2.0 SYNOPSIS

Name of the Sponsor: Affymax, Inc.	**Individual Study Table Referring to Part of the Dossier:**	**For National Authority Use Only**
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Title of Study:

A Phase 2, Open-label, Multi-center, Sequential Dose Finding Study of the Safety, Pharmacodynamics, and Pharmacokinetics of Multiple Doses of AF37702 Injection (Hematide™) in Chronic Kidney Disease Patients Not on Dialysis and Not on Erythropoiesis Stimulating Agent (ESA) Treatment

Investigators and Study Centers:

Patients were enrolled at six sites in the United Kingdom and seven sites in Poland.

Publications: (Publications Based on the Study)

Macdougall IC, Leong R, Wiecek A, Duliege A, Lang W, Iwashita J, et al. Use of Hematide™, a Novel Synthetic Peptide-Based Erythropoiesis Stimulating Agent, in the Management of Hemoglobin (Hb) in Non-Dialysis and Hemodialysis Chronic Kidney Disease (CKD) Patients. Oral presentation World Congress of Nephrology Conference 2007; Rio De Janeiro, Brazil. Abstract published in World Congress of Nephrology 2007 Book of Abstracts, Section 6.5, Abstract M-FC-045. p. 212.

Macdougall IC, Wiecek A, Leong R, Duliege AM, Lang W, Iwashita J, et al. Management of Anaemia in Chronic Kidney Disease with Hematide™, a Novel Synthetic Peptide-Based Erythropoiesis Stimulating Agent. Poster presentation XLIV Congress of the European Renal Association European Dialysis and Transplant Association (ERA-EDTA) 2007; Barcelona, Spain. Abstract published in Nephrology Dialysis Transplantation, July 2007, Volume 22, Supplement 6, Abstract SaP334. p. vi345.

Macdougall IC, Tucker B, Yaqoob M, Mikhail A, Nowicki M, MacPhee I, et al. Hematide™, a Synthetic Peptide-Based Erythropoiesis Stimulating Agent (ESA), Achieves Correction of Anemia and Maintains Hemoglobin (Hb) in Patients with Chronic Kidney Disease (CKD) Not on Dialysis. Oral presentation American Society of Nephrology Annual Meeting 2006; San Diego, California. Abstract published in J Am Soc Nephrol, 2006 Abstracts Issue, Volume 17, Abstract F-FC079. p. 53A.

Macdougall IC, Wiecek A, Mikhail A, Tucker B, MacPhee I, Yaqoob M, et al. Hematide™, a Synthetic Peptide-Based Erythropoiesis Stimulating Agent (ESA), Achieves Correction of Anaemia in Patients with Chronic Kidney Disease (CKD). Poster presentation 7th International Lübeck Conference on the Pathophysiology and Pharmacology of Erythropoietin and other Hemopoietic Growth Factors 2006; Lübeck, Germany. Abstract published in Ann Hematol. 2006; 85:649 Abstract 23.

Macdougall IC, Wiecek A, Mikhail A, Tucker B, Yaqoob M, Nowicki M, et al. Hematide™, a Synthetic Peptide-Based Erythropoiesis Stimulating Agent, Achieves Correction of Anaemia in Patients with Chronic Kidney Disease. Oral presentation XLIII Congress of the European Renal Association European Dialysis and Transplant Association (ERA-EDTA) 2006; Glasgow, United Kingdom. Abstract published in Nephrology Dialysis Transplantation, July 2006, Volume 21, Supplement 4, Abstract SO021. p. iv10.

Wiecek A, Macdougall IC, Mikhail A, Tucker B, Yaqoob M, Nowicki M, et al. Long-Term Safety, Tolerability, and Pharmacodynamics of Hematide™, a Synthetic Peptide-Based Erythropoiesis Stimulating Agent in a Phase II, Multi-Dose Study in Patients with Chronic Kidney Disease. Poster presentation XLIII Congress of the European Renal Association European Dialysis and Transplant Association (ERA-EDTA) 2006; Glasgow, United Kingdom. Abstract published in Nephrology Dialysis Transplantation, July 2006, Volume 21, Supplement 4, Abstract SP419. p. iv155.

