2.0 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 Escalation Study of the Safety, Pharmacodynamics, and Pharmacokinetics of Subcutaneously Administered AF37702 Injection (Hematide™) in Anemic Cancer Patients Receiving Chemotherapy

Study Centers:

Guys and St. Thomas Hospital, London, UK; Facultni Nemocnice Olomouc, Olomouc, Czech Republic; University Hospital, Hradec Karlova, Czech Republic; Samodzieny Publiczny Szpital Klinniczny, Gdansk, Poland; Wielkopolskie Centrum Chorob Pluc i Gruzlicy, Poznan, Poland; Faculty Hospital, Brno, Czech Republic; Masarykuv Onkologicky Ustav, Brno, Czech Republic; St. Georges Hospital, London, UK; Onkologicke oddeleni, Nemocnice Pribram, Pribram, Czech Republic; Chorob I Nowotworow Pluc Uniwersytetu Medycznego, Ul. Okolna 181, Poland; Specjalistyczny Szpital im. Szczecin, Poland; Szpital Uniwersytecki w Krakowie, Krakow, Poland; Wojewodzki Szpital Specjalistyczny im. L. Rydygiera, Krakow, Poland; University College London Hospital, London.

Publications:

Pickering L, Cwiertka K, Jassem J, Petera J, Pettengell R, Ramlau R, et al. Correction of Anemia with Hematide™, a Synthetic Peptide-Based Erythropoiesis Stimulating Agent (ESA), in Oncology Patients Receiving Chemotherapy. Poster presentation, 49th American Society of Hematology Annual Meeting, December 8-11, 2007; Atlanta, Georgia. Abstract published in ASH Annual Meeting Abstracts 2007;110 (11):3666.

Pickering LM, Cwiertka K, Jassem J, Petera J, Pettengell R, Ramlau R, et al. Hematide™, a Synthetic Peptide-Based Erythropoiesis Stimulating Agent (ESA), Assessed for Correction of Anemia in Oncology Patients Receiving Chemotherapy. Poster presentation, 48th American Society of Hematology Annual Meeting, December 9-12, 2006; Orlando, Florida. Abstract published in ASH Annual Meeting Abstracts 2006;108 (11):1290.

Study Period:	**Development Phase:**
27 Jan 2006 (first patient dosed) to 18 Jun 2007 (last patient visit)	Phase 2

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Objectives:

The primary objective of this study was to determine the dose of AF37702 Injection administered every three weeks (Q3W) by subcutaneous (SC) injection associated with a hemoglobin (Hgb) increase of ≥ 1 g/dL in ≥ 50% of anemic cancer patients receiving chemotherapy at 9 weeks following Dose 1. Secondary objectives were: to evaluate the safety profile of up to four doses of AF37702 Injection administered SC Q3W to anemic cancer patients receiving concomitant myelosuppressive chemotherapy; to determine the change from baseline in Hgb at each dose level of AF37702 Injection; to determine the proportion of patients who had a Hgb response to AF37702 Injection; to determine the dose of AF37702 Injection administered SC that increased and maintained Hgb in the target range of 11 to 13 g/dL; and to evaluate the pharmacokinetic (PK) profile of up to four doses of AF37702 Injection administered SC in a subset of study patients.

Methodology:

This was a Phase 2, open-label, multi-center, sequential dose finding trial with up to 6 treatment cohorts receiving chemotherapy with 15 patients per cohort. A minimum of 30 and a maximum of 90 patients (not including replacements) could be enrolled in this trial at up to 20 clinical centers. Each patient was to receive an open-label dose of AF37702 Injection administered SC Q3W for a total of four doses. The first dose of AF37702 Injection was to be administered on Day 1 of a chemotherapy cycle with subsequent doses administered Q3W thereafter regardless of the schedule of subsequent chemotherapy cycles. Each patient in the first cohort was to receive a starting dose of 0.1 mg/kg. Subsequent cohorts were to receive doses up to a maximum of 0.4 mg/kg, including intermediate doses. Protocol-specific individual patient dose adjustment guidelines were to be followed. Patients were to participate for approximately 13 weeks following Dose 1 (28 days following administration of Dose 4), or stabilization of adverse events (AEs), or until Hgb values were ≤ 13 g/dL or start of commercial ESA therapy, whichever occurred latest. PK was to be monitored in a subset of patients to assess PK parameters.

Number of Patients Planned:

A minimum of 30 and a maximum of 90 patients were planned.

Number of Patients Enrolled:

A total of 60 patients overall were enrolled; 15 patients in each of four dose cohorts.

