical Academy for Postgraduate Studies enrolled 6 patients in study AFX01-15. The consult review is ongoing but has not identified any significant protocol violations or concerns for any of the study sites that were inspected.

## 3.2 Compliance with Good Clinical Practices

All studies were conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization Guidelines for Good Clinical Practices and local regulatory requirements. The protocols and any amendments were approved by an Institutional Review Board prior to initiation and implementation of these studies and changes. Written informed consent provided by the patient was required and written consent forms for the studies supporting this submission were reviewed.

## 3.3    Financial Disclosures

The sponsor reported that two investigators who participated in the clinical development program for peginesatide for the treatment of anemia in patients with CKD have significant payments in excess of $25,000 for disclosure. These are as follows:

- ██████████████ (b) (6), who participated in AFX01-13 and AFX01-14, had payments of approximately $41,000.
- ██████████████████ (b) (6) who participated in AFX01-12, with had payments of approximately $54,000.

The sponsor stated that the potential for these financial interests to bias the outcome of the studies is minimal for the following reasons:

- The number of subjects enrolled at ██████████████████████ (b) (6) was limited relative to the size of the studies as a whole. ████████ (b) (6) enrolled (b (6) subjects in Study AFX01-13 (total enrollment of 493 subjects across 62 sites in the US and European Union (EU)) and (b)(6) subjects in Study AFX01-14 (total enrollment of 823 subjects across 86 sites in the United States and EU.
- ████████ (b) (6) enrolled (b)(6) subjects in Study AFX01-12 (total enrollment of 803 subjects across 92 sites in the United States).

*Reviewer comment for section 3:  The ethical and clinical practices considerations for this submission appear to be acceptable.*

# 4    Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1    Chemistry Manufacturing and Controls (CMC)

Peginesatide injection is a synthetic ESA.  Peginesatide is manufactured as an acetate salt.  The dimeric peptide has an approximate molecular weight of 4,900 daltons and is covalently linked to a single lysine-branched bis-(methoxypoly(ethylene glycol)) (PEG) chain which has an approximate molecular weight of 40,000 daltons. The structure of peginesatide is shown in the sponsor's figure below.   Peginesatide is formulated for intravenous (IV) or subcutaneous (SC) administration as either a sterile, preservative-free solution or a sterile, preserved solution.

**Figure 1:** Structure of peginesatide acetate
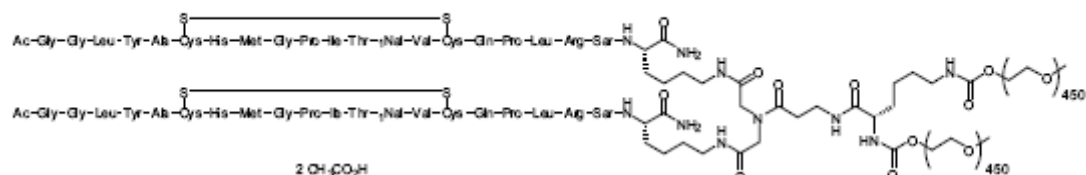


## 4.2 Clinical Microbiology

Not applicable

## 4.3 Preclinical Pharmacology/Toxicology

The sponsor states that peginesatide was noncarcinogenic in a long term carcinogenicity study in rats administered the drug for up to 2 years at 0.01, 0.1, and 0.5 mg/kg doses administered every 3 weeks by IV injection. In a 26-week carcinogenicity study in rasH2 transgenic mice, there was a trend for an increased incidence in splenic hemangiosarcomas in males when administered peginesatide by IV injection at doses of 0.1, 0.25, or 0.5 mg/kg/dose every 3 weeks and an increase in splenic hemangiosarcomas in males at the mid dose of 0.25 mg/kg/dose. The sponsor states that the increased incidence of splenic hemangiosarcomas in this predisposed strain was likely secondary to the physiological perturbations, i.e., hemoconcentration and splenic congestion associated with administration of an ESA to an initially normocythemic animal. The sponsor also states that peginesatide did not exhibit any mutagenic or clastogenic activity in the in vitro Ames assay, in vitro mammalian chromosome aberration assay, and an in vivo mouse erythrocyte micronucleus assay.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

Peginesatide binds to and activates the human erythropoietin receptor and stimulates erythropoiesis in human red cell precursors in vitro in a manner similar to recombinant ESAs. Production of endogenous erythropoietin is impaired in patients with CKD. Erythropoietin deficiency is the primary cause of anemia in patients with CKD.

### 4.4.2 Pharmacodynamics

The sponsor states that in patients with anemia associated CKD who were previously treated with an ESA and then converted to peginesatide (IV or SC) once every four weeks, resulted in reticulocytes reaching a maximum 1 to 2 weeks after dose administration.

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### 4.4.3   Pharmacokinetics

The sponsor states that the mean half-life of peginesatide is $25.0 \pm 7.59$ hours following IV administration and $53.0 \pm 17.70$ hours following SC administration in healthy subjects.  The half-life in dialysis patients is $47.9 \pm 16.53$ hours following IV administration.  Following single IV and SC injections at doses ranging from 0.03 to 0.14 mg/kg to dialysis patients, the maximum concentrations of peginesatide were achieved in approximately 48 hours. No accumulation is observed following administration every 4 weeks following IV or SC administration. The sponsor states that the pharmacokinetics of peginesatide in patients with CKD on dialysis or not on dialysis are not altered by age, gender or race based on population pharmacokinetic analyses.

*Reviewer comment for section 3:  Peginesatide has similar mechanism of action compared to recombinant ESAs.  Peginesatide administered once every four weeks to patients with anemia associated with CKD resulted in an increase in reticulocytes 1 to 2 week after dose administration.  Hemangiosarcoma was not reported as an adverse event in the pivotal clinical trials, i.e., AFX01-12, AFX01-14, AFX01-11 or AFX01-13.  The CMC and pharmacology considerations for this submission appear to be acceptable.*

# 5   Sources of Clinical Data

## 5.1   Tables of Clinical Studies

The table below shows the clinical studies supporting this application.

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## Table 2: Tabular Listing of Clinical Studies

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| BA | AFX01_102 | 5.3.1.2 | PK and relative bioavailability of two formulations (multiple dose vial [MDV] and single dose vial [SDV]) | Open-label, single dose, single center, randomized, two-period crossover, two formulations | AF37702 Injection single dose 0.05 mg/kg MDV formulation compared to AF37702 Injection 0.05 mg/kg SDV formulation; IV | 20 enrolled (crossover: 20 dosed with MDV formulation, 20 dosed with SDV formulation) | Normal healthy volunteers | Single dose | Complete; Full |
| BA/BE | AFX01_103 | 5.3.1.2 | Bioequivalence of two formulations (MDV and SDV) | Open-label, single dose, single center, randomized, two-period crossover, two formulations | AF37702 Injection single dose 0.05 mg/kg MDV formulation compared to AF37702 Injection 0.05 mg/kg SDV formulation; SC | 36 enrolled (crossover: 36 dosed with MDV formulation, 36 dosed with SDV formulation) | Normal healthy volunteers | Single dose | Complete; Full |
| BA/BE | AFX01_104 | 5.3.1.2 | Bioavailability of two concentrations (10 mg/mL and 16 mg/mL) of the SDV formulation of AF37702 Injection | Open-label, randomized, single-dose, multicenter (2 sites), two-period crossover, two concentrations of one formulation | AF37702 Injection 0.05 mg/kg (16 mg/mL concentration) compared to AF37702 Injection 0.05 mg/kg (10 mg/mL concentration); SC | 80 enrolled (crossover: 80 dosed with 10 mg/mL concentration, 80 dosed with 16 mg/mL concentration) | Normal healthy volunteers | Single dose | Complete; Full |
| BA/BE | AFX01_105 | 5.3.1.2 | Bioavailability of two concentrations (2 mg/mL and 10 mg/mL) of the SDV formulation of AF37702 Injection | Open-label, randomized, single-dose, multicenter (2 sites), two-period crossover, two concentrations of one formulation | AF37702 Injection 0.05 mg/kg (2 mg/mL concentration) compared to AF37702 Injection 0.05 mg/kg (10 mg/mL concentration); SC | 80 enrolled (crossover: 80 dosed with 2 mg/mL concentration, 80 dosed with 10 mg/mL concentration) | Normal healthy volunteers | Single dose | Complete; Full |

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| PK | AFX01-0401 | 5.3.3.1 | First-in-man evaluation of safety, PD, and PK | Double-blind, placebo-controlled, single dose, single center, randomized, sequential cohort, dose-escalation | AF37702 Injection single dose, 0.025, 0.05, or 0.1 mg/kg, compared to acetate buffered saline; IV | 28 enrolled (dosed 20:8 AF37702 Injection: placebo) | Normal healthy volunteers | Single dose | Complete; Full |
| PK | AFX01-02 | 5.3.3.2 | Proof of concept in subjects with CRF; safety, PD, and PK | 4-week, randomized, single-dose, double-blind, single center, placebo-controlled, sequential cohort, dose escalation study | AF37702 Injection single dose, 0.025, 0.05, or 0.1 mg/kg, compared to acetate buffered saline; IV | 17 enrolled (dosed 13:4 AF37702 Injection: Placebo) | Subjects with CRF not on ESA treatment and not on dialysis | Single dose | Complete; Full |
| PK/Safety | AFX01_101 | 5.3.4.1 | Evaluation of effects of AF37702 Injection on QTc intervals in healthy adults | Single dose, multi-center, randomized, double-blind, double-dummy, placebo and active controlled, three-period crossover | AF37702 Injection single dose 0.1 mg/kg, compared to 0.9% sodium chloride for Inj USP IV; moxifloxacin tablet compared to oral placebo; IV | 65 enrolled (crossover: 64 dosed with AF37702 Injection, 62 dosed with moxifloxacin, 62 dosed with placebo) | Normal healthy volunteers | Single dose | Complete; Full |
| PD | AFX01-03 | 5.3.4.2 | Dose finding; evaluate ability of AF37702 Injection to maintain stable Hgb levels (9.5–13.0 g/dL) in dialysis subjects previously on Epoetin alfa; safety, PD and PK | 13- or 27-week, open-label, multiple-dose (3–6 doses), multicenter, titrated dose, sequential cohort, dose-escalation study | AF37702 Injection Q4W x 3–6 doses; conversion factors mg/kg, tiered mg/kg, or tiered fixed mg; IV | 165 enrolled (164 dosed, 1 terminated prior to dosing) | Subjects with CRF on dialysis previously treated with Epoetin alfa | 13 or 27 weeks | Complete; Full |

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| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| PD | AFX01-04 | 5.3.4.2 | Dose finding; evaluate ability of AF37702 Injection to increase Hgb levels and correct anemia (11.0–13.0g/dL) in subjects not on dialysis and not on ESA treatment; Safety, PD and PK | 25 to 27-week, open-label, multicenter, titrated dose, multiple-dose, sequential cohort, dose-escalation | AF37702 Injection Q4W x 6 doses, or Q2W x 12 doses; mg/kg or fixed mg; SC, IV | 139 enrolled (139 dosed) | Subjects with CRF not on ESA treatment and not on dialysis | 25 to 27 weeks | Complete; Full |
| PD | AFX01-07 | 5.3.4.2 | Dose confirmation; evaluate ability of AF37702 Injection to maintain stable Hgb levels in subjects previously maintained on Epoetin alfa or beta; safety, PD and PK | 29-week, open-label, multiple-dose, multicenter, sequential cohort, titrated dose, dose confirmation | AF37702 Injection Q4W x 7 doses; tiered mg/kg; IV, SC | 91 enrolled (91 dosed) | Subjects with CRF on dialysis and previously on Epoetin | 29 weeks | Complete; Full |

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy | AFX01-11 | 5.3.5.1 | Safety and efficacy of AF37702 Injection (non-inferiority to darbepoetin alfa in increasing Hgb) for the correction of anemia | 52–104+ week, multiple-dose, randomized, active-controlled, open-label, multicenter, titrated dose | AF37702 Injection Q4W, starting dose 0.025 or 0.04 mg/kg, compared to darbepoetin alfa 0.75 mcg/kg Q2W; SC | 490 enrolled (490 dosed: 161:165:164 0.025 mg/kg AF37702 Injection: 0.04 mg/kg AF37702 Injection: darbepoetin alfa) | Subjects with CRF not on dialysis and not on ESA treatment | Minimum 52 weeks | Complete; Full |
| Efficacy | AFX01-12 | 5.3.5.1 | Safety and efficacy of AF37702 Injection (non-inferiority to Epoetin alfa) for the maintenance treatment of anemia | 52–104+ week, multiple-dose, randomized, active-controlled, open-label, multicenter, titrated dose | AF37702 Injection Q4W, tiered starting dose based on previous Epoetin dose, compared to Epoetin alfa 1–3 times per week; IV | 803 enrolled (793 dosed: 524:269 AF37702 Injection: Epoetin alfa) | Subjects with CRF on dialysis previously treated with Epoetin alfa | Minimum 52 weeks | Complete; Full |
| Efficacy | AFX01-13 | 5.3.5.1 | Safety and efficacy of AF37702 Injection (non-inferiority to darbepoetin alfa in increasing Hgb) for the correction of anemia | 52–104+ week, multiple-dose, randomized, active-controlled, open-label, multicenter, titrated dose | AF37702 Injection Q4W, starting dose 0.025 or 0.04 mg/kg, compared to darbepoetin alfa 0.75 mcg/kg Q2W; SC | 493 enrolled (493 dosed: 167:163:163 0.025 mg/kg AF37702 Injection: 0.04 mg/kg AF37702 Injection: darbepoetin alfa) | Subjects with CRF not on dialysis and not on ESA treatment | Minimum 52 weeks | Complete; Full |