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Publications (Cont'd):

Wiecek A, Tucker B, Nowicki M, Yaqoob M, Mysliwiec M, Leong R, et al. Comparison of Monthly Dosing Schemes Using Hematide™, a Synthetic Peptide-Based Erythropoiesis Stimulating Agent (ESA), to Correct Anemia in Patients with Chronic Kidney Disease (CKD) Not on Dialysis. Poster presentation American Society of Nephrology Annual Meeting 2007; San Francisco, California. Abstract published in J Am Soc Nephrol, October 2007 Abstracts Issue, Volume 18, Abstract SU-PO777 p. 756A.

Macdougall I, Tucker B, Nowicki M, Yaqoob M, Mysliwiec M, Wiecek A, et al. Doses of Hematide™ to Increase and Maintain Haemoglobin in Non-Dialysis Patients Are Similar Regardless of Baseline Renal Function. Poster presentation World Congress of Nephrology Conference; 2009; Milan, Italy. Abstract available on WCN web site http://www.abstracts2view.com/wcn/view.php?nu=WCN09L_3120&terms=.

Study Period: 19 September 2005 (first patient dosed) to 8 November 2007 (last patient visit)	**Development Phase:** Phase 2

Objectives:

The primary objective of this study was to determine the range of doses of AF37702 Injection administered subcutaneously (SC) every 4 weeks (Q4W) that increased and maintained hemoglobin (Hgb) at 11 to 13 g/dL in patients with chronic renal failure (CRF) not on dialysis.

Secondary objectives were to evaluate the following in patients not on dialysis: (1) safety profile, and pharmacokinetic (PK) profiles in a subset of patients of up to six doses of AF37702 Injection administered SC Q4W, (2) safety and pharmacodynamic (PD) profiles, and PK profiles in a subset of patients, of up to six doses of AF37702 Injection administered intravenously (IV) Q4W, and (3) safety and PD profiles, and PK profiles in a subset of patients, of up to 12 doses of AF37702 Injection administered every 2 weeks (Q2W).

Methodology:

This was a Phase 2, open-label, multi-center, sequential dose finding trial designed to evaluate 2 to 12 treatment cohorts of up to 15 patients per cohort. Two dose level cohorts were initially planned to be sequentially enrolled. Depending on the observed safety profile and pharmacological response, up to 10 additional cohorts could be added to study additional and/or repeat dose levels as determined by the independent safety monitor (ISM) and Sponsor. Of the additional cohorts, the IV route of administration could be studied in one to two cohorts at dose level(s) studied in previous SC cohort(s). A Q2W dosing schedule by SC administration (with up to 12 doses) could be studied in one to two additional cohorts. PK could also be studied in an optional repeat dose cohort of 7 to 15 patients for whom PK evaluations were mandatory. Fixed dosing using SC administrations could also be studied in optional additional cohort(s). Individual patient dose adjustments were allowed starting at Week 5 (after one dose on the Q4W schedule and after two doses on the Q2W schedule) according to protocol-specified criteria. The first cohort was to receive a SC dose of AF37702 Injection Q4W for a total of six doses at a starting dose of 0.05 mg/kg. The Independent Safety Monitor (ISM) and Sponsor were to review the clinical and laboratory data on an ongoing

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Methodology (Cont'd):

basis to determine when dose escalation, de-escalation, additional cohort, or stopping criteria, as defined in the protocol, had been met.

