.0 SYNOPSIS

Name of the Sponsor: Affymax, Incorporated	**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, 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

Investigators and Study Centers:

Patients were enrolled at nine sites in Bulgaria, five sites in Romania, and one site in the United Kingdom.

Publications:

Pergola P, Geronemus R, Zeig S, Whittier F, Zabaneh R, Nenov K, et al. Once Monthly Hematide Maintains Hb in HD Pts with Different Baseline Iron and CRP Status. Poster presentation National Kidney Foundation Spring Clinical Meeting; 2009; Nashville, Tennessee. Abstract published in National Kidney Foundation 2009 Spring Clinical Meetings Abstracts Book, Abstract 104. p. 63.

Covic A, Ardelean L, Manuelyan L, Nenov K, Paunova P, Tarnovo V, et al. A Phase 2, Open-Label, Multi-Center, Dose Finding Study of the Safety, Pharmacodynamics, and Pharmacokinetics of Hematide™ for the Maintenance of Anaemia in Haemodialysis Patients Previously Treated with Epoetin. Poster presentation XLV Congress of the European Renal Association European Dialysis and Transplant Association (ERA-EDTA); 2008; Stockholm, Sweden. Abstract published in Nephrology Dialysis Transplantation Plus, June 2008, Volume 1, Supplement 2, Abstract MP390. p. ii366.

Study Period: 20 December 2006 (first patient dosed) to 29 April 2008 (last patient visit)	**Development Phase:** Phase 2

Objectives:

The primary objective of this study was to determine the dose ranges of AF37702 Injection, administered intravenously (IV) or subcutaneously (SC) every 4 weeks (Q4W) or every 2 weeks (Q2W), that maintained hemoglobin (Hgb) within 1.0 g/dL below baseline to 1.5 g/dL above baseline, inclusive, in dialysis patients whose Hgb values were stable on Epoetin. Secondary objectives were to evaluate and compare safety, pharmacodynamics (PD), and in a subset of patients pharmacokinetics (PK) of AF37702, following IV or SC administration of AF37702 Injection Q4W or Q2W.

Methodology:

This was a Phase 2, open-label, multicenter, dose finding study with up to 16 treatment cohorts of 15 dialysis patients per cohort. A minimum of 120 and a maximum of 240 patients were to be enrolled at up to 40 clinical centers. Patients ≥18 years of age with stable Hgb maintained on a stable dose of commercially available Epoetin (alfa or beta) who met all other eligibility criteria were to be enrolled. Two initial cohorts on a Q4W dosing schedule were to be enrolled in parallel, with the IV route of administration studied in one cohort and the SC route of administration in the other cohort. Once the first IV or SC cohort had completed enrollment, enrollment of the next IV or SC cohort, respectively, could have been initiated to test lower, higher, intermediate (between the current or previously studied), or repeat (confirmatory) dose levels of AF37702 Injection. Once an appropriate dose conversion level had been identified with the Q4W dosing schedule, the Q2W dosing schedule was to be initiated. The initial

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Q2W dose was to be one-half or less than a previously studied Q4W dose. The need for a transition period (period between the last dose of Epoetin and the first dose of AF37702 Injection during which time the patient did not receive any ESA doses) and the duration of this transition period were to be determined based on the safety and PD results from other clinical trials involving AF37702 Injection and/or previous cohort(s) of this study. Based on data from Study AFX01-03, a 1-week transition period was evaluated in this study.

Individual patient dose adjustments were allowed from Week 5 onwards according to protocol-specified criteria. After the first dose, patients were to be seen at least weekly. During the study, iron status was to be maintained per the European Best Practice Guidelines for the Management of Anemia in Patients with Chronic Renal Failure as appropriate. Patients were to be followed for a minimum of 4 weeks after the last dose of AF37702 Injection or until stabilization of AEs, whichever occurred later. 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:

A minimum of 120 and a maximum of 240 patients were planned. A total of 91 patients were enrolled; 91 patients were included in the safety analyses, 90 patients were included in the modified intent-to-treat (mITT) analyses, 87 patients were included in the PD analyses, 51 patients were included in the PD analyses that excluded Romanian site patients, and 22 patients were included in the PK analyses. Enrollment was stopped after 91 patients were enrolled, all in Q4W cohorts, because a sufficient amount of data from this study, and from prior studies with both Q4W and Q2W dosing regimens, were available to determine the Phase 3 dosing regimen.

Number of Patients Enrolled:

A total of 91 patients were enrolled; 15 patients in each of five dose cohorts, and 16 patients in one dose cohort.