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| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy | AFX01-14 | 5.3.5.1 | Safety and efficacy of AF37702 Injection (non inferiority to Epoetin) for the maintenance treatment of anemia | 52–104+ week, multiple-dose, randomized, active-controlled, open-label, multicenter, titrated dose | AF37702 Injection Q4W, tiered starting dose based on previous Epoetin dose, compared to Epoetin 1–3 times per week; IV or SC | 823 enrolled (815 dosed: 542:273 AF37702 Injection: Epoetin) | Subjects with CRF on dialysis previously treated with Epoetin | Minimum 52 weeks | Complete; Full |
| Efficacy | AFX01-15 | 5.3.5.1 | Safety and efficacy of two starting doses of AF37702 Injection | 29-week, multiple-dose, randomized, active-controlled, open-label, multicenter, titrated dose | AF37702 Injection Q4W, starting dose 0.04 or 0.08 mg/kg, compared to Epoetin alfa 50 U/kg TIW; IV | 114 enrolled 114 dosed: 39:37:38 0.04 mg/kg AF37702 Injection: 0.08 mg/kg AF37702 Injection: Epoetin alfa) | Anemic dialysis subjects not on ESA treatment | 29 weeks | Complete; Full |
| Uncontrolled | AFX01-09 | 5.3.5.2 | Safety and tolerability of AF37702 Injection treatment for the long-term maintenance of Hgb in patients with CRF | Long-term (up to 54 months), multiple-dose, open-label, multicenter, titrated dose, follow-up treatment in subjects in the US who completed a previous 6-month study with AF37702 Injection | AF37702 Injection Q4W x up to 54 doses; mg/kg; IV | 81 enrolled (81 dosed) | Subjects with CRF on dialysis | Up to 54 months | Complete; Full |

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Uncontrolled | AFX01-10 | 5.3.5.2 | Safety and tolerability of AF37702 Injection treatment for the long-term maintenance of Hgb in patients with CRF | Long-term (up to 54 months), multiple-dose, open-label, multicenter, titrated dose, follow-up treatment in subjects in Europe who completed a previous 6-month study with AF37702 Injection | AF37702 Injection Q4W x 54 doses or Q2W x 108 doses, mg/kg; IV, SC | 114 enrolled (114 dosed) | Subjects with CRF on dialysis and not on dialysis | Up to 54 months | Complete; Full |
| Uncontrolled | AFX01_202 | 5.3.5.2 | Safety and efficacy of conversion of CRF subjects who are on dialysis or not on dialysis from darbepoetin alfa to AF37702 Injection Q4W | 25-week, multiple-dose, open label, multicenter, single-arm, titrated dose | AF37702 Injection Q4W x 25 weeks, starting dose 0.04, 0.08, 0.12, or 0.16 mg/kg; IV, SC | 102 enrolled (101 dosed) | Subjects with CRF who are on dialysis or not on dialysis and previously treated with darbepoetin alfa | 25 weeks | Complete; Full |
| Uncontrolled | AFX01_201 | 5.3.5.2 | Safety and efficacy of conversion in peritoneal dialysis subjects from SC Epoetin (alfa or beta) to AF37702 Injection Q4W | 25-week, multiple-dose, open-label, multicenter, single-arm, uncontrolled, titrated dose | AF37702 Injection Q4W x 25 weeks, starting dose 0.04, 0.08, 0.12, or 0.16 mg/kg; SC | 59 enrolled (59 dosed) | Peritoneal dialysis subjects previously treated with Epoetin | 25 weeks | Complete; Full |

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| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Other Study Reports | AFX01-06 | 5.3.5.4 | Rescue treatment; evaluate ability of AF37702 Injection to increase, maintain Hgb levels in transfusion-dependent subjects with CRF and EPO-antibody mediated PRCA; Safety and efficacy | Long-term (up to 60 months), open-label, multiple-dose, multicenter, titrated dose | AF37702 Injection Q4W, starting dose 0.05 mg/kg; SC | 18 enrolled (as of 30 April 2010; ongoing) | Subjects with CRF and EPO-antibody mediated PRCA, on dialysis and not on dialysis | Up to 60 months | Interim |
| Other Study Reports | AFX01-05 | 5.3.5.4 | Safety, PD, and PK study of AF37702 Injection | 12-week, open-label, multicenter, four-dose, titrated dose, sequential cohort, dose escalation | AF37702 Injection Q3W x 4 doses, starting dose 0.05, 0.1, 0.15, or 0.2 mg/kg; SC | 60 enrolled (60 dosed) | Subjects with cancer with CIA | 12 weeks | Complete; Full |
| Other Study Reports | AF37702_101 | 5.3.5.4 | Safety and tolerability of AF37702 Injection in cancer subjects receiving cytotoxic chemotherapy, including a taxane | 7-week, minimum of two doses, open-label, multicenter, sequential cohort, titrated dose, dose escalation | AF37702 Injection Q3W, starting dose 0.075 mg/kg (Cohort 1); SC | 2 enrolled (2 dosed) | Subjects with refractory non-small cell lung, breast, or prostate cancer who are anemic and receiving cytotoxic taxane chemotherapy | Minimum of 2 doses given Q3W | Complete; Full |

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Other Study Reports | CPH-001 | 5.3.5.4 | Evaluation of safety, and PK | Single-blind, single dose, single center, randomized, placebo-controlled, sequential cohort, dose-escalation | AF37702 Injection single dose, 0.0125, 0.025, 0.05, or 0.1 mg/kg, compared to placebo; IV, SC | 93 enrolled (80 dosed), (dosed 64:16 AF37702 Injection: placebo) | Normal healthy volunteers | Single dose | Complete; Truncated* |

\* Truncated study report consists of the body of the report per ICH E3 guidance document (Sections 1-13 and the reference list). In FDA correspondence (Type C Biostatistical-Clinical Advice Meeting, FDA Meeting Minutes 21 October 2008), FDA indicated that these studies are viewed as supportive studies only and that a proposal by Affymax to submit only SAE information from these studies was acceptable. Since that time, Affymax decided to include additional pharmacokinetic information from these studies in the NDA so additional information on these studies is provided.

## 5.2 Review Strategy

The medical review of studies AFX01-12, AFX01-14, AFX01-11 and AFX01-13 is included in this document. The studies AFX01-12 and AFX01-14 were the primary studies used to understand the safety and efficacy of peginesatide for the treatment of patients with anemia associated with CKD in patients on dialysis. The studies AFX01-11 and AFX01-13 were the primary studies used to understand the safety and efficacy of peginesatide for the treatment of anemia associated with CKD in patients not on dialysis. Summaries of the other studies submitted by the sponsor to support peginesatide's efficacy and safety in the treatment of patients with anemia associated with CKD were also reviewed.

In addition, in NDA 202799 submission 9 letter date September 23, 2011 the sponsor submitted the 120 Day Safety Update Report. This submission primarily updated safety information for study AFX01-06 which is being conducted to evaluate the safety and efficacy of peginesatide therapy in patients with anemia associated with CKD who have a history of anti-erythropoietin antibodies.

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## 5.3 Discussion of Individual Studies

This section describes the plan and design of the major efficacy studies in the application. Study efficacy results are discussed under section 6 below. The principal active control comparative trials that were submitted to support the approval of peginesatide are shown in the table below.

**Table 3: Principal Peginesatide clinical trials**

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

### 5.3.1 On Dialysis Studies

AFX01-12 and AFX01-14 Objectives:

The primary objective was to determine efficacy and safety while maintaining the hemoglobin level in the 10- 12 g/dL range.

AFX01-12 and AFX01-14 Design:

Studies AFX01-12 and AFX01-14 were similarly designed studies conducted in patients with anemia due to CKD who were on dialysis and previously treated with an ESA. These trials were Phase 3, open label, randomized (2:1), multicenter studies conducted in the United States and Europe and enrolled adult patients with CKD and anemia who were iron replete. Patients were randomized to receive treatment with either peginesatide intravenously or subcutaneously, or with epoetin alpha or beta in the control arm of the study. Patients were stratified based on Hgb ≤ 11.4g/dL or ≥ 11.5g/dL and New York Heart Association (NYHA) Heart Failure class 0-1 or class ≥ 2. In the two trials combined, there were a total of 1066 patients enrolled into the Peginesatide arm and 542 patients enrolled into the epoetin treatment arm. The studies consisted of a 6 week screening period, up to 28 weeks of dose titration, followed by a 6 week evaluation

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period and then a longer term safety evaluation period for 15 weeks or more. Hemoglobin levels were measured once during the screening period, every 2 weeks during the titration period, every week during the evaluation period, and every 2 weeks during the long term safety period. The study schedule is shown in the sponsor's table below.

**Table 4. Study Schedule for Studies AFX01-12 and AFX01-14**

Schedule of Events: Screening and Titration Periods

| Study Period: | Screening | | Titration | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week # | -4 to 0 | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 |
| Informed consent | X | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | |
| Physical exam, dry weight | | X[2] | | | | | | | | | | | | | | |
| Chemistry[1] | | X | | X | | X | | X | | X | | X | | X | | X |
| Folate & B[12] | X | | | | | | | | | | | | | | | |
| Pregnancy test[3] | X | | | | | | | | | | | | | | | |
| Hgb[1,4] | X[5] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| CBC with differential[1] | | X | | X | | X | | X | | X | | X | | X | | X |
| Iron Status (Ferritin & TSAT)[1] | X | X | | | | | | X | | | | | | X | | |
| hsCRP[1] | | X | | | | | | | | | | | | | | |
| AF37702-specific antibodies[1,6] | | X | | X | | X | | X | | X | | X | | X | | X |
| Anti-EPO antibodies[1,7] | X | X | | | | | | | | | | | | | | |
| Transfusion and phlebotomy collection | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| AE collection | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Composite safety endpoint data collection[8] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication collection | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | **Dosing Schedule (Timing of dosing is independent of visit schedule)** | | | | | | | | | | | | | | |
| Vital signs[1,9] | | X | | | | | | Q4W | | | | | | | | |
| AF37702 Injection Group[4] | | ESA-free Interval[10] | | | | | | AF37702 Injection Administration Q4W | | | | | | | | |
| Epoetin Alfa Group[4] | | | | | | | | Epoetin Alfa Administration 1 to 3 times per week | | | | | | | | |

Note: Randomization occurs between Screening and Titration periods.

[1] Laboratory specimens will be drawn prior to dialysis throughout the study.

[2] PE at Week 0 will be done pre-dose 1 and includes height by measurement or patient report.

[3] For women of child-bearing potential only.

[4] In the event of a dose delay, Hgb values must be evaluated weekly. Throughout the study, a Hgb must be obtained within 1 week prior to dosing for dose adjustment evaluation.

[5] Four eligible values obtained in the four weeks prior to randomization.

[6] AF37702-specific antibody samples will be collected only for patients randomized to the AF37702 Injection group.

[7] Anti-EPO antibody samples will be collected for all patients.

[8] Patients who prematurely withdraw from treatment will remain on study and continue to be followed for composite safety endpoint data.

[9] Vital signs will be obtained pre-dose. Vital signs will also be obtained approximately 15 minutes post-dose every 4 weeks through Week 12.

[10] ESA-free interval is the one week period during which patients randomized to the AF37702 Injection treatment group will discontinue Epoetin alfa prior to receipt of Dose 1 of AF37702 Injection (e.g., if the patient's last Epoetin alfa dose was Wednesday, the patient will receive Dose 1 of AF37702 Injection the following Wednesday).

**Schedule of Events: Evaluation and Long Term Safety and Efficacy Periods**

| Study Period: | Evaluation | | | | | | | | Long Term Safety and Efficacy Periods[1] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week # | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37+ ⟶ | | Termination |
| Physical exam, dry weight | | | | | | | | X | Q24W | | X |
| Chemistry[2] | | | | | | | | X | Q12W | | X |
| Hgb[2,3] | X | X | X | X | X | X | X | X | Q2W | | X |
| CBC with differential[2] | | | | X | | | | X | Q12W | | X |
| Iron Status (Ferritin & TSAT)[2] | | | | | | | | X | Q12W | | X |
| hsCRP[2] | | | | | | | | X | | | X |
| AF37702-specific antibodies[2,4] | | | | X | | | | X | Q12W | | X |
| Anti-EPO antibodies[2,5] | | | | | | | | | | | X |
| Transfusion and phlebotomy collection | X | X | X | X | X | X | X | X | Q2W | | X |
| AE/SAE collection | X | X | X | X | X | X | X | X | Q2W | | X |
| Composite safety endpoint data collection[6] | X | X | X | X | X | X | X | X | Q2W | | X |
| Concomitant medication collection | X | X | X | X | X | X | X | X | Q2W | | X |
| Dosing Schedule (Timing of dosing is independent of visit schedule) | | | | | | | | | | | |
| Vital signs[2] | Q4W on day of dosing | | | | | | | | Q12W on day of dosing | | X |
| AF37702 Injection Group[3] | AF37702 Injection Q4W Administration | | | | | | | | | | |
| Epoetin Alfa Group[3] | Epoetin Alfa Administration 1 to 3 times per week | | | | | | | | | | |

[1] All patients will remain on study treatment and should continue to follow the 'Long Term Safety and Efficacy Period' procedures for a period of 52 weeks after the last patient is enrolled. Assuming that the enrollment for the study is 52 weeks, patients who do not withdraw from the study will undergo a minimum of 52 weeks and an approximate maximum of 104 weeks of treatment.