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Diagnosis and Main Criteria for Eligibility:

Eligible patients were males and females ≥ 18 and ≤ 80 years of age with a life expectancy > 6 months who: provided written informed consent; had histologically confirmed solid tumor malignancy or lymphoma and were scheduled to receive at least 9 weeks of cyclic or continuous myelosuppressive chemotherapy while on study; had an ECOG Performance Status of 0 to 2; within 1 week prior to study drug administration had Hgb value of ≥ 8 and < 11 g/dL, one absolute neutrophil count ≥ 1.0 x 10^9/L, and one platelet count ≥ 75 x 10^9/L; and within 4 weeks prior to study drug administration had one reticulocyte Hgb content > 29 pg, one transferrin saturation ≥ 15%, one serum or red cell folate level above the lower limit of normal, and one vitamin B_{12} level above the lower limit of normal.

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, 30, or 50 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, Tween® 20 (polysorbate 20), sorbitol, sodium hydroxide, and Water for Injection. Doses of AF37702 Injection were to be administered SC Q3W for a total of four doses. Four starting dose levels of AF37702 Injection were evaluated in this study: 0.1 mg/kg (Cohort 1), 0.15 mg/kg (Cohort 2), 0.2 mg/kg (Cohort 3), and 0.05 mg/kg (Cohort 4). The lot numbers of AF37702 Injection used in the trial were PLI005-05 (10 mg/mL), PLI006-06 (10 mg/mL), PLI040-06 (10 mg/mL), PLI023-05 (30 mg/mL), and PLI012-06 (50 mg/mL).

Duration of Treatment:

Doses of AF37702 Injection were to be administered SC Q3W for a total of four doses equaling 9 weeks of treatment. All patients were to be followed for a minimum of 28 days following the last dose of AF37702 Injection.

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

Not applicable.

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Criteria for Evaluation:

Pharmacodynamics: Pharmacodynamics (PDs) were assessed by evaluation of Hgb, reticulocytes, red blood cell (RBC) count, hematocrit, reticulocyte Hgb content, ferritin, transferrin saturation, and soluble transferrin receptor protein. The PD population (N=49) consisted of patients who received at least two doses of AF37702 Injection and had at least two Hgb values at or after 6 weeks following Dose 1.

Safety: Safety was assessed through AEs, laboratory evaluations, vital signs, antibody evaluations, transfusions, bleeding events, phlebotomies, and physical findings. The safety population (N=60) consisted of all patients who received at least one dose of study drug.

Pharmacokinetics: The PKs of AF37702 Injection were determined from the plasma concentration-time data. The PK population consisted of a subset of patients with serial blood draws for AF37702 concentration measurements with records of the times of dosing and blood draws.

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 of means, medians, standard deviations, and minimum and maximum values for continuous measures. Summary statistics were presented for each dose group. Individual patient listings of all data reported on the case report forms were prepared. PK parameters were calculated by compartmental methods using SAAM II Version 1.2.1 and included C_{max}, $AUC_{(0-\infty)}$, T_{max}, CL/F, V/F, and $T_{1/2}$.

Summary and Conclusions:

Pharmacodynamic Results, PD population (N=49)

The primary objective of this study was to determine the dose of AF37702 Injection administered Q3W by SC injection associated with a Hgb increase of ≥ 1 g/dL in ≥ 50% of anemic cancer patients receiving chemotherapy at 9 weeks following Dose 1. In the PD population, the 0.1 mg/kg and 0.15 mg/kg dose groups were both associated with a Hgb increase of ≥ 1 g/dL in ≥ 50% patients at 9 weeks following Dose 1, 63.6% in both dose groups. The 0.05 mg/kg and 0.2 mg/kg dose groups had smaller proportions, 16.7% and 33.3 %, respectively. A Hgb increase of ≥ 1 g/dL in ≥ 50% patients was also seen at 3, 6, and 12 weeks following Dose 1 in the 0.1 mg/kg dose group, and at 6 and 12 weeks following Dose 1 in the 0.15 mg/kg dose group. The median time to achieve Hgb increase ≥ 1 g/dL from baseline was shortest in the 0.1 mg/kg dose group (24.0 days) followed by the 0.15 mg/kg and 0.05 mg/kg dose groups (29.0 days each), and the 0.2 mg/kg dose group (50.0 days). In the 0.05 mg/kg dose group, mean Hgb values were maintained near baseline during the study.