Diagnosis and Main Criteria for Eligibility:

Eligible patients were males or females ≥18 years of age, clinically stable on dialysis for ≥3 months, on Epoetin (alfa or beta) maintenance therapy of ≥50 and ≤200 U/kg/week at the same dosing frequency, continuously prescribed for 8 weeks prior to study start and, within 4 weeks prior to study start had: three mid- or end-of-week Hgb values of ≥10.0 g/dL and ≤12.5 g/dL with ≤1.2 g/dL difference between any of the three values, one transferrin saturation (TSAT) value ≥20%, one ferritin value ≥100 ng/mL, one serum or red cell folate value ≥ lower limit of normal (LLN), one vitamin B_{12} value ≥LLN, one C-reactive protein value ≤30 mg/L, urea clearance/volume (Kt/V) ≥1.2, one white blood cell count ≥3.0 x 10^9/L, and one platelet count ≥100 x 10^9/L and ≤500 x 10^9/L.

Test Product, Dose and Mode of Administration, Batch 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 United States Pharmacopoeia/National Formulary compendial excipients: sodium phosphate dibasic, sodium phosphate monobasic, polysorbate 20, sorbitol, sodium hydroxide, and Water for Injection.

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Doses of AF37702 Injection were to be administered Q4W for a total of 7 doses or Q2W for a total of 14 doses as rapid IV bolus injections or as SC injections during dialysis. For the starting IV and SC Q4W cohorts, each patient in a cohort was to receive open-label doses of AF37702 Injection starting at a pre-specified Epoetin-to-AF37702 Injection conversion tier as a weight-based (mg/kg) dose. For subsequent cohorts, the starting dose could have been confirmed or modified by 25 to 50% based on the PD and safety results obtained in previous cohort(s). Patients were to receive AF37702 Injection via the same route of administration as Epoetin had been administered at the time of screening.

Six dose cohorts were evaluated in this study. Q4W SC Cohort 1 and Q4W IV Cohort 2, both without a transition period, evaluated AF37702 Injection tiered starting doses of 0.05, 0.075, or 0.1 mg/kg for patients on an Epoetin dose of ≤100 U/kg/week, >100 to 150 U/kg/week, or >150 U/kg/week, respectively. Q4W SC Cohort 3 and Q4W IV Cohort 4, both with a 1-week transition period, evaluated these same tiered dosing regimens. Q4W SC Cohort 5 and Q4W IV Cohort 6, both with a 1-week transition period, evaluated tiered starting doses of 0.04 mg/kg or 0.075 mg/kg for patients with an Epoetin dose of ≤100 U/kg/week or 100 to 150 U/kg/week, respectively. Individual patient dose adjustments were allowed from Week 5 onwards according to protocol-specified criteria. Q2W dosing was not evaluated in this study.

Medicines and Healthcare products Regulatory Agency (MHRA) and Romanian Regulatory authorities were notified of a Serious Breach of Good Clinical Practice that affected all study sites in Romania. Due to unauthorized and undocumented transportation of study drug among Romanian clinical sites, the chain of custody for the study drug was not assured, and storage and handling of the drug could not be verified. Despite the fact that procedures at the Romanian sites may have been carried out according to protocol, verification that patients received the intended study drug that had been properly handled and stored was not possible. In addition, two sites in Romania were closed due to specific activities of site staff that were incompatible with adherence to ICH GCP and the AFX01-07 study protocol. Due to the issues that affected all Romanian study sites, PD parameter analyses were conducted for the PD population both including and excluding Romanian site patients.

Lot numbers of AF37702 Injection used for patients in this study were PLI006-06 (10 mg/mL) and PLI040-06 (10 mg/mL).

The majority of patients (91.2%) received all seven planned doses during the study; mean dose at Dose 1 was 0.053 mg/kg and the mean dose during the study was 0.055 mg/kg.

Duration of Treatment:

Doses of AF37702 Injection were to be administered Q4W for a total of 7 doses or Q2W for a total of 14 doses (28-week duration). Q2W dosing was not evaluated in this study.

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

Not applicable.

Criteria for Evaluation:

~~Pharmacodynamics:~~ PD was assessed by evaluation of Hgb, reticulocytes, red blood cell (RBC) count, hematocrit (Hct), ferritin, and TSAT.

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~~Pharmacokinetics:~~ The PK of AF37702 following administration of AF37702 Injection was determined from the plasma concentration-time data and summarized by nominal dose.