[2] Laboratory specimens will be drawn prior to dialysis throughout the study.

[3] In the event of a dose delay, Hgb values must be evaluated weekly. Throughout the study a Hgb must be obtained within 1 week prior to dosing for dose adjustment evaluation.

[4] AF37702-specific antibody samples will be collected only for patients randomized to the AF37702 Injection group.

[5] Anti-EPO antibody samples will be collected for all patients.

[6] Patients who prematurely withdraw from treatment will remain on study and continue to be followed for composite safety endpoint data.

AFX01-12 and AFX0-14 Study Drug Administration:

Patients were randomized to either peginesatide (starting doses of 0.04 to 0.16 mg/kg based on prior maintenance epoetin dose) administered intravenously (IV) or subcutaneously (SC) once every 4 weeks, following a 1 week ESA free period from last dose of epoetin; or to continuing treatment with epoetin administered at the current dose 1-3 times per week.  Study drug was administered according to the following table:

**Table 5:  Peginesatide Starting Doses**

| Screening Epoetin Dose (U/kg/week) | Peginesatide (mg/kg/q4week) |
|---|---|
| <100 | 0.04 |
| 100 to 199 | 0.08 |
| 200 to 299 | 0.12 |
| ≥ 300 | 0.16 |

Peginesatide was adjusted according to the following guidelines:

- 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 ≥ 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%.

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- If Hgb has increased by > 1.0 g/dL over the past two weeks, the dose should be reduced by 25%.

Epoetin was adjusted according similar guidelines with the following exceptions:

- If Hgb is 12.0 to 12.4 g/dL, the dose should be reduced by 25%.
- If Hgb ≥ 12.5 g/dL, the dose should be delayed until Hgb is < 12.5 g/dL and the dose should then be reduced by 25%.

AFX01-12 and AFX01-14 Inclusion and Exclusion Criteria:

The key inclusion criteria were that patients had to be on dialysis for ≥ 3 months and were receiving ESA therapy. Also, patients had to have a mean baseline Hgb ≥10g/dL to ≤ 12g/dL. Additional inclusion criteria were as follows:

- Males or females ≥ age 18 years.
- Females of child-bearing potential who are sexually active must be willing to practice a highly effective method of birth control for at least 4 weeks prior to randomization, and must be willing to continue birth control until at least 4 weeks after the last dose of study treatment.
- On stable IV Epoetin alfa maintenance therapy continuously prescribed for a minimum of 8 weeks prior to randomization. Stability is defined as ≤ 30% change from the maximum prescribed weekly dose (i.e., [max-min]/max ≤ 0.3) with no change in prescribed frequency.
- Four consecutive Hgb values with a mean ≥ 10.0 and ≤ 12.0 g/dL during the screening period, with ≤ 1.3 g/dL difference between any of the four values and taken no less than 3 days apart. (Note: a maximum of six Hgb values may be obtained during screening).
- One transferrin saturation (TSAT) ≥ 20% within 4 weeks prior to randomization.
- One ferritin level ≥ 100 ng/mL within 4 weeks prior to randomization.
- One serum or red cell folate level ≥ lower limit of normal within 4 weeks prior to randomization.
- One vitamin B12 level ≥ lower limit of normal within 4 weeks prior to randomization.

The exclusion criteria were as follows:

- Females who are pregnant or breast-feeding.
- Known intolerance to any ESA, parenteral iron supplementation, or pegylated molecules.
- Known bleeding or coagulation disorder.
- Known hematologic disease or cause of anemia other than renal disease (e.g., pure red cell aplasia [PRCA], homozygous sickle-cell disease, thalassemia, multiple myeloma, hemolytic anemia and myelodysplastic syndrome).
- Poorly controlled hypertension within 4 weeks prior to randomization, per Investigator's clinical judgment.
- Any clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a patient's ability to give informed consent.

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- Evidence of active malignancy within one year (except non-melanoma skin cancer or carcinoma in situ that has been completely excised) prior to randomization.
- Temporary (un-tunneled) dialysis access catheter.
- A scheduled kidney transplant (Note: patients currently on a transplant wait list are not excluded unless there is an identified donor).
- A scheduled surgery that may be expected to lead to significant blood loss.
- RBC or whole blood transfusion within 12 weeks prior to randomization.
- Previous exposure to any investigational agent within 4 weeks prior to randomization, or planned receipt of an investigational agent, other than as specified by this protocol, during the study period.
- Previous exposure to AF37702 Injection.

AFX01-12 and AFX01-14 Efficacy Endpoints:

The primary efficacy analysis for these studies was a comparison of the mean change in Hgb from baseline to the evaluation period (weeks 29 to 36) between the two treatment groups. Secondary endpoints included proportion of patients receiving a transfusion and the proportion of patients whose Hgb was maintained in the range of ≥ 10g/dL to ≤ 12 g/dL.  The applicant proposed that peginesatide would be considered non-inferior to epoetin if the lower limit of the two-sided 95% CI for the difference between the two treatment group's mean changes of Hgb (Peginesatide - Epoetin) from baseline was ≥ -1.0 g/dL. The applicant provided support for this choice of a non-inferiority margin of 1.0 g/dL by showing that a statistical lower bound for the effect of ESA therapy based on data from historical ESA registration studies was appreciably greater than 1.0 g/dL. The clinical importance of a 1.0 g/dL change in Hgb was also considered in selecting this margin. Further support was provided by citing the impact of evolving clinical practice including the timing of initiation of ESA therapy and changes in Hgb targets.

AFX01-12 and AFX01-14 Safety Considerations:

Adverse events were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v. 3.0.  The composite safety endpoint (CSE) was the primary protocol specified safety endpoint.  The CSE consisted of the endpoints of death, stroke, myocardial infarction (MI), congestive heart failure (CHF), unstable angina and arrhythmia requiring hospitalization.  On-Study death was defined as deaths that occurred through 28-days following discontinuation of the study drug and was used for the composite safety event death analysis.  The CSE analysis was designed to compare the HR associated with the time to the first positively adjudicated event for peginesatide relative to the comparator groups across the combined Phase 3 studies. The sample size of the overall Phase 3 program was determined to provide at least 89% power to exclude a HR of 1.3 (peginesatide compared comparator ESA), using a one-sided 95% CI.  An upper limit of the HR of 1.3 was prespecified and was chosen to reflect the observed and clinically relevant increase in the risk of CV events found when higher Hgb targets were used for treatment as described in the literature regarding patients with CRF on hemodialysis and patients with CRF not on dialysis.  In the analysis of the composite events, a patient who experienced any of the composite endpoint events was counted only once (e.g., if a

myocardial infarction occurred before a stroke, only the time from first dose of study medication to the myocardial infarction will be included in the composite endpoint for the patient). The hazard ratio along with the 95% confidence interval (one-sided or the comparable 90% two-sided interval) was calculated using Cox regression stratified by the randomization factors.

AFX01-12 and AFX01-14 Ethical Considerations:

The studies were conducted according to the Declaration of Helsinki and Good Clinical Practices Guidelines. A Data Monitoring Committee and an independent Event Review Committee reviewed and monitored the study.

## 5.3.2 Non-Dialysis Studies

AFX01-11 and AFX01-13 Objectives:

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.

AFX01-11 and AFX01-13 Design:

Studies AFX01-11 and AFX01-13 were similarly designed studies conducted in patients with anemia due to CKD who were not on dialysis and not on ESA therapy for at least the preceding 12 weeks. 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. Patients were stratified based on Hgb $\leq$ 10.4g/dL or $\geq$ 10.5g/dL and NYHA Heart Failure 0-1 or $\geq$ Class 2. Patients were randomized to receive treatment with either peginesatide subcutaneously or with darbepoetin. In the two trials combined, there were 656 patients enrolled into the peginesatide arms and 327 patients enrolled into the darbepoetin arms in the US and EU. 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. Similar study schedules to that shown above for studies AFX01-12 and AFX01-14 were used for studies AFX01-11 and AFX01-13 but were adjusted for the timing of the various periods of the study.

AFX01-11 and AFX01-13 Study Drug Administration:

Patients were randomized 1:1:1 to either peginesatide at starting doses of 0.025 mg/kg SC once every four weeks or 0.04 mg/kg SC once every four weeks or to darbepoetin 0.75 µg/kg SC once every 2 weeks.

Study drug doses were adjusted according to the following guidelines which were similar to those for studies AFX01-12 and AFX01-14:

- If Hgb is > 12.0 g/dL, the dose should be reduced by 25%.
- If Hgb is ≥ 12.5 g/dL, the dose should be delayed until Hgb is < 12.5 g/dL and the dose should be reduced by 25%.
- If Hgb has increased by > 1.0 g/dL over the past 2 weeks, the dose should be reduced by 25%.
- If Hgb has decreased by 0.5-0.9 g/dL from baseline, the dose should be increased by 25%.
- If Hgb has decreased by ≥ 1.0 g/dL from baseline, the dose should be increased by 50%.
- If Hgb has increased by < 1.0 g/dL over the past 4 weeks and Hgb < 11.0 g/dL, the dose should be increased by 25%.

AFX01-11 and AFX01-13 Inclusion and Exclusion Criteria:

Studies AFX01-11 and AFX01-13 had similar inclusion criteria compared to studies AFX01-12 and AFX01-14 with the following exceptions:

- CKD with an estimated glomerular filtration rate (GFR) < 60 mL/min/1.73m$^2$ using the 4-variable Modification of Diet in Renal Disease (MDRD) formula within 4 weeks prior to randomization, and not expected to begin dialysis for at least 12 weeks.
- Two consecutive Hgb values ≥ 8.0 g/dL and < 11.0 g/dL within 4 weeks prior to randomization, with ≤ 1.3 g/dL difference between the two values and no less than 5 days apart, with the last value within 10 days prior to randomization.

Studies AFX01-11 and AFX01-13 had similar exclusion criteria compared to studies AFX01-12 and AFX01-14 with the following exception:

- Treatment with an ESA in the 12 weeks prior to randomization.

AFX01-11 and AFX01-13 Efficacy Endpoints:

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.

ADX01-11 and AFX01-13 Safety Considerations:

The safety considerations for these studies were similar to those of studies AFX01-12 and AFX01-14.

AFX01-12 and AFX01-14 Ethical Considerations:

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The ethical considerations for these studies were similar to those for studies AFX01-12 and AFX01-14.

*Reviewer comment for section 5: The studies AFX01-12 and AFX01-14 were the primary studies used to understand the safety and efficacy of peginesatide for the treatment of patients with anemia associated with CKD in patients on dialysis. The studies AFX01-11 and AFX01-13 were the primary studies used to understand the safety and efficacy of peginesatide for the treatment of anemia associated with CKD in patients not on dialysis. The objectives, inclusion and exclusion criteria, efficacy, safety and ethical considerations for the studies appear to be acceptable to evaluate the safety and efficacy of peginesatide for the proposed indication. However, the patients not on dialysis were not on stable doses of ESA at the time they began treatment in the study whereas the patients on dialysis were on stable doses of ESA. Although these studies were open label studies, the efficacy endpoints used in the studies were objective in nature, i.e., Hgb level. The composite safety endpoint (CSE) consisting of death, stroke, myocardial infarction (MI), congestive heart failure (CHF), unstable angina and arrhythmia was the primary protocol specified safety endpoint. The more subjective components of the CSE endpoint, namely, congestive heart failure, unstable angina and arrhythmia, are more difficult to ascertain, and may allow for more subjectivity on behalf of both the reporting physician and the adjudication committee. These more subjective endpoints may be less clinically important in that they may not have the permanent consequences of the outcomes included in the major cardiac events (MACE) composite endpoint. MACE endpoints are considered objective endpoints and include death, MI and stroke. The median duration of exposure to study drug was <1.5 years for both the on dialysis studies (AFX01-12 and AFX01-14) and the not on dialysis studies (AFX01-11and AFX01-13). This duration of exposure was somewhat short given that patients with CKD essentially require life-long therapy or until they receive a kidney transplant. It has been reported that only 14% of Americans with end stage renal disease will receive a kidney transplant. The average waiting time for a cadaveric kidney transplant is approximately 5 years.[8] However, International Conference on Harmonization Guidelines for chronically administered drug recommend that approximately 300-600 patients receive study drug for 6 months and 100 patients receive study drug for one year.[9] In the trials supporting the application 1722 patients in Phase 3 controlled studies received peginesatide for average patient exposure years per patient of 1.16 and average patient follow-up years per patient of 1.24.*

# 6 Review of Efficacy

## 6.1 Indication

The sponsor proposes the following indication:

- Omontys (Peginesatide) is an erythropoiesis stimulating agent (ESA) that is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

## 6.1.1  Methods

The clinical data upon which this application is submitted is based on studies AFX01-12, AFX01-14, AFX01-11 and AFX01-13.  Studies AFX01-12 and AFX01-14 evaluated peginesatide therapy in patients with anemia associated with CKD in patients who were on dialysis.  Studies AFX01-11 and AFX01-13 evaluated peginesatide therapy in patients with anemia associated with CKD in patients who were not on dialysis.