After the first dose (Week 1), patients were to be seen at least weekly through Week 13, and every other week thereafter. During the study, iron status was to be maintained per European Best Practice Guidelines as appropriate. Patients were to be followed until the latest occurrence of the following criteria: (1) 28 days after the last administration of study drug, or (2) stabilization of adverse events (AEs), or (3) Hgb <13 g/dL. If, however, a patient enrolled into a separate long-term extension study of AF37702 Injection within 4 weeks from the last dose in this study, the patient was to be terminated from this study and followed under the extension study.

Number of Patients Planned and Analyzed:

Two to twelve treatment cohorts of up to 15 patients per cohort were planned; a minimum of 30 and a maximum of 180 patients. A total of 139 patients were enrolled; 139 patients were included in the safety analyses, 139 patients were included in the mITT population analyses, 137 patients were included in the PD population analyses, and 53 patients were included in the PK population analyses.

Number of Patients Enrolled: A total of 139 patients among ten dose cohorts were enrolled; 15 patients in each of nine dose cohorts, and 4 patients in one dose cohort.

Diagnosis and Main Criteria for Eligibility:

Eligible patients were males or females ≥18 and ≤85 years of age with chronic kidney disease (CKD) stage 3 or 4 (estimated glomerular filtration rate of ≤60 mL/min within 28 days prior to study drug administration) and not expected to begin dialysis for at least 12 weeks who provided written informed consent, and, within 4 weeks prior to study drug administration had: two Hgb values ≥9.0 and <11.0 g/dL (including at least one of the values within 7 days prior to dosing), one serum ferritin level ≥100 µg/L and transferrin saturation ≥20%, one serum or red cell folate level above the lower limit of normal, one vitamin B_{12} level above the lower limit of normal, weight ≥45 kg, one white blood cell count ≥3.0 x 10^9/L, and one platelet count ≥100 x 10^9/L.

Test Product, Dose and Mode of Administration, Lot Number:

AF37702 Injection was supplied as a preservative-free aseptically manufactured, sterile parenteral solution provided in a 2 mL, single-use, clear glass vial. Each vial contained 1 mL of solution at a concentration of 10 mg/mL of AF37702 in an isotonic phosphate buffered solution at pH 6.0 (±0.5). The formulation included the following USP/NF compendial excipients: sodium phosphate dibasic, sodium phosphate monobasic, polysorbate 20, sorbitol, sodium hydroxide, and Water for Injection.

Doses of AF37702 Injection were to be administered SC or IV Q4W for a total of 6 doses or SC Q2W for a total of 12 doses (6-month duration). For the IV route of administration, the dose was to be given as a rapid IV bolus injection.

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Test Product, Dose and Mode of Administration, Lot Number (Cont'd):

Ten dose cohorts were evaluated in this study. Five dose cohorts evaluated a weight-based Q4W SC regimen; Cohorts 1, 2, and 8 evaluated a starting dose of 0.05 mg/kg, Cohort 3 evaluated a starting dose of 0.075 mg/kg, and Cohort 4 evaluated a starting dose of 0.025 mg/kg. Two dose cohorts evaluated a weight-based Q2W SC regimen; Cohort 6 evaluated a starting dose of 0.025 mg/kg and Cohort 7 evaluated a starting dose of 0.0375 mg/kg. Two dose cohorts evaluated a fixed dose Q4W SC regimen; Cohort 9 evaluated a starting dose of 4.0 mg and Cohort 10 evaluated a starting dose of 3.0 mg. One dose cohort evaluated an IV Q4W dosing regimen; Cohort 5 evaluated a starting dose of 0.05 mg/kg.

Lot numbers of AF37702 Injection used in this trial were PLI005-05, PLI006-06, and PLI040-06.

The majority of Q4W cohort patients (101/120, 84.2%) received all six planned doses during the study; mean dose decreased during the course of the study from 0.049 mg/kg for Dose 1 to 0.034 mg/kg for Dose 6. The majority of Q2W cohort patients (17/19, 89.5%) received all twelve planned doses during the study; mean dose decreased during the course of the study from 0.028 mg/kg for Dose 1 to 0.009 mg/kg for Dose 12.