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

Statistical Methods:

Summary statistics and statistical evaluations were presented for all patients and consisted of the number and percentages of responses in each category for discrete measures, and the number of observations, 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.

AF37702 plasma concentration-time data were analyzed by noncompartmental methods using WinNonlin (Version 5.2, Pharsight Corp.) and the actual blood sampling times relative to dosing, and included area under the plasma concentration-time curve up to infinite time ($AUC_{0-\infty}$), maximum observed plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), systemic clearance (CL) or apparent systemic clearance (CL/F), and volume of distribution (V_d) or apparent volume of distribution (V_d/F). Concentrations of AF37702 in plasma were summarized by nominal dose and by nominal time.

Summary and Conclusions:

~~Pharmacodynamic Results, Pharmacodynamic Population (N=87)~~

Conclusions are based on results in the PD population; similar results generally were noted in the mITT population.

- Proportions of patients with Hgb values within 1 g/dL below baseline to 1.5 g/dL above baseline:
  - Over all cohorts, 32.9% and 48.1% of patients had Hgb values within 1 g/dL below to 1.5 g/dL above baseline during Weeks 2-21 and Weeks 22-29, respectively. Within cohorts, IV Cohort 6 (lower tiered starting dose, with a transition) had the highest proportion of patients with Hgb values within 1 g/dL below to 1.5 g/dL above baseline during Weeks 2-21 (42.9%), and IV Cohort 4 (tiered starting dose, with a transition) had the highest proportion during Weeks 22-29 (61.5%).
  - During Weeks 2-5 and Weeks 6-9, when the presence of a transition period between the last dose of Epoetin and the first dose of AF37702 Injection would likely have the greatest clinical impact, transition cohorts tended to have higher proportions of patients with Hgb values within range than nontransition cohorts. During Weeks 2-5, proportions varied from 80.0% to 86.7% in the transition cohorts versus 73.3% and 83.3% in the two nontransition cohorts, SC Cohort 1 and IV Cohort 2, respectively. During Weeks 6-9, proportions varied from 66.7% to 78.6% in the transition cohorts versus 66.7% and 60.0% in nontransition Cohorts 1 and 2, respectively.
- Proportions of patients with Hgb values within baseline range of 10 g/dL to 12.5 g/dL:
  - Over all cohorts, 23.2% and 49.4% of patients had Hgb values within 10 g/dL to 12.5 g/dL during Weeks 2-21 and Weeks 22-29, respectively. Within cohorts, SC Cohort 1 (without a transition) had the highest proportion of patients with Hgb values within 10 g/dL to 12.5 g/dL during Weeks 2-21 (41.7%) and

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Weeks 22-29 (75.0%).

- Proportions of patients with Hgb values within 0.5 g/dL of baseline range (i.e., within 9.5 g/dL to 13 g/dL):
  - Over all cohorts, 61.0% and 80.2% of patients had Hgb values within 9.5 g/dL to 13 g/dL during Weeks 2-21 and Weeks 22-29, respectively. Within cohorts, SC Cohort 1 (without a transition) had the highest proportion of patients with Hgb values within 9.5 g/dL to 13 g/dL during Weeks 2-21 (83.3%), and IV Cohort 4 (tiered starting dose, with a transition) had the highest proportion during Weeks 22-29 (92.3%).
- The proportions of patients with Hgb values within baseline ranges generally were comparable between cohorts dosed SC and those dosed IV, and between cohorts with lower tiered starting doses (0.04-0.075 mg/kg) and those with tiered starting doses in the 0.05-0.10 mg/kg range.
- Hgb by time point and change from baseline:
  - Over all cohorts, mean Hgb increased slightly from 11.2 g/dL at baseline to 11.6 g/dL at End of Study. Mean Hgb values over Weeks 2-21, Weeks 22-29, and Weeks 2-29 were comparable (11.7 g/dL, 11.6 g/dL, and 11.7 g/dL, respectively), and all were slightly above baseline.
  - Within cohorts, mean Hgb values generally were comparable at baseline. Mean Hgb values generally increased slightly over the course of the study, with the trend most notable in SC Cohort 3 (tiered starting dose, with a transition), IV Cohort 4 (tiered starting dose, with a transition), and SC Cohort 5 (lower tiered starting dose, with a transition). Cohorts with a transition period (Cohorts 3, 4, 5, and 6) generally tended to have less initial fluctuation in mean Hgb values than cohorts without a transition period (Cohorts 1 and 2).
  - Mean Hgb values generally were comparable between cohorts dosed SC and those dosed IV, and between cohorts with lower tiered starting doses and those with tiered starting doses in the 0.05-0.10 mg/kg range.
- RBC count:
  - Over all cohorts, mean RBC count generally remained the same over the course of the study. Within cohorts, mean RBC counts varied depending on the cohort, but generally remained near baseline values.
- Hct:
  - Over all cohorts, mean Hct increased slightly above baseline over the course of the study. Within cohorts, mean Hct values varied depending on the cohort, but generally remained near baseline values.
- Reticulocyte response:
  - Over all cohorts and within each cohort, reticulocyte counts followed a cyclical pattern after AF37702 Injection dosing, with mean values generally above baseline 1 to 2 weeks after dosing and decreasing to near or below baseline 3 to 4 weeks after each dose. Cohorts dosed SC had higher maximum reticulocyte values compared with cohorts dosed IV.
- Ferritin:
  - Over all cohorts and within each cohort, mean serum ferritin values generally fluctuated slightly above and below baseline throughout the study, with the exception of values in SC Cohort 3 (tiered starting dose, with