## 6.1.2  Demographics

Studies AFX01-12 and AFX01-14:

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

**Table 6: Baseline Demographics AFX01-12 and AFX01-14 (On Dialysis)**

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

Studies AFX01-11 and AFX01-13:

The table below shows key demographic features of the pooled Phase 3 non-dialysis population.  In this patient population there were some baseline imbalances which may have been prognostically unfavorable for the peginesatide treatment arm.  These imbalances include a greater proportion of patients with diabetes mellitus, peripheral vascular disease, and coronary artery disease.  It is not possible to determine the prior use of darbepoetin in patients not on dialysis because the sponsor did not record the history of prior ESA use.

**Table 7: Demographics in Studies AFX01-11 and AFX01-13 combined**

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

PVD: peripheral vascular disease
CAD: coronary artery disease

### 6.1.3   Patient Disposition

Overall:

In the four Phase 3 studies patients were scheduled to be treated for a minimum of 52 weeks. In these studies, 2,591 subjects received at least one dose of study medication; 1,722 subjects received peginesatide and 869 received comparator (epoetin or darbepoetin).

Studies AFX01-12 and AFX01-14:

In studies AFX01-12 and AFX01-14 there were 1066 patients treated with peginesatide starting doses of 0.04 to 0.16 mg/kg administered once every four weeks based on prior maintenance epoetin dose and 542 patients treated with epoetin administered one to three times a week.  The average patient follow-up time for patients in these studies was 1.24 years for peginesatide treated patients and 1.25 years for epoetin treated patients.   In these studies there were 1289 patients enrolled in the US and 319 patients enrolled outside the US. In study AFX01-12 the comparator was epoetin alfa while in study AFX01-14 the comparator was either epoetin alfa or epoetin beta.  Epoetin beta is not marketed in the US.  A total of 107 patients were enrolled in Europe in study AFX01-14.  The average peginesatide exposure per patient in the dialysis studies, AFX01-12 and AFX01-14, was 1.16 years and the average exposure to epoetin per patient in these studies was 1.20 years.  There were 329/1066 (31%) of patients treated with peginesatide and 144/542 (27%) of patients treated with epoetin that prematurely discontinued study drug.  The primary reason for premature discontinuation in patients treated with peginesatide was death in both groups.  In these studies there were 59/1066 (6%) patients who were treated with peginesatide who died within 28 days of the final drug dose compared to 53/542 (10%) of patients treated with epoetin who died within 28 days of the final drug dose.

Studies AFX01-11 and AFX01-13:

In studies AFX01-11 and AFX01-13 there were a total of 656 patients treated with peginesatide. There were 328 patients who were started on a peginesatide dose of 0.025mg/kg once every 4 weeks and 328 patients who were started on a peginesatide dose of 0.04mg/kg once every 4 weeks. There were 327 patients who were started on a darbepoetin dose of 0.75µg/kg once every two weeks. The average patient follow-up time for patients in these studies was 1.37 years for patients treated with peginesatide and 1.41 years for patients treated with darbepoetin. In these studies there were 903 patients enrolled in the US and 80 patients enrolled outside the US. The average peginesatide exposure per patient in the non-dialysis studies, AFX01-11 and AFX01-13, was 1.29 years and the average exposure to darbepoetin per patient was 1.33 years. In these studies there were 188/656 (29%) of patients treated with peginesatide and 77/327 (24%) of patients treated with epoetin who prematurely discontinued study drug. The primary reason for discontinuation of peginesatide was adverse events 48/656 (7%). The primary reason for discontinuation of darbepoetin was withdrawal of consent 17/327 (5%).

### 6.1.4   Analysis of Primary Endpoints

Studies AFX01-12 and AFX01-14:

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

**Table 8**:  **Primary Efficacy Analysis for Studies AFX01-12 and AFX01-14**

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

Studies AFX01-11 and AFX01-13:

The primary efficacy analysis shows that 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 sponsor's pre-specified criteria because the lower limit of the two-sided 97.5% CI difference between the two treatment groups mean changes of Hgb (Peginesatide - Epoetin) from baseline was > -1.0 g/dL.  The table below summarizes the primary efficacy analysis for studies AFX01-11 and AFX0-1-13.

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

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

The table below shows summarizes the primary efficacy results for studies AFX01-11 and AFX013 separately. Again, the results show that Peginesatide can be considered non-inferior to epoetin by the sponsor's pre-specified criteria because the lower limit of the two-sided 97.5% CI difference between the two treatment groups mean changes of Hgb (Peginesatide - Epoetin) from baseline was > -1.0 g/dL.

**Table 10: Separate Primary Efficacy Analyses for Studies AFX01-11 and AFX01-13 (Not on Dialysis)**

| | AFX01-11 | | | AFX01-13 | | |
|---|---|---|---|---|---|---|
| | **Peg. 0.025 mg/kg q4wk N= 328** | **Peg. 0.04 mg/kg q4wk N = 328** | **Dar. 0.75 µg/kg q2wk N = 327** | **Peg. 0.025 mg/kg q4wk N= 328** | **Peg. 0.04 mg/kg q4wk N = 328** | **Dar. 0.75 µg/kg q2wk N = 327** |
| **Baseline Hgb g/dL Mean (SD)** | 10.05 (0.62) | 9.95 (0.69) | 10.05 (0.64) | 10.02 (0.63) | 10.03 (0.62) | 10.03 (0.65) |
| **Evaluation period mean Hgb g/dL (SD)** | 11.47 (0.73) | 11.61 (0.86) | 11.47 (0.75) | 11.55 (0.74) | 11.71 (0.86) | 11.40 (0.73) |
| **Hgb mean change from baseline to Weeks 25-36 g/dL** | 1.39 | 1.64 | 1.37 | 1.50 | 1.68 | 1.35 |
| **Difference from Darbepoetin by Least Squares mean (2 sided 97.5% CI)** | 0.03 (-0.19, 0.26) | 0.26 (0.04, 0.48) | | 0.14 (-0.09, 0.36) | 0.31 (0.08, 0.54) | |

Peg. = Peginesatide, Dar. = Darbepoetin, wk = week, Hgb = Hemoglobin

### 6.1.5  Analysis of Secondary Endpoints

AFX01-12 and AFX01-14:

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

**Table 11: Secondary Efficacy Analysis – Proportion of Patients Receiving Transfusions during the titration and evaluation intervals**

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

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

**Table 12: Secondary Efficacy Analysis – Proportion of Patients with Hgb in Target Range during the evaluation interval**

| | AFX01-12 | | AFX01-14 | |
|---|---|---|---|---|
| | Peginesatide (n=524) | Epoetin (n=269) | Peginesatide (n=542) | Epoetin (n=273) |
| Patients with mean Hgb within target range (10-12 g/dL) during evaluation period, n (%) | 330 (63) | 193 (72) | 344 (64) | 180 (66) |
| Relative Response Rate* (95 %CI) | 0.88 (0.79,0.97) | | 0.96 (0.87,1.07) | |

 * Peginesatide relative to epoetin by Cochran Mantel Haenszel procedure

AFX01-11 and AFX01-13:

The secondary efficacy analysis of the proportion of patients receiving transfusions in studies AFX01-11 and AFX01-13 during the titration and evaluation intervals is shown in the table below. In the studies similar proportions of patients received transfusions in the three treatment arms.

**Table 13: Secondary Efficacy Analysis – Proportion of Patients Receiving Transfusions during the titration and evaluation intervals**

| | AFX01-11 and AFX01-13 | | |
|---|---|---|---|
| | Peginesatide  0.025 mg/kg q4wk N= 328 | Peginesatide 0.04 mg/kg q4wk N = 328 | Darbepoetin 0.75µg/kg q2wk N = 327 |
| Patients receiving transfusions, n (%) | 29 (9) | 29 (9) | 16 (5) |

The secondary efficacy analysis of the proportion of patients with mean Hgb within the sponsor's target range of 11g/dL to 12 g/dL during the evaluation period in the dialysis studies is shown in the table below. Similar proportions of patients in the three treatment arms were able to maintain hemoglobin with the sponsor's target range of 11-12 g/dL.

**Table 14: Secondary Efficacy Analysis – Proportion of Patients with Hgb in Target Range during the evaluation interval**

|  | AFX01-11 and AFX01-13 | | |
|---|---|---|---|
|  | Peginesatide 0.025 mg/kg q4wk N= 328 | Peginesatide 0.04 mg/kg q4wk N = 328 | Darbepoetin 0.75μg/kg q2wk N = 327 |
| **Patients with mean Hgb within target range (11-12 g/dL) during evaluation period, n (%)** | 131 (81) | 137 (83) | 143 (87) |
| **Relative Response Rate* (95% CI)** | 0.93 (0.85, 1.02) | 0.95 (0.87, 1.04) | |

*Peginesatide relative to darbepoetin

## 6.1.6 Analysis of Clinical Information Relevant to Dosing Recommendations
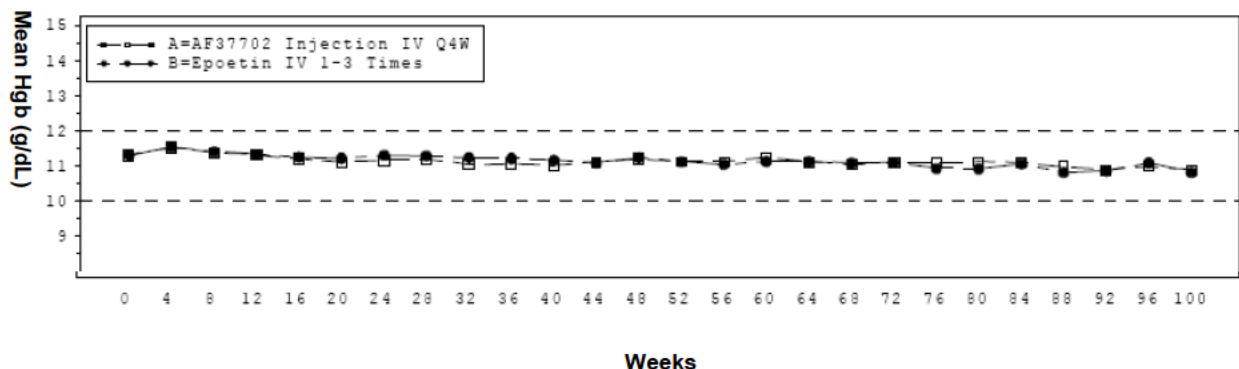
AFX01-12 and AFX01-14:

The overall proportions of patients with a dose alteration or postponements due to out-of-range-Hgb levels in studies AFX01-12 and AFX01-14 are shown in the table below. In the studies AFX01-12 and AFX01-14, in patients on dialysis, there fewer dose alterations and postponements for peginesatide as compared to epoetin.

**Table 15: Dose Alterations and Postponements in Studies AFX01-12 and AFX01-14**

|  | Study AFX01-12 | | AFX01-14 | |
|---|---|---|---|---|
|  | Peginesatide n=524 | Epoetin n= 269 | Peginesatide n= 542 | Epoetin n= 273 |
| **≥ 1 Dose Increase, n (%)** | 379 (75) | 260 (97) | 393 (75) | 235 (88) |
| **≥ 1 Dose Decrease, n (%)** | 389 (77) | 261 (97) | 415 (79) | 242 (90) |
| **≥ 1 Dose Postponement, n (%)** | 233 (46) | 253 (94) | 192 (37) | 221 (82) |

The figure below shows the mean hemoglobin achieved over the course of the dialysis studies in either treatment arm. The two lines representing the 2 treatment arms, peginesatide and epoetin overlap.

## Figure 2. Mean Hemoglobin Over Time in Studies AFX01-12 and AFX01-14 (On Dialysis)



AFX01-11 and AFX01-13:

The overall proportions of patients with a dose alteration or postponement due to out-of-range Hgb levels in studies AFX01-11 and AFX01-13 are shown in the table below. In the studies AFX01-11 and AFX01-13, in patients not on dialysis, there were slightly more patients treated with peginesatide 0.025 mg/kg or 0.04 mg/kg compared to patients treated with darbepoetin that required a dose increase (78% of patients treated with peginesatide compared to 75% of patients treated with darbepoetin). During the early part of the studies, i.e., during the titration period of the studies, there were 199/328 (61%) patients that required an increase in the dose of peginesatide who were started on the 0.025 mg/kg dose, 171/328 (52%) patients that required an increase in the dose of peginesatide who were started on the 0.04 mg/kg dose and 173/327 (53%) patients that required an increase in the dose of darbepoetin who were started on the 0.75 µg/kg dose.