Duration of Treatment:

Doses of AF37702 Injection were to be administered SC or IV Q4W for a total of 6 doses, or SC Q2W for a total of 12 doses (6-month duration).

Reference Therapy, Dose and Mode of Administration, Lot Number:

Not applicable.

Criteria for Evaluation:

Pharmacodynamics: PD were assessed by evaluation of Hgb, reticulocytes, red blood cell (RBC) count, hematocrit (Hct), content of Hgb in reticulocytes (CHr), ferritin, transferrin saturation, and soluble transferrin receptor protein.

Pharmacokinetics: The PK of AF37702 following administration of AF37702 Injection were determined from the plasma concentration-time data.

Safety: Safety was assessed through AEs, laboratory evaluations, vital signs, antibody evaluations, electrocardiograms, transfusions, phlebotomies, and physical findings.

Statistical Methods:

Summary statistics and statistical evaluations were presented for all patients and consisted of numbers and percentages of responses in each category for discrete measures, and the number of observations (n), means, medians, standard deviations, and minimum and maximum values for continuous measures. Summary statistics were presented for each dose cohort. Individual patient listings of all data reported on the case report form were prepared.

PK parameters were calculated by non-compartmental modeling using WinNonlin® Pro Version 5.1 and included area under the plasma concentration-time curve (AUC), maximum observed plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and apparent terminal half-life ($T_{1/2}\lambda_z$). Due to the variability of AF37702

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Statistical Methods (Cont'd):

Injection dose within each cohort (protocol-specified individual patient dose adjustments), concentrations of AF37702 in plasma were summarized by nominal dose and by nominal time in order to provide meaningful PK comparison between nominal dose levels.

Summary and Conclusions:

Pharmacodynamic Results, mITT population (N=139)

- Target Hgb responses (Hgb ≥11.0 g/dL and an increase of ≥1.0 g/dL from baseline at any time during the study) were comparable among the dose cohorts. A target Hgb response was achieved by 95.7% of patients overall, and ranged from 86.7% to 100% for the Q4W cohorts and was 93.3% and 100% for the Q2W cohorts.
- Rapid rates of Hgb increase (i.e., >1 g/dL in any 2-week period and >2 g/dL in any 4-week period) and Hgb excursions above 13 g/dL through 8 weeks after initial dosing occurred more frequently overall in the Q2W cohorts than in the Q4W cohorts.
  - Hgb increases of >1 g/dL in any 2-week period through 8 weeks after initial dosing occurred in 86.7% of patients in Q2W Cohort 6 (starting dose 0.025 mg/kg) and in the highest starting dose Q4W weight-based cohort, Cohort 3 (starting dose 0.075 mg/kg), 75.0% of patients in Q2W Cohort 7 (starting dose 0.0375 mg/kg), and 53.3% to 80.0% of patients among the other Q4W cohorts.
  - Hgb increases of >2 g/dL in any 4-week period through 8 weeks after initial dosing occurred in 80.0% of patients in Q2W Cohort 6 (starting dose 0.025 mg/kg), 25.0% of patients in Q2W Cohort 7 (starting dose 0.0375 mg/kg), and from 0% to 33.3% of patients among the Q4W cohorts. Cohort 7 typically had larger proportions of patients with dose decreases, and dose delays and decreases, for Doses 2, 3, and 4, which may account for the smaller proportion of patients in Cohort 7 with Hgb increases of >2 g/dL in any 4-week period through 8 weeks after initial dosing as compared to Cohort 6.
  - Hgb >13 g/dL during the first 8 weeks after initial dosing occurred in 33.3% and 25.0% of patients in Q2W Cohorts 6 and 7, respectively, as compared to 0.0% to 20.0% of patients among the Q4W weight-based cohorts, and 6.7% of patients in the fixed dose cohorts.
- The proportion of patients with Hgb levels in the range of 11 to 13 g/dL or 11 to 12.5 g/dL at least once during Weeks 2 to 25 (Weeks 2–27 for Q2W cohorts) was 97.1% overall; proportions were comparable among the dose cohorts and ranged from 93.3% to 100% for both the Q4W and Q2W cohorts.
- Confirmed Hgb responses (Hgb value in a specified range at least once during an interval and there were not two consecutive subsequent values that were not in the specified range during the same interval) were comparable among dose cohorts of similar starting dose and dosing regimen, and typically increased during the course of the study.
  - Confirmed Hgb responses within 11 to 13 g/dL increased from 54.0% during Weeks 2 to 5, to 65.5% and 64.0% during Weeks 6 to 9 and Weeks 10 to 13, respectively, to 78.4%, 77.7%, and 74.1% during Weeks 14 to 17, Weeks 18 to 21, and Weeks 22 to 25, respectively.