A Hgb response was defined as a ≥ 2 g/dL increase in Hgb from baseline, or a Hgb increase of ≥ 1 g/dL to at least 12 g/dL, at 3, 6, 9, and 12 weeks following Dose 1, in the absence of RBC transfusion in the previous 28 days. The 0.1 mg/kg dose group had the largest proportion of patients with a Hgb response at 3, 6, 9, and 12 weeks following Dose 1 (45.5%, 54.5%, 63.6%, and 54.5%, respectively) followed by the 0.15 mg/kg dose group (18.2%, 45.5%,

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45.5%, and 45.5%, respectively). The median time to achieve a Hgb response was the shortest in the 0.1 mg/kg dose group (36.0 days) followed by the 0.15 mg/kg dose group (43.0 days).

A majority of patients in the 0.1 mg/kg dose group had Hgb in the target range of 11 to 13 g/dL at 3, 6, and 12 weeks following Dose 1 (54.5% at each time point). Less than half of the patients in the 0.15, 0.2, and 0.05 mg/kg dose groups had Hgb in the target range at 3, 6, 9 or 12 weeks following Dose 1; the 0.15 mg/kg dose group had the largest proportion at 9 weeks following Dose 1 (45.5%). The 0.1 mg/kg, 0.15 mg/kg, and 0.2 mg/kg dose groups had increases in mean Hgb from baseline with sustained increases through 13 weeks following Dose 1 (end of study). Mean Hgb in the target range of 11 to 13 g/dL was achieved 4 weeks following Dose 1 and maintained thereafter through the end of study in the 0.1 mg/kg dose group, and achieved at 4 weeks following Dose 1 and maintained from 6 weeks following Dose 1 to the end of the study in the 0.15 mg/kg dose group. The 0.2 mg/kg dose group initially achieved mean Hgb levels in the target range of 11 to 13 g/dL at 4 weeks following Dose 1, but levels within this target range were not sustained. Mean Hgb levels in the target range were not achieved in the 0.05 mg/kg dose group.

Weekly monitoring of reticulocyte values showed that AF37702 Injection resulted in a predictable cyclical reticulocyte response pattern following dosing in all dose groups.

<u>Safety Results, safety population (N=60)</u>

Of the 60 patients who received AF37702 Injection, 45 (75.0%) experienced an AE: 60.0% in the 0.1 mg/kg dose group, 73.3% in the 0.15 mg/kg dose group, 93.3% in the 0.2 mg/kg dose group, and 73.3% in the 0.05 mg/kg dose group. The most frequently reported AEs were nausea (21.7%), pyrexia (11.7%), vomiting (11.7%), anaemia (10.0%), and dyspnoea (10.0%) across dose groups.

Three AEs were assessed by the Investigator as Grade 5 (death related to AE) per the NCI-CTCAE: peripheral T-cell lymphoma unspecified (1 patient in the 0.15 mg/kg dose group), pulmonary oedema (1 patient in the 0.15 mg/kg dose group), and renal failure (1 patient in the 0.05 mg/kg dose group). Grade 4 (life-threatening or disabling) AEs were: neutropenic sepsis (5.0%), pancytopenia (5.0%), febrile neutropenia (3.3%), leukopenia (3.3%), neutropenia (3.3%), acute respiratory distress syndrome (1.7%), alopecia (1.7%), anaemia (1.7%), diarrhoea (1.7%), platelet count decreased (1.7%), and thrombocytopenia (1.7%).

Eighteen patients (30.0%) experienced an AE reported as serious by the Investigator: 20.0% in the 0.1 mg/kg dose group, 33.3% in the 0.15 mg/kg dose group, 33.3% in the 0.2 mg/kg dose group, and 33.3% in the 0.05 mg/kg dose group. Serious adverse events (SAEs) reported in two or more patients were: febrile neutropenia (5 patients, 8.3%), neutropenia (3 patients, 5.0%), pancytopenia (3 patients, 5.0%), neutropenic sepsis (3 patients, 5.0%), anaemia (2 patients, 3.3%), and infection (2 patients, 3.3%).

Four deaths occurred during the study, none of which were reported as treatment-related: pleural effusion and decreased performance status (0.1 mg/kg dose group), pulmonary oedema (0.15 mg/kg dose group), peripheral T-cell lymphoma unspecified (0.15 mg/kg dose group), and renal failure (0.05 mg/kg dose group).

Ten patients withdrew from the study due to AEs.