**Table 16: Dose Alterations and Postponements in Studies AFX01-11 and AFX01-13**

| | Peginesatide 0.025 mg/kg n=328 | Peginesatide 0.04 mg/kg n=328 | Darbepoetin 0.75 µg/kg n=327 |
|---|---|---|---|
| ≥ 1 Dose Increase, n (%) | 256 (78) | 255 (78) | 245 (75) |
| ≥ 1 Dose Decrease, n (%) | 276 (84) | 293 (89) | 304 (93) |
| ≥ 1 Dose Postponement, n (%) | 217 (66) | 255 (78) | 294 (90) |

*Reviewer comment for section 6: For both the dialysis and non-dialysis populations the treatment arms were balanced in terms of demographics except for CAD in studies AFX01-12 and AFX01-14 and diabetes, PVD and CAD in studies AFX01-11 and AFX01-13 (all more prevalent in the peginesatide group). Patients were exposed to study drug for approximately 1.2 years which is less than would be expected in practice since the waiting time for a cadaveric kidney transplant is about 5 years. However, the protocol specified efficacy analyses show non-*

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*inferiority of peginesatide as demonstrated for both groups on dialysis and not-on-dialysis, with the statistical results as follows:*

- *Dialysis Least Squares Mean and 95% CI*

  - *AFX01-12*
    - *Peginesatide 0.04 mg/kg starting dose = -0.15 (-0.30,-0.01)*
  - *AFX01-14*
    - *Peginesatide 0.04 mg/kg starting dose = 0.10 (-0.05, 0.26)*

- *Not-on Dialysis Least Squares Mean and 97.5% CI*

  - *AFX01-11*
    - *Peginesatide 0.025 mg/kg starting dose = 0.03 (-0.19,0.26)*
    - *Peginesatide 0.04 mg/kg starting dose = 0.26 (0.04, 0.48)*
  - *AFX01-13*
    - *Peginesatide 0.025 mg/kg starting dose = 0.14 (-0.09,0.36)*
    - *Peginesatide 0.04 mg/kg starting dose = 0.31 (0.08, 0.54)*

*Peginesatide can be considered non-inferior to ESA because the lower limit two-sided 95% or 97.5% CI difference between the two treatment groups mean changes of Hgb from Baseline was > -1.0 g/dL. The secondary endpoints analyses support the efficacy of peginesatide for the treatment of patients with anemia associated with CKD on dialysis and not on dialysis. Patients on dialysis who were treated with peginesatide required fewer changes in dose overall compared to patients treated with epoetin while patients treated with peginesatide who were not on dialysis had similar dose alterations compared to those treated with darbepoetin.*

# 7   Review of Safety

## 7.1   Methods

A review of studies AFX01-12, AFX01-14, AFX01-11 and AFX01-13 for safety is included in this document. Studies AFX01-12 and AFX01-14 were the primary studies submitted to support the safety of peginesatide for the treatment of patients with anemia associated with CKD in patients on dialysis. Studies AFX01-11 and AFX01-13 were the primary studies submitted to support the safety of peginesatide for the treatment of anemia associated with CKD in patients not on dialysis. Summaries of the other studies submitted by the sponsor to support peginesatide safety in the treatment of patients with anemia associated with CKD were also reviewed.

In addition, in NDA 202799 submission 9 letter date September 23, 2011 the sponsor submitted the 120 Day Safety Update Report. This submission primarily updated safety information for study AFX01-06 which is being conducted to evaluate the safety and efficacy of peginesatide

therapy in 18 patients with anemia associated with CKD who have a history of anti-erythropoietin antibodies.

## 7.1.1  Adequacy of Data

Overall in the four major controlled studies there were 1722 patients who were exposed to peginesatide and 869 exposed to comparator ESA.  Patients in studies AFX01-12 and AFX01-14, i.e., patients on dialysis were followed for approximately 1.2 years.  Patients in studies AFX01-11 and AFX01-13, i.e., patients who were not dialysis were followed for approximately 1.4 years.  The table below shows the weight based doses of study drug.  The average epoetin alfa or beta dose (based on all doses received during the course of the included studies) was 113 U/week/kg and median average darbepoetin dose (based on all doses received during the course of the included studies) was 0.47µg/kg.

**Table 17.  Mean Study Drug Dose During Study**

|  | Pooled AFX01-12 and AFX01-14 (Dialysis) | | Pooled AFX01-11 and AFX01-13 (Non-Dialysis) | |
|---|---|---|---|---|
|  | Peginesatide (n=1066) mg/kg | Epoetin-alfa/beta (n=542) U/week/kg | Peginesatide (n=656) mg/kg | Darbepoetin (n=327) mg/kg |
| **Mean Dose During Study** | 0.07 | 113 | 0.03 | 0.47 |

The table below shows the number of patients that received peginesatide or comparator ESA for particular lengths of time (results are mutually exclusive).  In the two sets of studies, similar proportions of patients received peginesatide or epoetin for similar lengths of time.

**Table 18.  Duration of Therapy**

| | Pooled AFX01-12 and AFX01-14 (Dialysis) | | Pooled AFX01-11 and AFX01-13 (Non-Dialysis) | |
|---|---|---|---|---|
| **Weeks on Therapy** | **Peginesatide (n=1066) N (%)** | **Epoetin (n=542) N (%)** | **Peginesatide (n=656) N (%)** | **Darbepoetin (n=327) N (%)** |
| **<20** | 116 (11) | 41 (8) | 52 (8) | 25 (8) |
| **20-40** | 83 (8) | 44 (8) | 54 (8) | 13 (4) |
| **40-60** | 197 (18) | 90 (17) | 96 (15) | 50 (15) |
| **60-80** | 507 (47) | 264 (48) | 212 (32) | 114 (35) |
| **>80** | 178 (16) | 106 (19) | 242 (37) | 125 (38) |

## 7.1.2   Pooling Data Across Studies

Safety data was pooled for studies AFX01-12 and AFX01-14.  Safety data was also pooled for studies AFX01-11 and AFX01-13.

## 7.2   Adequacy of Safety Assessments

### 7.2.1   Overall Exposure and Demographics of Target Populations

Patients on dialysis and not on dialysis were exposed to study drug for approximately 1.2 years. For both the dialysis and non-dialysis populations the treatment arms were balanced in terms of demographics except for CAD in studies AFX01-12 and AFX01-14 and diabetes, PVD and CAD in studies AFX01-11 and AFX01-13.

### 7.2.2   Routine Clinical Testing

Laboratory testing and patient evaluations were performed as shown in the study schedule (see section 5.3 Discussion of Individual Studies in this review).

### 7.2.3   Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Safety events for the composite safety endpoint (CSE), i.e., all cause death, stroke, myocardial infarction (MI), congestive heart failure (CHF) requiring hospitalization and arrhythmia requiring hospitalization were adjudicated by an independent Event Review Committee.  The primary safety objective in the four controlled trials was to rule out an increase of 30% or more in the risk of CSE based on a two-sided 90% confidence interval for the CSE hazard ratio.  A key secondary safety analysis consisted of a time to event analysis of major adverse cardiac events (MACE) endpoints, including death, stroke and MI.  A similar time to event analysis was performed in the TREAT trial described in section 2.4 Important Safety Issues with Consideration to Related Drugs in this review.  Additional safety analyses for seizures, which are adverse events that are described in the labeling of other ESAs were done.

## 7.3   Major Safety Results

### 7.3.1   Deaths

The table below shows the on drug and on study deaths in studies AFX01-12 and AFX01-14.  A slightly greater proportion of patients died within 28 days of their final dose study drug in the epoetin treatment group compared to the peginesatide treatment group.

**Table 19. Mortality Rates in Studies AFX01-12 and AFX01-14 (On Dialysis)**

|  | Studies AFX01-12 and AFX01-14 | |
|---|---|---|
|  | Peginesatide n = 1066 | Epoetin n = 542 |
| **On Study Deaths, n (%)** | 115 (11) | 64 (12) |
| **On Drug Deaths (Within 28 days of Final Dose), n (%)** | 59 (6) | 53 (10) |

The table below shows the on drug and on study deaths in studies AFX01-11 and AFX01-13. Similar proportions of patients died in each treatment group in these studies.

**Table 20. Mortality Rates in Studies AFX01-11 and AFX01-13 (Not On Dialysis)**

|  | Studies AFX01-11 and AFX01-13 | |
|---|---|---|
|  | Peginesatide n = 656 | Epoetin n = 327 |
| **On Study Deaths, n (%)** | 58 (9) | 22 (7) |
| **On Drug Deaths (Within 28 days of Final Dose), n (%)** | 29 (4) | 13 (4) |

An analysis of the time to first event for all cause death and death that occurred through 28 days after study termination is shown in the table below. The table shows that the HR for all cause death and death that occurred through 28 days after study termination was similar in both treatment groups for patients on dialysis. The HR for all cause death and death that occurred through 28 days after study termination was unfavorable for peginesatide but was not statistically significant because the 95% CI crossed unity.

**Table 21. Time to First Event Analyses:  All Cause Death and On Study Deaths***

|  | Dialysis | | Non-Dialysis | |
|---|---|---|---|---|
|  | Peginesatide (N=1066) | Epoetin (N=542) | Peginesatide (N=656) | Darbepoetin (N=327) |
| **All Cause Death** | | | | |
| **Number of Events, n (%)** | 136 (13) | 67 (12) | 73 (11) | 24 (7) |
| **HR (95% CI)** | 0.97 (0.72, 1.30) | | 1.52 (0.95, 2.42) | |
| **Death Occurred Through 28 Days Post Study Termination (On Study)** | | | | |
| **Number of Events, n (%)** | 115 (11) | 64 (12) | 58 (9) | 22 (7) |
| **HR (95% CI)** | 0.90 (0.67, 1.23) | | 1.42 (0.86, 2.35) | |

* Median Follow-up Peginesatide, Comparator (weeks):  Dialysis: 64, 64; Non-Dialysis: 74, 75

The table below shows a summary of the designated cause of all deaths.  A slightly higher proportion of patients died with the designated cause of death listed as "other" in the peginesatide group compared to the darbepoetin group in the non-dialysis studies.

**Table 22.  All Cause Deaths**

| Cause of Death | AFX01-12 and AFX01-14 | | AFX01-11 and AFX01-13 | |
| --- | --- | --- | --- | --- |
| | Peginesatide n=1066 N (%) | Epoetin n = 542 N (%) | Peginesatide n= 656 N (%) | Darbepoetin n=327 N (%) |
| Myocardial Infarction | 11 (1) | 3 (1) | 7 (1) | 2 (1) |
| Stroke | 7 (1) | 5 (1) | 2 (<1) | 0 (0) |
| Congestive Heart Failure | 4 (<1) | 2 (<1) | 6 (1) | 0 (0) |
| Arrhythmia | 5 (1) | 3 (1) | 2 (<1) | 1 (<1) |
| Pulmonary Embolism | 1 (<1) | 0 (0) | 0 (0) | 0 (0) |
| Chronic Kidney Disease | 8 (1) | 1 (<1) | 7 (1) | 3 (1) |
| Infection | 19 (2) | 11 (2) | 3 (1) | 3 (1) |
| Cancer | 4 (<1) | 3 (1) | 4 (1) | 3 (1) |
| Trauma | 1 (<1) | 0 (0) | 1 (1) | 0 (0) |
| Sudden Death | 4 (<1) | 0 (0) | 4 (1) | 2 (1) |
| Other | 72 (7) | 39 (7) | 37 (6) | 10 (3) |

The deaths listed as "other" in the non-dialysis studies were examined by Dr. Dmytrijuk and are shown in the reviewer's table below.  A slightly higher proportion of patients died due to cardiac arrest in the peginesatide group compared to the darbepoetin group.

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**Table 23. Study AFX01-11 and AFX01-13 (Non-Dialysis) Deaths Listed as "Other"**

| Other – Cause | Peginesatide n= 656 N (%) | Darbepoetin n =327 N (%) |
|---|---|---|
| Aortic Rupture | 1 (<1) | 0 (0) |
| Cardio-Pulmonary Arrest/Coronary Artery Disease | 13 (2) | 4 (1) |
| Cardiomyopathy | 2 (<1) | 1 (<1) |
| Hypotension/Cardiovascular Insufficiency | 2 (<1) | 2 (1) |
| Hypertension | 1 (<1) | 0 (0) |
| Failure to Thrive | 1 (<1) | 0 (0) |
| Multi-Organ Failure | 2 (<1) | 0 (0) |
| Respiratory Failure | 0 (0) | 1 (<1) |
| Gastrointestinal Hemorrhage | 1 (<1) | 0 (0) |
| Pulmonary Edema | 1 (<1) | 0 (0) |
| Chronic Hepatic Failure | 1 (<1) | 0 (0) |
| Cause Unknown/Unavailable | 12 (2) | 2 (1) |
| Total Other | 37 (6) | 10 (3) |

### 7.3.2  Nonfatal Serious Adverse Events

The table below shows the adverse events (AEs) in trials AFX01-12 and AFX01-14, i.e., the on dialysis studies, including serious adverse events (SAEs).  In the Phase 3 dialysis subjects the type and frequency of adverse events, serious adverse events, on study deaths up to 28 days after the last dose of drug, adverse events ≥ grade 3 or adverse events leading to permanent discontinuation of the study drugs were similar between the Peginesatide treatment group and the Epoetin treatment group.

