

EXHIBIT L

**Pre-clinical Pharmacokinetics and
Pharmacodynamics of CERA
(Continuous Erythropoiesis Receptor Activator)
Indicate a Superior New Therapy for Anemia**

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Pre-clinical Pharmacokinetics and Pharmacodynamics of CERA (Continuous Erythropoiesis Receptor Activator) Indicate a Superior New Therapy for Anemia

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Abstract

Background: Correction of anemia associated with cancer and other chronic diseases requires long-term treatment with epoetin. The development of an agent that allows less frequent dosing with improved efficacy should improve the quality and quality of life of patients. CERA (Continuous Erythropoiesis Receptor Activator) is an innovative agent for the treatment of anemia currently in clinical development.

Purpose and Methods: The pharmacokinetic and pharmacodynamic properties of CERA were determined in rodents and non-rodent species. The efficacy of CERA was evaluated in a rat model of anemia. The pharmacokinetic and pharmacodynamic properties of CERA were compared in the pharmacokinetic model using single doses as well as daily following injection of single doses. The influence of route of administration on CERA activity was also evaluated. In addition, the erythropoietic activity of CERA was tested in a non-rodent model treated once weekly over a period of 4 weeks.

Results: In these animal models, the systemic clearance of CERA was much lower than that of epoetin. In rats that received a subcutaneous injection of CERA, the mean half-life was approximately 100 hours, compared with 18 hours for the same dose of epoetin. The mean elimination half-life of CERA was approximately 100 hours. A single injection of 20 µg/kg of CERA resulted in an increase in mean hemoglobin of 10% (n=12), compared with an increase of 8% for the same dose of epoetin. The mean duration of response lasted 4 weeks. In contrast, CERA was 3 days shorter than epoetin in terms of mean hemoglobin. In addition, CERA was 3 days shorter than epoetin in terms of mean hemoglobin. In addition, CERA was 3 days shorter than epoetin in terms of mean hemoglobin. In addition, CERA was 3 days shorter than epoetin in terms of mean hemoglobin.

Background

- Anemia is a very common complication in patients with hematologic malignancies, with incidence rates of over 50%.
- Low hemoglobin (Hb) levels have been associated with fatigue and poor response resulting in a compromised quality of life.
- There is consensus in cancer that anemia may worsen prognosis.
- In fact, the treatment of anemia to reduce an integral part of cancer management.
- Treatment with recombinant human erythropoietin (rHuEPO) has been shown to improve the quality of life in patients with hematologic malignancies. Despite this, a considerable number of cancer patients with anemia do not receive erythropoietic therapy.
- An important advance in the management of anemia would be the development of a novel erythropoietic agent that allowed:
 - less frequent dosing (e.g. weekly or 4 weeks or every 3 months or longer)
 - improved or improved efficacy.

Purpose and Methods

- The properties of CERA (Continuous Erythropoiesis Receptor Activator) were assessed in several studies in rodent and dog models. Pharmacokinetic parameters (clearance and half-life) were determined in rats and dogs. Pharmacodynamic parameters (hemoglobin and erythropoietin) were determined in rats and dogs. The mean duration of response lasted 4 weeks. In contrast, CERA was 3 days shorter than epoetin in terms of mean hemoglobin. In addition, CERA was 3 days shorter than epoetin in terms of mean hemoglobin.

Results

- In animal models, the systemic clearance of CERA was much lower than that of epoetin. In dogs that received a subcutaneous injection of CERA, the mean half-life was approximately 100 hours, compared with 18 hours for the same dose of epoetin. The mean elimination half-life of CERA was approximately 100 hours. A single injection of 20 µg/kg of CERA resulted in an increase in mean hemoglobin of 10% (n=12), compared with an increase of 8% for the same dose of epoetin. The mean duration of response lasted 4 weeks. In contrast, CERA was 3 days shorter than epoetin in terms of mean hemoglobin. In addition, CERA was 3 days shorter than epoetin in terms of mean hemoglobin.