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Summary and Conclusions (Cont'd):

- Confirmed Hgb responses within 11 to 12.5 g/dL increased from 48.9% during Weeks 2 to 5, to 51.8% during Weeks 6 to 9, decreased to 34.5% at Weeks 10 to 13, and then increased to 56.1%, 66.9%, and 66.2% during Weeks 14 to 17, Weeks 18 to 21, and Weeks 22 to 25, respectively.
- Confirmed Hgb responses within 11 to 13 g/dL or within 11 to 12.5 g/dL during 4-week intervals were:
  - Comparable between 0.05 mg/kg and 0.075 mg/kg starting dose Q4W SC cohorts; a delayed response was observed for the 0.025 mg/kg starting dose Q4W cohort.
  - Comparable between SC and IV Q4W dose cohorts of the same starting dose (0.05 mg/kg).
  - Comparable between weight-based and fixed dose regimens of similar starting dose (0.05 mg/kg and 4 mg fixed dose).
  - Smaller for the 0.025 mg/kg starting dose Q2W cohort during the first three 4-week intervals as compared to the 0.05 mg/kg and 0.075 mg/kg starting dose Q4W cohorts, and comparable during the final 4-week intervals. Confirmed Hgb responses were either smaller, comparable, or larger for the 0.0375 mg/kg starting dose Q2W cohort as compared to the 0.05 mg/kg and 0.025 mg/kg starting dose Q4W cohorts depending on the 4-week interval; however, 0.0375 mg/kg starting dose Q2W cohort with n=4 was too small a cohort for comparisons to be meaningful.

- AF37702 Injection SC starting doses of 0.050 mg/kg and 0.075 mg/kg, with subsequent monthly dose titration, resulted in mean Hgb ≥11.0 g/dL by 2 weeks after the first dose with mean Hgb maintained in the range of 11.0 g/dL and 12.7 g/dL thereafter; SC starting dose of 0.025 mg/kg, with subsequent monthly dose titration resulted in mean Hgb ≥11.0 g/dL by 6 weeks after the first dose, with mean Hgb maintained in the range of 11.0 g/dL and 12.2 g/dL thereafter. Mean Hgb was comparable between SC and IV Q4W cohorts of the same starting dose (0.05 mg/kg), and between weight-based and fixed dose Q4W cohorts of similar starting doses (0.05 mg/kg and 4 mg fixed dose). Mean Hgb values for the 0.025 mg/kg and 0.0375 mg/kg SC Q2W cohorts were typically larger as compared to the 0.050 mg/kg SC Q4W cohorts, and larger as compared to the 0.025 mg/kg Q4W cohort.
- A prominent reticulocyte response was observed with every AF37702 Injection SC or IV dose, and a dose dependent increase with increasing AF37702 Injection SC starting dose was observed. RBC count, Hct, and soluble transferrin receptor protein increased for all dose cohorts, and among the weight-based Q4W cohorts, increases occurred in a dose-dependent manner. Decreases in ferritin and CHr were observed in all dose groups, followed by a return to baseline values.