**Table 24.  Adverse Events in Studies AFX01-12 and AFX01-14**

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

*On study

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The number of patients on dialysis that reported serious adverse events were 572/1066 (54%) in the peginesatide group and 309/542 (57%) in the epoetin treatment group. Serious AEs of infectious complications and heart failure were the most common and observed with similar frequency in the peginesatide and epoetin groups. Serious AEs reported in ≥3% of patients in the peginesatide group on dialysis are summarized in the sponsor's table blow.

**Table 25. Serious Adverse Events with Patient Incidence ≥ 3% in the Peginesatide Group (On Dialysis)**

| Preferred Term | Peginesatide (N=1066) % | Epoetin (N=542) % |
|---|---|---|
| Pneumonia | 6 | 6 |
| Cardiac failure congestive | 6 | 7 |
| Hyperkalemia | 5 | 4 |
| Fluid Overload | 4 | 5 |
| Sepsis | 3 | 5 |
| Cellulitis | 3 | 3 |
| Respiratory failure | 3 | 2 |

Overall, in the non-dialysis studies the proportion of patients who had adverse events, serious adverse events, on study deaths, adverse events ≥ grade 3 and adverse events leading to permanent discontinuation of the study drugs was higher among those treated with peginesatide compared to those treated with darbepoetin.

**Table 26. Adverse Events in Studies AFX01-11 and AFX01-13**

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

*On Study

The number of patients not on dialysis that reported serious adverse events was 318/656 (49%) in the peginesatide treatment group compared to the 141/327 (43%) in the darbepoetin treatment group. An increased frequency of acute renal failure as an SAE was observed in the peginesatide group (8.5% vs. 4.3% darbepoetin group) however the sponsor reports that progression to end stage renal disease was similar in the two treatment groups. Serious AEs reported in ≥3% of patients in the peginesatide group not on dialysis are summarized in the sponsor's table blow.

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**Table 27.  Serious Adverse Events with Patient Incidence ≥ 3% in the Peginesatide Group (Not On Dialysis)**

| Preferred Term | Peginesatide (N=656) % | Darbepoetin (N=327) % |
|---|---|---|
| Cardiac failure congestive | 9 | 8 |
| Acute renal failure | 9 | 4 |
| Pneumonia | 5 | 4 |
| Chronic renal failure | 5 | 5 |
| Urinary tract infection | 4 | 2 |
| Anemia | 4 | 2 |

### 7.3.3   Significant Adverse Events

The sponsor's table below shows the proportion of patients with adverse events that occurred in ≥ 10 % of patients in studies AFX01-12 and AFX01-14, i.e., the on dialysis studies.  The adverse events reported more frequently in the peginesatide treatment group were diarrhea, vomiting, hypertension and arthralgia.  However, these adverse events were not the leading adverse events that lead to treatment discontinuation.

**Table 28. Adverse Events with Patient Incidence ≥ 10% in the Peginesatide Treatment Group (On Dialysis)**

| Preferred Term | Peginesatide (N=1066) % | Epoetin (N=542) % |
|---|---|---|
| Diarrhea | 18 | 16 |
| Dyspnea | 18 | 19 |
| Nausea | 17 | 20 |
| Arteriovenous fistula complication | 16 | 17 |
| Cough | 16 | 17 |
| Headache | 15 | 16 |
| Muscle spasms | 15 | 17 |
| Vomiting | 15 | 13 |
| Hypotension | 14 | 15 |
| Hypertension | 13 | 11 |
| Pyrexia | 12 | 14 |
| Hyperkalemia | 11 | 12 |
| Upper respiratory tract infection | 11 | 12 |
| Back pain | 11 | 11 |
| Pain in extremity | 11 | 13 |
| Procedural hypotension | 11 | 13 |
| Arthralgia | 11 | 10 |

The sponsor's table below shows the proportion of patients with adverse events that occurred in ≥ 10 % of patients in studies AFX01-11 and AFX01-13, i.e., the not on dialysis studies. The adverse events reported more frequently in the peginesatide treatment group were peripheral edema, hyperkalemia, urinary tract infection, arthralgia, back pain, vomiting, nasopharyngitis, congestive heart failure, cough and pain in the extremity. However, these adverse events were not the leading adverse events that lead to treatment discontinuation.

**Table 29. Adverse Events with Patient Incidence ≥ 10% in the Peginesatide Treatment Group (Not On Dialysis)**

| Preferred Term | Peginesatide (N=656) % | Darbepoetin (N=327) % |
|---|---|---|
| Peripheral edema | 20 | 16 |
| Hyperkalemia | 18 | 17 |
| Urinary tract infection | 17 | 17 |
| Hypertension | 16 | 17 |
| Nausea | 15 | 15 |
| Diarrhea | 13 | 17 |
| Arthralgia | 12 | 9 |
| Back pain | 12 | 7 |
| Vomiting | 11 | 10 |
| Nasopharyngitis | 11 | 11 |
| Dizziness | 11 | 14 |
| Cardiac failure congestive | 11 | 9 |
| Cough | 11 | 7 |
| Pain in extremity | 10 | 10 |

### 7.3.4  Submission Specific Primary Safety Concerns

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

**Table 30: Applicant's Composite Safety Endpoint (On Dialysis, On study)**

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

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

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

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

**Table 31: Composite Safety Endpoint for Trials 11 and 13 Combined (Non Dialysis, On Study)**

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

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

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

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**Table 32: Time to First Event Analysis – MACE events***

| | Dialysis | | Non-Dialysis | |
|---|---|---|---|---|
| | Peginesatide (N=1066) | Epoetin (N=542) | Peginesatide (N=656) | Darbepoetin (N=327) |
| **MACE** | | | | |
| **Number of Events, N (%)** | 161 (15) | 96 (18) | 80 (12) | 30 (9) |
| **HR (95% CI)** | 0.83 (0.65, 1.07) | | 1.28 (0.84, 1.94) | |
| **All Cause Death** | | | | |
| **Number of Events, N (%)** | 136 (13) | 68 (13) | 73 (11) | 24 (7) |
| **HR (95% CI)** | 0.99 (0.74, 1.33) | | 1.37 (0.86, 2.17) | |
| **Stroke** | | | | |
| **Number of Events, N (%)** | 122 (11) | 72 (13) | 53 (8) | 23 (7) |
| **HR (95% CI)** | 0.84 (0.63, 1.13) | | 1.10 (0.67, 1.80) | |

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

Additional analyses were performed to explore the possible impact of imbalances of baseline characteristics on the comparison of safety events between peginesatide and darbepoetin. Analyses of demographic covariates which may have influenced the safety outcomes are shown in the tables below. The history of coronary artery disease is an independent significant covariate, i.e., a history of coronary artery disease would significantly increase the MACE events. However, there is no interaction between the history of coronary artery disease and treatment. A history of coronary artery disease does not appear to change the treatment effect on MACE endpoints.

**Table 33: MACE Outcomes by History of Coronary Artery Disease (CAD) for AFX01-12 and AFX01-14 Combined**

| | Peginesatide N (%) | Epoetin N (%) |
|---|---|---|
| **History of CAD*** | 97 (21.7%) | 45 (23.6%) |
| **No History of CAD** | 64 (10.3%) | 51 (14.5%) |

*CAD = Coronary Artery Disease

**Table 34: MACE Outcomes by History of Coronary Artery Disease (CAD) for AFX01-11 and AFX01-13 Combined**

| | Peginesatide N (%) | Darbepoetin N (%) |
|---|---|---|
| **History of CAD*** | 41 (15.5%) | 17 (13.6%) |
| **No History of CAD** | 39 (10.0%) | 13 (6.4%) |

*CAD = Coronary Artery Disease

In addition, there does not appear to be an interaction between the history of diabetes and treatment effect as is shown in the tables below.

**Table 35: MACE Outcomes by History of Diabetes for AFX01-12 and AFX01-14 Combined**

|  | Peginesatide N (%) | Epoetin-alfa/beta N (%) |
|---|---|---|
| **History of Diabetes** | 98 (18.3%) | 54 (19.6%) |
| **No History of Diabetes** | 63 (11.9%) | 42 (15.7%) |

**Table 36: MACE Outcomes by History of Diabetes for AFX01-11 and AFX01-13 Combined**

|  | Peginesatide N (%) | Darbepoetin N (%) |
|---|---|---|
| **History of Diabetes** | 58 (13.1%) | 19 (9.6%) |
| **No History of Diabetes** | 22 (10.4%) | 11 (8.5%) |

Additional analyses that evaluated for an interaction with estimated glomerular filtration rate (eGFR) with MACE outcomes for patients in the non-dialysis studies showed no interaction as shown in the tables below.

**Table 37:  MACE Outcomes by eGFR in Studies AFX01-11 and AFX01-13 Combined**

| eGFR <30 ml/min/1.73m$^2$ | Peginesatide (N=369) | Darbepoetin (N=186) |
|---|---|---|
| **Number of Events, N (%)** | 44 (12) | 17 (9) |
| **HR (95% CI)** | 0.969 (0.812, 1.157) | |
|  |  |  |
| eGFR ≥30 ml/min/1.73m$^2$ | Peginesatide (N = 251) | Darbepoetin (N=141) |
| **Number of Events, N (%)** | 36 (14) | 13 (9) |
| **HR (95% CI)** | 1.009 (0.824, 1.234) | |

## 7.4   Supportive Safety Results

### 7.4.1   Laboratory Findings

The proportion of patients with hemoglobin excursions from the time after the first dose of study drug to the end of treatment who were treated with peginesatide compared to comparator ESA is shown in the table below. There did not appear to be a trend for hemoglobin excursions between peginesatide treated patients and patients treated with epoetin alfa or beta in those patients who were on dialysis.  However, there is a possible trend for hemoglobin excursions in patients treated with peginesatide compared to patients treated with darbepoetin in patients not on dialysis.  The median number of days for hemoglobin excursions above 13 g/dL ranged from 19-22 days in the various treatment groups.

**Table 38. Hemoglobin Excursions**

|  | Pooled AFX01-12 and AFX01-14 (Dialysis) | | Pooled AFX01-11 and AFX01-13 (Non-Dialysis) | |
|---|---|---|---|---|
|  | Peginesatide (n=1066) N (%) | Epoetin-alfa/beta (n=542) N (%) | Peginesatide (n=656) N (%) | Darbepoetin (n=327) N (%) |
| **>12 g/dL** | 728 (68) | 395 (73) | 466 (71) | 221 (68) |
| **>13 g/dL** | 236 (22) | 106 (20) | 109 (17) | 35 (11) |
| **>14 g/dL** | 25 (2) | 9 (2) | 8 (1) | 2 (1) |
| **Median Days >13 g/dL** | 22 | 20 | 22 | 19 |

Hematology lab results for patients with CKD on dialysis or not on dialysis are shown in the table below. There do not appear to be significant differences between the treatment groups with respect to Leukocytosis defined as WBC > 15,000/µL or thrombocytosis defined as platelets > 600,000/µL.

**Table 39. Leukocytosis and Thrombocytosis**

|  | Chronic Kidney Disease on Dialysis | |
|---|---|---|
|  | Peginesatide (n=1066) N (%) | Epoetin (n=542) N (%) |
| **Leukocytosis > 15,000/µL** | 24 (2) | 29 (6) |
| **Thrombocytosis > 600,000/µL** | 13 (1.2) | 2 (0.38) |
|  | Chronic Kidney Disease Not On Dialysis | |
|  | Peginesatide (n=656) N (%) | Darbepoetin (n=327) N (%) |
| **Leukocytosis > 15,000/µL** | 23 (3.5) | 15 (4.7) |
| **Thrombocytosis > 600,000/µL** | 9 (1.4) | 4 (1.2) |

## 7.4.2  Vital Signs

No significant differences in vital signs were observed in patients treated with peginesatide when compared to comparator ESA for patients on dialysis or not on dialysis.

## 7.4.3  Electrocardiograms (ECGs)

In the Phase 3 studies, i.e., on dialysis and not on dialysis, SAEs of cardiac arrhythmia were adjudicated by the Event Review Committee as one of the component events of the composite safety endpoint (CSE). The incidence in the studies was similar in the peginesatide and epoetin groups. Adverse events of ventricular arrhythmias were similar (<1%) in each treatment group in

each of the Phase 3 studies. No instances of Torsades de Pointes were observed with peginesatide.

## 7.4.4  Immunogenicity

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

## 7.5   Other Safety Explorations

Seizures have been reported as an event of concern with currently approved ESAs in anemic subjects during the initial treatment period. Although there is no direct evidence of a causal relationship between onset of seizures and ESA therapy, this remains an event of concern and is highlighted in the labeling of marketed ESAs.  Analysis of seizure events is shown in the table below.