Treatment-related AEs (i.e., AEs considered possibly or probably related to AF37702 Injection) were experienced

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by 8 patients (13.3%) among three of the four dose groups: 2 (13.3%) occurred in the 0.15 mg/kg dose group, 4 (26.7%) in the 0.2 mg/kg dose group, and 2 (13.3%) in the 0.05 mg/kg dose group. The most frequently reported treatment-related AEs were constipation, nausea, vomiting, haematology test abnormal, and reticulocyte count increased, each experienced by 2 of 60 (3.3%) patients.
One treatment-related AE of alopecia (0.2 mg/kg dose group) was assessed by the Investigator as Grade 4, with all other treatment-related AEs assessed as Grade 1 or 2. No treatment-related AEs were assessed as Grade 5.
One treatment-related AE was reported as serious: thrombophlebitis, Grade 2, with onset 19 days following Dose 1 (0.15 mg/kg dose group); this was the only treatment-related AE for which study drug was discontinued. One patient withdrew from the study due to a non serious AE that was reported as treatment-related: thrombophlebitis superficial, Grade 2, with onset 21 days following Dose 1 (0.05 mg/kg dose group).

Pharmacokinetic Results

Four patients were enrolled into the PK subgroup of the study; all four patients were enrolled in the 0.1 mg/kg dose group. One of the four patients dropped out of the study after the second dose. Concentration data from this one patient were included in calculation of mean and median concentration data, but not in the model-derivation of PK parameters due to insufficient data.
Following SC injection, AF37702 is absorbed slowly (ka = 0.026 ± 0.010 h^{-1}) with an absorption lag time of 4.10 ± 3.74 hours.
Once absorbed systemically, the distribution and elimination of AF37702 are first order. Mean elimination rate is 0.007 ± 0.002 h^{-1} giving a terminal half-life of 107.0 ± 31.6 hours
Apparent clearance and apparent volume of distribution are 0.98 ± 0.30 mL/h•kg and 145.9 ± 50.7 mL/kg, respectively. Intravenous data in this patient population is required for determination of absolute clearance, absolute volume of distribution and bioavailability of AF37702.
No change in PK is observed following repeated (Q3W) SC injection of AF37702 at a dose of 0.1 mg/kg. No accumulation was detected.

Conclusions

The primary objective of this study was to determine the dose of AF37702 Injection administered Q3W by SC injection associated with a Hgb increase of ≥ 1 g/dL in ≥ 50% of anemic cancer patients receiving chemotherapy at 9 weeks following Dose 1. In the PD population, the 0.1 mg/kg and 0.15 mg/kg dose groups were both associated with a Hgb increase of ≥ 1 g/dL in ≥ 50% patients at 9 weeks following Dose 1, 63.6% in both dose groups, while the 0.05 mg/kg and 0.2 mg/kg dose groups had lower proportions, 16.7% and 33.3 %, respectively.
Pharmacologic activity was observed at AF37702 Injection doses of 0.05, 0.1, 0.15, and 0.2 mg/kg, administered SC Q3W, although a dose-response relationship was not apparent in the 0.1 to 0.2 mg/kg dose range. Dosing at 0.1 and 0.15 mg/kg Q3W achieved mean Hgb in the target range of 11 to 13 g/dL and sustained target levels through 13 weeks following Dose 1 (end of study). The 0.2 mg/kg dose group had the highest frequency of dose reductions although conclusions regarding the impact of dose reductions on PD parameters cannot be made due to the small sample size.

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Among the dose groups, the highest dose group, 0.2 mg/kg, had the largest proportion of patients with AEs. The 0.1 mg/kg dose group had the lowest proportion of patients with AEs. Two thrombovascular events were experienced by two patients, one of which was reported as serious and both of which were reported as treatment-related (possibly or probably related to AF37702 Injection): thrombophlebitis and thrombophlebitis superficial. The most frequent AEs across the dose groups were consistent with those seen in this patient population.

Due to the small sample size (n=3) used to characterize the AF37702 PK in this study, the data should not be taken as definitive until more determinations are made.

At all starting doses evaluated, AF37702 Injection given Q3W SC demonstrated the ability to increase Hgb in cancer patients undergoing chemotherapy, but clinically meaningful and sustained increases were only seen with the 0.1 and 0.15 mg/kg Q3W starting dose cohorts. The lack of apparent dose response is most likely due to the relatively small numbers of patients in each cohort. Multiple SC doses of AF37702 Injection were well tolerated by these cancer patients receiving chemotherapy. While the safety and pharmacodynamic findings of this study are encouraging, larger trials are needed to fully define the role of AF37702 Injection in the treatment of anemia due to chemotherapy.

Date of Report: 28 October 2008