Two Cohort 6 patients were excluded from the PD population analyses as they received all doses IV instead of SC. Results for the PD population (N=137) were comparable to those for the mITT population.

Pharmacokinetic Results, pharmacokinetic population (N=53)

- Following SC administration of AF37702 Injection, plasma concentration of AF37702 increased gradually with a median T_{max} of approximately 48 hours postdose for most dose levels (0.025, 0.03, 0.04, 0.05, 0.075, and 0.08 mg/kg dose levels). An absorption lag time of approximately 0.5 to 2 hours, i.e., when AF37702 plasma

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Summary and Conclusions (Cont'd):

concentrations were not detectable, was observed in most patients following SC administration of AF37702 Injection.

- A broad plasma AF37702 peak was observed following SC administration after which the concentration declined to below the assay's lower limit of quantification.
- The apparent terminal half-life following SC injection (median $T_{1/2}\lambda_z$ range = 46 to 139 hours over a dose range of 0.025 to 0.08 mg/kg/dose) tended to be prolonged as compared to IV route of administration. The extended half-life suggested that SC absorption could be rate limiting in some patients.
- While systemic exposure defined by AUC appeared to increase proportionally with dose over a SC dose range of 0.025 to 0.08 mg/kg/dose, the small number of patients in each dose group for whom PK data were available precluded a definitive analysis of dose-linearity.
- In most instances peak plasma concentration of AF37702 was attained shortly after IV injection and declined thereafter; with a median T_{max} of 0.5 hours (0.05 mg/kg dose) and 2.0 hours (0.03 mg/kg dose). The median plasma half-lives were 37 and 52 hours for 0.03 mg/kg (n=1) and 0.05 mg/kg (n=4) doses, respectively.
- The PK profiles of AF37702 in male and female patients were similar after either IV or SC administration. No significant differences were found in AUC, C_{max}, half-life, clearance, and volume of distribution between the sexes.
- No systemic accumulation of AF37702 was detected following repeated Q4W or Q2W SC or IV injections. The lack of accumulation was anticipated based on the half-life of AF37702 and the dosing interval used in this study.

Safety Results, safety population (N=139)

AEs were assessed using the World Health Organization (WHO) Toxicity Criteria.

Of the 139 patients who received AF37702 Injection, 112 (80.6%) experienced an AE. The most frequently reported AEs were nasopharyngitis (12.9%), hypertension (10.1%), diarrhoea (7.2%), urinary tract infection (7.2%), nausea (6.5%), back pain (5.8%), oedema peripheral (5.8%), renal failure chronic (5.8%), and blood pressure increased (5.0%).

AEs assessed as Grade 4 were renal failure chronic (2.2%), diabetic ketoacidosis (1.4%), acute myocardial infarction (0.7%), vomiting (0.7%), gangrene (0.7%), hypoglycaemia (0.7%), and renal failure (0.7%). None of the Grade 4 events were reported by the Investigator as related to study treatment.

Twenty-seven (19.4%) patients experienced an AE reported as serious by the Investigator. The most frequently reported SAEs were renal failure chronic (4.3%), bronchitis (1.4%), and diabetic ketoacidosis (1.4%). One SAE was reported as related to study treatment; embolic cerebral infarction in a patient with a history of atrial fibrillation.

Two deaths occurred during the study, one due to renal failure chronic (Grade 3), and one due to acute myocardial infarction (Grade 4) and bronchitis (Grade 1). These events were reported as not related to study treatment.

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Summary and Conclusions (Cont'd):

In addition to the two deaths resulting in premature study termination, six other patients prematurely withdrew from the study due to one or more AEs, one of which was reported as treatment related; dizziness, reported as not serious.