In studies AFX01-12 and AFX01-14, i.e., the dialysis studies, the incidence of seizures was 2% in patients treated with peginesatide and 2% in patients treated with epoetin.  However, confounding factors for seizure analysis were also reported with these patients, e.g., cerebrovascular accident (CVA), fluid overload, hypertension and concomitant medication were reported as contributory to the events. Additionally, the onset day for a majority of these patients with seizures was reported at >90 days after the first dose in both treatment groups.  The incidence of seizures was similar between the treatment groups (1% in the peginesatide treatment group and <1% in the darbepoetin treatment group) in studies AFX01-11 and AFX01-13. Similar to the patients on dialysis confounding factors were reported, e.g., CVA, hypoglycemia, and hypertension.  The onset day for the majority of these subjects was reported at >90 days after first dose in both treatment groups.

**Table 40.  Seizure Events**

| | Studies AFX01-12 and AFX01-14 | | Studies AFX01-11 and AFX01-13 | |
|---|---|---|---|---|
| | **Peginesatide (N=1066) N (%)** | **Epoetin (N=542) N (%)** | **Peginesatide (N=656) N (%)** | **Darbepoetin (N=327) N (%)** |
| **Number of Events** | 23(2) | 11(2) | 8 (1) | 1(<1) |

## 7.6 Additional Safety Explorations

### 7.6.1 Human Carcinogenicity

The recurrence of cancer or tumor progression in patients with pre-existing cancer and anemia treated with ESAs has been identified as a safety concern for the ESA class of drugs. The table below shows the proportion of patients with malignancy at baseline and those that had malignancy as an adverse event during the study.  Overall, the proportion of patients with malignancy at baseline was similar in the pooled on dialysis studies but there was a slight numeric imbalance in the number of patients with malignancy at baseline in the non-dialysis studies, i.e., 16% in the peginesatide group and 12% in the darbepoetin group.  However, malignancy was reported as an adverse event in similar proportions of patients treated with peginesatide or epoetin or darbepoetin either in those who were on dialysis or not on dialysis.

**Table 41.  Proportion of Patients with Malignancy**

|  | Pooled AFX01-12 and AFX01-14 (Dialysis)* | | Pooled AFX01-11 and AFX01-13 (Non-Dialysis)** | |
|---|---|---|---|---|
|  | Peginesatide (n=1066), N (%) | Epoetin (n=542) N (%) | Peginesatide (n=656) N (%) | Darbepoetin (n=327) N (%) |
| **History of Baseline Malignancy** | 131 (12) | 61 (11) | 102 (16) | 40 (12) |
| **Malignancy Adverse Event** | 42 (4) | 23 (4) | 31 (5) | 14 (4) |

*Duration of Exposure (mean Patient Exposure Years/patient): Peginesatide 1.16; Epoetin 1.20
**Duration of Exposure (mean Patient Exposure Years/patient): Peginesatide 1.29; Darbepoetin 1.33

### 7.6.2 Pediatrics and Effect on Growth

The sponsor has not evaluated peginesatide treatment in pediatric patients.  The sponsor requests a waiver for the study of peginesatide in pediatric patients < 12 months of age due to low prevalence of anemia secondary to CKD in this age group who are on dialysis and not undergoing kidney transplantation.  Also the sponsor states that significant blood volume constraints exist in this age group with this condition, i.e., anemia with CKD.

The sponsor requests a deferral for studies in pediatric patients (age ≥ 12 months to < 18 years) with CRF on dialysis.  A proposed pediatric plan was submitted on October 21, 2010.  The sponsor proposes to conduct the following studies:

- Study 1: Phase 2 open-label study to evaluate the safety, efficacy, and pharmacokinetics of AF37702 Injection for maintenance treatment of anemia in pediatric subjects with

chronic kidney disease (CKD) on hemodialysis and already receiving ESA therapy. Proposed report submission 2016.

- Study 2: Phase 2 open-label follow-up study to evaluate the safety, tolerability and efficacy of AF37702 Injection for the maintenance treatment of anemia in pediatric subjects with CKD on hemodialysis. Proposed report submission 2017.

- Study 3: Phase 3 randomized, active-controlled, open-label, multicenter study to evaluate the efficacy and safety of AF37702 Injection for the maintenance treatment of anemia in pediatric subjects with CKD on dialysis. Proposed report submission 2025.

- Study 4: Phase 3 open-label follow-up extension study to evaluate the safety, tolerability and efficacy of AF37702 Injection for the maintenance treatment of anemia in pediatric subjects with CKD on dialysis. Proposed report submission 2026.

## 7.6.3  Overdose and Drug Abuse Potential

The potential for drug overdose is similar to that of other marketed ESAs.  The potential for drug abuse is similar to that of the other marketed ESAs.

## 7.7  Additional Submissions

In submission NDA 202799/0008 submission 9 letter date September 23, 2011 the sponsor submitted the 120 Day Safety Update Report.  No new adverse events or new patients were reported.  An update for study AFX01-06 was included in the 120 Day Safety Update Report.

In addition, in the 120 day Safety Update the sponsor stated that study AFX01-06 is ongoing. This is an open label, single arm, Phase 2 study of peginesatide for the treatment of anemia in patients with CKD who have anti-erythropoietin (EPO) antibody-mediated pure red cell aplasia (PRCA).  There are 19 patients enrolled in this study.  In the ongoing study no new safety signals were identified in the data collected between the cut-off date for the Interim Clinical Study Report (30 April 2010) and the cut-off date for the 120 Safety Update Report, i.e., March 4, 2011.

The sponsor reports that in study AFX01-06 Subject 06-14-32 was a Caucasian male on hemodialysis with a history of hypertension, gastritis, and duodenitis who interrupted study treatment (after Dose 9) to undergo kidney transplant surgery. Approximately 3 months after the transplant, AF37702 Injection was restarted; the subject continued receiving a regimen of immunosuppressants to maintain the transplanted graft. Approximately 4½ years after starting treatment with peginesatide, the subject was diagnosed with colon cancer metastatic. He died at age 64, approximately 1 month after the diagnosis. This AE of colon cancer metastatic was the first reported event in this study.  The event was considered by the investigator as possibly/probably related to study treatment.

The sponsor also reports that in Study AFX01-06 Subject 06-14-35 was a Caucasian male on hemodialysis with a history of atrial flutter, hypertension, and stroke (with full recovery). During the study, he experienced AEs of atrial fibrillation, myocardial ischemia, and left ventricular failure. He died at age 90 due to cardiac failure. The subject received approximately 16 months of treatment with peginesatide. This event was not considered possibly/probably related to study treatment by the investigator.

In study AFX01-06 Subject 06-39-5 was a Caucasian male on hemodialysis who died at home at age 95 (verbatim term: death due to high age). He received approximately 4 years of study treatment. This event was not considered possibly/probably related to study treatment by the investigator.

Additional information on one subject described in the AFX01-06 Interim Clinical Study Report is provided. A fatal TESAE of urinary tract infection in Subject 06-14-33 occurred shortly after the 30 April 2010 database cut-off date (subject died on           (b) (6)

The sponsor reported in the 120 Day Safety Report that there was one previously unreported SAE in a subject receiving the comparator agent at a Phase 3 study site (AFX01-14, the primary investigator was Dr Oguagha). The sponsor reports that Subject 14-1017-250 was a 68-year-old Black female assigned to the Epoetin treatment group of Study AFX01-14. The subject's medical history included end stage renal disease on hemodialysis, diabetic retinopathy, peripheral neuropathy, secondary hyperparathyroidism, peripheral arterial disease, hyperphosphatemia, and insomnia. The subject was admitted to the hospital for chest pain approximately 1 year after starting study treatment. At the time of the SAE, the subject was receiving Epoetin alfa 3300 units three times per week (TIW). The chest pain was Grade 2 severity and considered not related to study treatment. Myocardial infarction was ruled out and the subject was discharged from the hospital hemodynamically stable 1 day later. The SAE was considered resolved without sequelae.

*Reviewer comment for section 7: Studies AFX01-12 and AFX01-14 were designed to evaluate the safety and efficacy of peginesatide treatment compared to epoetin treatment in patients with anemia due to CKD who were on dialysis. Studies AFX01-11 and AFX01-13 were designed to evaluate the safety and efficacy of peginesatide treatment compared to darbepoetin treatment in patients with anemia due to CKD who were not on dialysis. In patients on dialysis or not on dialysis, the analyses of these studies showed that peginesatide is non-inferior to epoetin or to darbepoetin, respectively, in its ability to maintain Hgb levels in the protocol target range of 10-12g/dL. Also, in patients with CKD who are on dialysis, peginesatide appeared to show similar safety results when compared to epoetin by both CSE and MACE outcomes.*

*However, in patients with CKD not on dialysis (trials AFX01-11 and AFX01-13), there is an imbalance in safety outcomes that was significantly different by the sponsor's planned analysis of CSE (HR 1.32 (90% CI = 1.02, 1.72), favoring darbepoetin. When assessed by MACE outcomes and with a 95% confidence interval, the difference, was still numerically unfavorable to peginesatide, but was not significantly different in these two trials. There were baseline imbalances unfavorable to peginesatide in the proportion of patients with diabetes, peripheral*

*vascular disease, and coronary heart disease. Exploratory analyses of the imbalances do not identify a treatment interaction.*

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

*The 120 Day Safety Update is consistent with information on the safety profile of peginesatide submitted in the NDA.* (b) (4)

*Longer term evaluation of immunogenicity in this patient population, and, generally in patients with anemia associated with CKD who are undergoing treatment with peginesatide is needed.*

*Globally, the prevalence of chronic kidney disease (CKD) stage II or lower in children is reported to be approximately 18.5-58.3 per million children. Disease prevalence is much lower than that in adults. The author states that a mean incidence of 12.1 cases per year per million in the age-related population (age range, 8.8-13.9 years) and a prevalence of 74.7 per million in this population. The author also states that the frequency of chronic kidney disease increases with age. Among children, chronic kidney disease is more common in children older than 6 years than in those younger than 6 years.[10] A waiver for the study of peginesatide in pediatric patients < 12 months of age due to low prevalence of anemia secondary to CKD in this age group who are on dialysis and not undergoing kidney transplantation should be given. A deferral for studies in pediatric patients (age ≥ 12 months to < 18 years) with CRF on dialysis should also be given.*

# 8   Postmarketing Experience

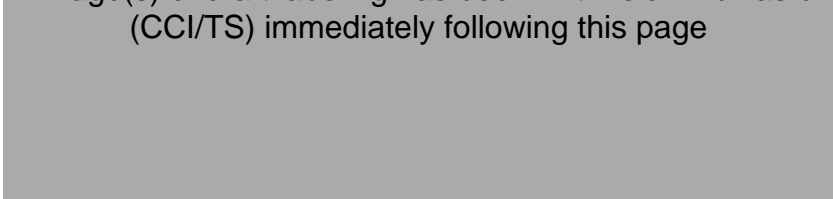Not applicable. Peginesatide is not currently marketed anywhere in the world.

# 9   Appendices

## 9.1   Literature Review

Peginesatide administration for the treatment of CRF has been discussed in the literature as a potentially promising drug.[11] In addition, the sponsor has a "Peginesatide Overview" as part of their website (see: http://www.affymax.com/view.cfm/23/Peginesatide--Overview, last accessed September 11, 2011).

## 9.2    Labeling Recommendations

Labeling recommendations are shown below.  Reviewer recommended deletions are shown as strikethrough and additions are underlined.  Further labeling recommendations may be added later based on the upcoming FDA Regulatory Briefing which is scheduled for January 13, 2012.

17 Page(s) of draft labeling has been Withheld in full as b4
(CCI/TS) immediately following this page

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## 9.3   Advisory Committee Meeting

An Oncology Drug Advisory Committee (ODAC) meeting was held on December 7, 2011.  In the application safety concerns were noted in the non-dialysis population. The safety of peginesatide appeared to be statistically inferior to darbepoetin using CSE outcomes. Also, MACE outcomes were numerically worse for peginesatide compared to darbepoetin in the nondialysis population.  The ODAC was asked to discuss the implications that these observed safety findings in the non-dialysis trials might have in formulating a benefit to risk evaluation in the dialysis population.  The majority of the Committee agreed that the observed safety findings in the non-dialysis trials have no implications on their formulation of a benefit to risk evaluation in the dialysis population. Some members indicated that the efficacy and safety profiles in the dialysis population were established in the two large randomized trials, and there is evidence that peginesatide offers an advantage in terms of monthly dosing. Other members voiced concern as to why the safety of peginesatide appears to be inferior to darbepoetin in the non-dialysis population and question how peginesatide, if approved, can be restricted in a way that prevents the use of this drug product in patients not on dialysis.  The Committee was asked to vote on the following question:

- 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? *Yes, No, or Abstain.*

There were 15 Yes votes and 1 No vote with 1 abstention.