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a transition), which generally increased slightly above baseline.

- TSAT:
  - Over all cohorts and within each cohort, mean TSAT values generally increased slightly above baseline over the course of the study.

~~Pharmacodynamic Results, Pharmacodynamic Population Excluding the Romanian Sites (N=51)~~

In general, overall results for the PD population excluding the Romanian sites were comparable to results based on the PD and mITT populations, although there were minor differences in some parameters, which could be attributed to the large decrease in cohort size rather than to meaningful clinical differences due to noncompliance at the Romanian sites.

~~Pharmacokinetic Results, Pharmacokinetic Population (N=22)~~

- Following IV administration of AF37702 Injection, plasma concentrations of AF37702 increased with increasing doses. Mean C_{max} values increased from 963 ng/mL to 1,727 ng/mL, 2,328 ng/mL, and 2,447 ng/mL at the 0.04, 0.05, 0.075, and 0.10 mg/kg dose levels, respectively. Mean $AUC_{0-\infty}$ also increased with increasing dose, from 50,160 ng•h/mL (0.04 mg/kg), to 90,420 ng•h/mL (0.05 mg/kg), 123,200 ng•h/mL (0.075 mg/kg), and 130,000 ng•h/mL (0.10 mg/kg). Mean T_{max} values ranged from 0.1 to 1.4 hours and mean CL ranged from 0.62 to 0.80 mL/h•kg. The slow CL contributed to a long elimination half-life with mean $t_{1/2}$ ranging from 27 to 39 hours. The mean V_d ranged from 24 to 45 mL/kg. The small number of patients in each dose group for whom PK data were available precluded a definitive analysis of dose proportionality for the IV regimen.
- Following SC administration of AF37702 Injection, plasma concentrations of AF37702 increased with increasing doses. Mean C_{max} values increased from 264 ng/mL, to 295 ng/mL, 402 ng/mL, and 455 ng/mL at the 0.04, 0.05, 0.075, and 0.10 mg/kg dose levels, respectively. Mean $AUC_{0-\infty}$ also increased with increasing dose, from 29,170 ng•h/mL (0.04 mg/kg), to 38,490 ng•h/mL (0.05 mg/kg), 47,640 (0.075 mg/kg), and 66,830 ng•h/mL (0.10 mg/kg). The extended absorption is reflected in the long mean T_{max} values, which ranged from 47 to 73 hours. Mean CL/F ranged from 1.43 to 1.57 mL/h•kg. The slow CL/F contributed to a long elimination half-life, with mean $t_{1/2}$ values ranging from 21 to 43 hours. The mean V_d/F ranged from 46 to 90 mL/kg. The available data suggested that the PK of AF37702 was reasonably linear following SC administration over the dose range.

In general, the mean C_{max} and AUC values for AF37702 following IV administration of AF37702 Injection were substantially higher than the respective values following SC administration. The estimated bioavailability of the SC regimen was approximately 46%. There was no systemic accumulation of AF37702 following multiple Q4W administrations, consistent with a dosing interval greater than four or five half-lives of the drug.

~~Safety Results, Safety Population (N=91)~~

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 11. Assessment of severity was based on the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-

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CTCAE) toxicity scale, Version 3.0.

AF37702 Injection was generally well tolerated in this patient population.