Treatment-related AEs (AEs reported by the Investigator as related to study treatment) were experienced by 16 (11.5%) patients. The most frequently reported treatment-related AE was hypertension (6.5%). Other treatment-related AEs were arthritis (1.4%), headache (1.4%), and arteriovenous fistula thrombosis, blood pressure increased, dizziness, embolic cerebral infarction, insomnia, iron deficiency, malaise, and laboratory test abnormal (elevation of soluble transferrin receptor protein) (0.7% each). No treatment-related AEs were assessed by the Investigator as Grade 4. One treatment-related AE was reported as serious: embolic cerebral infarction, Grade 2. One patient prematurely withdrew from the study due to a treatment-related AE: dizziness, Grade 1, reported as not serious.

Two patients developed AF37702-specific antibodies following SC administration; further investigation showed that these antibodies were specific for the peptide component of AF37702. These antibodies did not cross react with EPO, and did not result in any clinical signs or symptoms in the patients; no effect on Hgb levels was observed. One patient (SC Q4W Cohort 3) was assessed as antibody positive at Weeks 17, 21, and 25, with Hgb levels ranging from 11.2 to 11.9 g/dL during those weeks as compared to baseline Hgb of 10.7 g/dL. The other patient (SC Q2W Cohort 7) was assessed as antibody positive at Weeks 25 and 29, with Hgb levels ranging from 11.4 to 12.0 g/dL during those weeks, as compared to baseline Hgb of 9.9 g/dL.

Conclusions:

AF37702 Injection administered Q4W or Q2W over a 6-month period appeared to be generally well tolerated in this study population of patients with CRF not on dialysis and without prior ESA treatment. Pharmacologic activity was observed at all starting doses of AF37702 Injection evaluated. A prominent reticulocyte response was observed following each dose, and a dose-response relationship was observed with increasing AF37702 Injection SC starting dose. At all starting doses evaluated, AF37702 Injection demonstrated the ability to increase Hgb and sustain the increase; a starting dose dependent increase in Hgb was observed. The IV and SC routes of administration of the same starting dose showed similar Hgb responses. Weight-based and fixed dose regimens of similar starting doses (0.05 mg/kg and 4 mg, respectively) showed similar Hgb responses. Changes in other PD parameters (increases in RBC count, Hct, and soluble transferrin receptor protein, and transient decreases in ferritin and CHr) were consistent with stimulation of erythropoiesis.

PK analyses in a subset of study patients indicated that plasma concentrations of AF37702 following SC administration of AF37702 Injection increased gradually with a median T_{max} of approximately 48 hours for most dose levels (0.025, 0.03, 0.04, 0.05, 0.075, and 0.08 mg/kg). Peak plasma concentration of AF37702 was attained earlier after IV administration, as compared to SC administration, with a median T_{max} of 0.5 hours (0.05 mg/kg dose) and 2.0 hours (0.03 mg/kg dose), and declined thereafter. No systemic accumulation of AF37702 was detected following repeated Q4W or Q2W SC or IV administration. Systemic exposure, as defined by AUC, appeared to increase proportionally with dose over the SC dose range of 0.025 to 0.08 mg/kg. No differences in PK were found between male and female patients.

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Conclusions (Cont'd):

Q2W cohorts had a higher proportion of patients with Hgb >13 g/dL during the first 8 weeks after initial dosing as compared to the Q4W cohorts. The 0.025 mg/kg Q4W starting dose cohort (Cohort 4) took a longer period of time to achieve a Hgb response as compared to the 0.05 mg/kg Q4W starting dose cohorts (Cohorts 1, 2 and 8). Dose adjustments for Cohorts 1, 2, and 8 (0.05 mg/kg) resulted in lower mean final doses (Dose 6) ranging from 0.031 to 0.039 mg/kg, as compared to dose adjustments for Cohort 4 (0.025 mg/kg) which resulted in a mean final dose (Dose 6) of 0.023 mg/kg that was similar to the cohort's starting dose. A starting dose slightly lower than 0.05 mg/kg in future studies in CRF patients not on dialysis may be associated with fewer dose adjustments.

Date of Report: 17 August 2009