The majority of the committee agreed that the benefit: risk evaluation is favorable for peginesatide for use in patients with anemia associated with chronic renal failure who are on dialysis. The members who voted "Yes" noted that the trials in the dialysis population were consistent in both efficacy and safety. Those who voted "No" or "Abstained" were concerned with the trial design as the studies conducted were unblinded and the inclusion criteria was too narrow to detect a safety signal. Some members noted their concerns for the potential misuse of peginesatide in non-dialysis patients because of the favorable benefit: risk profile in dialysis patients.

## 9.4   Regulatory Briefing

A Regulatory Briefing was held on January 13, 2012.  The safety and efficacy of peginesatide was discussed.  The committee agreed that the benefit: risk evaluation is favorable for peginesatide for use in patients with anemia associated with chronic renal failure who are on dialysis.  However, the committee stated that the safety of peginesatide in the not on dialysis group was of concern.

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## 9.5   List of Abbreviations

| Abbreviation or Term | Definition/Explanation |
| --- | --- |
| AE | adverse event |
| ALT | alanine transaminase |
| ANOVA | analysis of variance |
| AST | aspartate aminotransaminase |
| BUN | blood urea nitrogen |
| CAD | coronary artery disease |
| CBC | complete blood count |
| CFR | US Code of Federal Regulations |
| CHF | congestive heart failure |
| CHOIR | Correction of Hemoglobin and Outcomes in Renal Insufficiency (trial) |
| CI | confidence interval |
| CMH | Cochran-Mantel-Haenszel |
| CREATE | Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (trial) |
| CRF | chronic renal failure |
| CRO | contract research organization |
| CSE | composite safety endpoint |
| CVD | cerebrovascular disease |
| dL | Deciliter |
| DMC | Data Monitoring Committee |
| DVT | deep vein thrombosis |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EPO | endogenous erythropoietin |
| ERC | Event Review Committee |
| ELISA | enzyme-linked immunosorbent assay |
| ESA | Erythropoiesis stimulating agent |
| EU | European Union |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |

| | |
|---|---|
| GLP | Good Laboratory Practice |
| Hct | hematocrit |
| HF | heart failure |
| Hgb | Hemoglobin |
| HLA | human leukocyte antigen |
| HR | hazard ratio |
| hsCRP | high-sensitivity C-reactive protein |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IRB | institutional review board |
| IV | intravenous(ly) |
| IVRS | interactive voice response system |
| KDOQI | Kidney Disease Outcomes Quality Initiative |
| Kt/V | urea clearance/volume |
| LDH | lactate dehydrogenase |
| LS | least square |
| LTSE | long term safety and efficacy |
| LUC | large unstained cell |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial infarction |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NYHA | New York Heart Association |
| PD | pharmacodynamic(s) |
| PE | pulmonary embolism |
| PEY | patient exposure years |
| PFY | patient follow up years |
| PK | pharmacokinetic(s) |
| PRCA | pure red cell aplasia |
| PT | preferred term |

| PVD | peripheral vascular disease |
| --- | --- |
| Q12W | every 12 weeks |
| Q2W | every 2 weeks |
| Q24W | every 24 weeks |
| Q4W | every 4 weeks |
| RBC | red blood cell |
| RRR | relative response ratio |
| SAE | serious adverse event |
| SC | Subcutaneous(ly) |
| SD | standard deviation |
| SMQ | standardized MedDRA query |
| SOC | system organ class |
| TEAE | Treatment-emergent adverse event |
| TESAE | Treatment-emergent serious adverse event |
| TIA | transient ischemic attack |
| TdP | Torsade de Pointes |
| TSAT | transferrin saturation |
| USP/NF | United States Pharmacopoeia – National Formulary |
| WHO-DRL | World Health Organization (WHO)-Drug Reference List (i.e., WHO Drug Dictionary) |

## 9.6   References:

[1] Mircera website.  http://www mircera.com/portal/mircera/prescribing_information.   Last accessed January 13, 2012.

[2] Besarab, A. et al.: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. 1998. NEJM. 339(9): 584-590.

[3] Drueke, T.B. et al.: Normalization of hemoglobin level in patients with chronic kidney disease and anemia.  2006. NEJM. 355(20): 2071- 2084.

[4] Singh, A. K. et al.: Correction of anemia with epoetin alfa in chronic kidney disease.  2006.  NEJM.  355(20): 2085- 2098.

[5] Pfeffer, M.A. et al.:  A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease.  2009.  NEJM. 361(21):2019-2032.

[6] Bacchus, S. et al.: Meeting new challenges in the management of anemia of chronic kidney disease through collaborative care with pharmacists.  2009.  Ann. Pharmacother.  43(11): 1857-1866.

[7] McKoy, J.M. et al.:  Epoetin associated pure red cell aplasia: past, present and future considerations.  2008. Transfusion.  48(8): 1754-1762.

[8] Matas, A.J. and Delmonico, F.L.:  Discard fewer kidneys. 2001.  Am. J. Transplant.  1:301-304.

[9] International Conference on Harmonisation website.
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf. Last accessed January 13, 2012.

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[10] Sanjeev. G.  Chronic kidney disease in children.  Medscape website.
http://emedicine.medscape.com/article/984358-overview#a0156. Last accessed January 13, 2012.
[11] Doss, S. and Schiller, B.: Peginesatide a potential erythropoiesis stimulating agent for the treatment of anemia of chronic renal failure.  2010. Nephrol. Nurs. J. 37(6):617-626.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 202799**  **Applicant: Affymax**  **Stamp Date: May 27, 2011**

**Drug Name: Peginesatide injection**  **NDA Type: Standard**

On initial overview of the NDA application for filing:

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | **FORMAT/ORGANIZATION/LEGIBILITY** | | | | |
| 1. | Identify the general format that has been used for this application, e.g. electronic CTD. | x | | | Electronic |
| 2. | On its face, is the clinical section organized in a manner to allow substantive review to begin? | x | | | |
| 3. | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin? | x | | | |
| 4. | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)? | x | | | |
| 5. | Are all documents submitted in English or are English translations provided when necessary? | x | | | |
| 6. | Is the clinical section legible so that substantive review can begin? | x | | | |
| | **LABELING** | | | | |
| 7. | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies? | x | | | |
| | **SUMMARIES** | | | | |
| 8. | Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)? | x | | | |
| 9. | Has the applicant submitted the integrated summary of safety (ISS)? | x | | | See section 2.7.4 Summary of Clinical Safety |
| 10. | Has the applicant submitted the integrated summary of efficacy (ISE)? | x | | | See section 2.7.3 Summary of Clinical Efficacy |
| 11. | Has the applicant submitted a benefit-risk analysis for the product? | x | | | See section 2.5.6 Risks and Benefits Conclusions |
| 12. | Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug? | x | | | 505(b)(1) |
| | **DOSE** | | | | |
| 13. | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: AFX01-03       Study Title: A Phase 2, Open Label, Multi-center, Sequential Dose Finding Study of the Safety, Pharmacodynamics and Pharmacokinetics of AF37702 Injection (Hematide) Administered Intravenously for the Maintenance Treatment of Anemia in Chronic Hemodialysis Patients    Sample Size: 165    Arms: 11 treatment cohorts | x | | | Dosing also supported in pivotal studies Phase 3studies AFX01-12, AFX01-14 and Phase 2 AFX01-15. |

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

1

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | Location in submission: 5.3.4.2<br>Study Number: AFX01-07<br>    Study Title: A Phase 2, Open Label, Multi-center, Dose Finding Study of the Safety, Pharmacodynamics, and Pharmacokinetics of AF37702 Injection (Hematide) for the Maintenance Treatment of Anemia in Hemodialysis Patients Previously Treated with Epoetin<br>    Sample Size: 91                Arms: 5<br>Location in submission: 5.3.4.2 | | | | |
| **EFFICACY** | | | | | |
| 14. | Do there appear to be the requisite number of adequate and well-controlled studies in the application?<br><br>Pivotal Study #1 AFX01-12<br>                       Indication: Treatment of Anemia in Patients with Chronic Renal Failure.<br>This study was a phase 3, randomized, active control, open label, multi-center study comparing peginesatide to epoetin in patients with chronic kidney disease on dialysis to maintain a target hemoglobin level between ≥ 10-≤12g/dL. In this study 524 patients were treated with peginesatide and 268 were treated with epoetin.<br><br>Pivotal Study #2 AFX01-14<br>                       Indication:  Treatment of Anemia in Patients with Chronic Renal Failure.<br>This study was a phase 3, randomized, active control, open label, multi-center study comparing peginesatide to epoetin in patients with chronic kidney disease on dialysis to maintain a target hemoglobin level between ≥ 10-≤12g/dL. In this study 542 patients were treated with peginesatide and 273 were treated with epoetin. | x | | | Patients in AFX01-12 and AFX01-14 had chronic renal failure were on dialysis and were previously treated with ESA.<br><br>Additional support provided by Phase 2 AFX01-15 (see also response for question 17). |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | x | | | No SPA. |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements?  Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | x | | | |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | x | | | AFX01-15 was conducted in Russia comparing AF37702 compared to EPO for anemia in dialysis patients not on ESA treatment.  The study is applicable due to lack of ESA naïve |

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | | | | | dialysis patients in USA and EU since dialysis and ESA initiated concurrently in USA and EU as per practice of medicine. |
| **SAFETY** | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | x | | | |
| 19. | Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)? | x | | | See section 5.3.4.1 study report for study AFX01_101 (QT study in healthy adults) |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | x | | | Information put into context of TREAT and CHOIR studies and KDOQI recommendations. |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious? | | | | 1519 total Phase 2 and 3 dialysis patients received at least 1 dose of AF37702. 1066 patients in Phase 3 studies received AF37702 for average patient exposure years per patient of 1.16 and average patient follow-up years per patient of 1.24. |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | x | | | |
| 23. | Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms? | x | | | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | x | | | Peginesatide potentially increases the risk of adverse events including: death, myocardial infarction, stroke, thrombosis, congestive heart failure, unstable |

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[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | | | | | angina and arrhythmia. |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | | x | | The sponsor should supply a narrative summary for each patient that had a composite safety endpoint event, serious adverse event or dropped out. |
| **OTHER STUDIES** | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | x | None requested. |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)? | | | x | |
| **PEDIATRIC USE** | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | x | | | Waiver requested for study in pediatric patients < 12months of age due to low prevalence in this age group of anemia secondary to CKD who are on dialysis and not undergoing kidney transplantation and significant blood volume constraints in this age group with this condition, i.e., anemia with CKD.<br><br>Deferral is requested for studies in pediatric patients (age <18) with CRF on dialysis. A proposed pediatric plan was submitted on October 21, 2010. Study 1: Phase 2 open-label study to evaluate the safety, efficacy, and pharmacokinetics of AF37702 Injection for maintenance treatment of anemia in pediatric subjects with chronic kidney disease (CKD) on hemodialysis and already receiving ESA therapy. Proposed report submission |

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | | | | | 2016. Study 2: Phase 2 open-label follow-up study to evaluate the safety, tolerability and efficacy of AF37702 Injection for the maintenance treatment of anemia in pediatric subjects with CKD on hemodialysis. Proposed report submission 2017. Study 3: Phase 3 randomized, active-controlled, open-label, multicenter study to evaluate the efficacy and safety of AF37702 Injection for the maintenance treatment of anemia in pediatric subjects with CKD on dialysis. Proposed report submission 2025. Study 4: Phase 3 open-label follow-up extension study to evaluate the safety, tolerability and efficacy of AF37702 Injection for the maintenance treatment of anemia in pediatric subjects with CKD on dialysis. Proposed report submission 2026. |
| **ABUSE LIABILITY** | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | x | |
| **FOREIGN STUDIES** | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | x | | | See comment for question 17. |
| **DATASETS** | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | x | | | Also see Statistics. |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | x | | | Also see Statistics. |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | x | | | Also see Statistics. |
| 34. | Are all datasets to support the critical safety analyses | x | | | Also see Statistics. |

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|---|
| | | available and complete? | | | | |
| 35. | | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | x | | | Also see Statistics. |
| **CASE REPORT FORMS** | | | | | | |
| 36. | | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | x | | | |
| 37. | | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | x | | | |
| **FINANCIAL DISCLOSURE** | | | | | | |
| 38. | | Has the applicant submitted the required Financial Disclosure information? | x | | | (b) (6) studies AFX01-13 (b)(6) subjects) and AFX01-14 (b) (6) received payments = $41,000; (b) (6) (b) (6) study AFX01-14 ((b)(6) subjects) received payments = $54,000 |
| **GOOD CLINICAL PRACTICE** | | | | | | |
| 39. | | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | x | | | |

## IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

The sponsor should supply a narrative summary for each patient that had a composite safety endpoint event for studies AFX01-12, AFX01-14.

Results of studies AFX01-11 and AFX01-13 in non-dialysis CRF patients suggest that safety of peginesatide relative to darbepoetin may be worse. Any implication these findings might have for the hemodialysis population will be a review issue.

                            July 22, 2011

_____      Date

Andrew Dmytrijuk, M.D.
Reviewing Medical Officer

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Kathy Robie-Suh, M.D.,Ph.D.    July 22, 2011
Clinical Team Leader