- Of the 91 patients who received AF37702 Injection, 51 (56.0%) experienced an AE. The most frequently reported AEs were hypertension (12.1%), headache (12.1%), hypertensive crisis (9.9%), and arteriovenous fistula site haemorrhage (5.5%).
- AEs assessed as Grade 4 were sudden death (3.3%), uveitis (1.1%) and keratitis (1.1%). None of the Grade 4 events were reported as related to study treatment.
- Twelve (13.2%) patients experienced an AE reported as serious by the Investigator; a total of 15 SAEs were reported during the study. The most frequently reported SAEs were arteriovenous fistula thrombosis (3.3%), sudden death (3.3%) and pyelonephritis chronic (2.2%). No SAEs were reported as related to study treatment.
- Three deaths occurred during the study, each reported as verbatim term sudden death. These events were reported by the Investigator as not related to study treatment. These three patients were a 59-year-old female patient with a history of hypertension, ischemic stroke, and chronic coronary disease who died suddenly 24 days following her sixth dose of AF37702 Injection (death certificate primary cause of death: chronic renal insufficiency); a 33-year-old male patient with a history of hypertension who was hospitalized 5 days following his second dose of AF37702 Injection due to gangrene requiring surgical intervention and died suddenly 12 days after Dose 2 (death certificate primary cause of death: rhythm disturbances as a consequence of uremia); and a 76-year-old male patient with a history of ischemic heart disease, type 2 diabetes, and hypertension who died suddenly 4 days after his second dose of AF37702 Injection (death certificate primary cause of death: cardio-pulmonary arrest). Cardiac disease is a major contributor to death in dialysis patients, and the frequency of sudden cardiac death has ranged from 7% to 37% in published studies.[1, 2, 3] Therefore the occurrence of sudden death in this study is considered to be within the anticipated occurrence for this patient population.
- In addition to the three deaths resulting in premature study termination, one patient prematurely withdrew from the study due to an AE; alanine aminotransferase increased, Grade 2, reported by the Investigator as not serious and not related to study treatment.
- Treatment-related AEs were experienced by 7 (7.7%) patients. The most frequently reported treatment-related AEs were blood pressure increased (3.3%) and headache (3.3%). Other treatment-related AEs were infusion site thrombosis (2.2%), and blood lactate dehydrogenase increased, fatigue, and arteriovenous fistula site haemorrhage (1.1% each). No treatment-related AEs were assessed by the Investigator as Grade 3 or 4. No treatment-related AEs were reported by the Investigator as serious, and no patient withdrew from the study due to a treatment-related AE.
- No AF37702-specific antibodies were detected during the study.

Conclusions:

AF37702 Injection administered Q4W SC or IV over a 28-week period appeared to be generally well tolerated in this study population of hemodialysis patients previously maintained on Epoetin alfa or beta. AEs described by the

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Investigator as related to the use of AF37702 Injection and occurring in two or more patients were blood pressure increased (3.3%), headache (3.3%), and infusion site thrombosis (2.2%).

AF37702 Injection generally maintained Hgb within baseline range during the study. Despite the use of a restrictive definition of maintenance of Hgb levels relative to baseline, 32.9% and 48.1% of patients overall had Hgb values within 1 g/dL below to 1.5 g/dL above baseline during Weeks 2-21 and Weeks 22-29, respectively. During the early weeks of the study (Weeks 2-5 and 6-9) when the presence of a transition period between the last dose of Epoetin and the first dose of AF37702 Injection would likely have the greatest clinical impact, transition cohorts tended to have higher proportions of patients with Hgb values within 1 g/dL below to 1.5 g/dL above baseline than nontransition cohorts. Mean Hgb increased slightly from 11.2 g/dL at baseline to 11.6 g/dL at End of Study. Mean Hgb values generally were comparable between SC and IV cohorts. Transitions cohorts generally tended to have less initial fluctuation in mean Hgb values than cohorts without a transition period.

In general, the plasma concentrations, C_{max}, and AUC values of AF37702 increased with increasing dose following administration of AF37702 Injection via the IV or the SC routes. Plasma concentrations, and therefore C_{max} and AUC values, were substantially higher following IV administration of AF37702 Injection. The small number of patients for whom PK data were available in each dose group precluded definitive dose-proportionality analysis; however, the available data suggested that the PK of AF37702 was reasonably linear following SC administration over the dose range of 0.040 and 0.10 mg/kg. No generalizations could be made regarding the linearity of the PK following IV administration. There was no systemic accumulation of AF37702 following multiple Q4W IV or SC administrations of AF37702 Injection.

Date of Report: 29 September 2009