Table 1. Mean plasma concentrations of CERA compared with epoetin following subcutaneous administration.

Administration route	CERA 2.5 µg/kg (n=12)		Epoetin 2.5 µg/kg (n=12)	
	C _{max} (ng/ml)	AUC _{0-24h} (ng·h/ml)	C _{max} (ng/ml)	AUC _{0-24h} (ng·h/ml)
SC	10.0 (3.0-14.0)	3.6 (1.5-6.0)	10.0 (3.0-14.0)	3.6 (1.5-6.0)
IV	10.0 (3.0-14.0)	3.6 (1.5-6.0)	10.0 (3.0-14.0)	3.6 (1.5-6.0)

Table 2. Effect on erythropoiesis in mice following SC administration of single dose CERA 20 µg/kg, single dose epoetin 20 µg/kg or multiple dose epoetin 20 µg/kg.

Group	Hb (g/dl)	Mean ± SD
Single dose CERA 20 µg/kg	13.1 ± 1.3	14 (10-18)
Single dose epoetin 20 µg/kg	12.8 ± 1.2	13 (10-16)
Multiple dose epoetin 20 µg/kg	12.5 ± 1.1	12 (10-14)

Figure 1. Effect on erythropoiesis in mice following SC administration of single dose CERA 20 µg/kg, single dose epoetin 20 µg/kg or multiple dose epoetin 20 µg/kg.

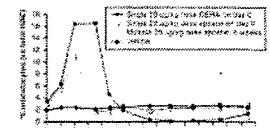


Figure 2. Effect on erythropoiesis in mice following SC or IV administration of single dose CERA 20 µg/kg, single dose epoetin 20 µg/kg or multiple dose epoetin 20 µg/kg.

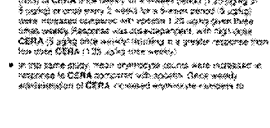


Figure 3. Effect on erythropoiesis in mice following SC or IV administration of single dose CERA 20 µg/kg, single dose epoetin 20 µg/kg or multiple dose epoetin 20 µg/kg.

17.1 ± 0.8 and 13.7 ± 0.7 g/dl at doses of 5 µg/kg and 1.25 µg/kg, respectively. After a single 2-week administration of CERA 2.5 µg/kg, mean hemoglobin levels in 12 mice were 13.1 ± 1.3 g/dl (range 10-18 g/dl), compared with 12.5 ± 1.1 g/dl (range 10-14 g/dl) in mice treated with epoetin. The mean duration of response lasted 4 weeks. In contrast, CERA was 3 days shorter than epoetin in terms of mean hemoglobin. In addition, CERA was 3 days shorter than epoetin in terms of mean hemoglobin.

Figure 2. Effect on erythropoiesis in mice following SC administration of single dose CERA 20 µg/kg, single dose epoetin 20 µg/kg or multiple dose epoetin 20 µg/kg.

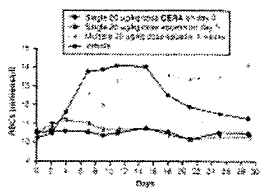


Figure 3. Effect on erythropoiesis in mice following SC or IV administration of single dose CERA 20 µg/kg, single dose epoetin 20 µg/kg or multiple dose epoetin 20 µg/kg.

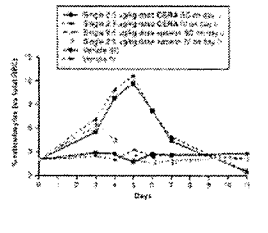


Figure 3. Effect on erythropoiesis in mice following SC or IV administration of single dose CERA 20 µg/kg, single dose epoetin 20 µg/kg or multiple dose epoetin 20 µg/kg.

- CERA was shown to be a more potent stimulator of erythropoiesis than epoetin in studies in mice. It steps the duration of erythropoietic response was increased with CERA compared with epoetin following both SC and IV administration.
- Administration of CERA to non-rodent species (mice, rats, dogs) under conditions of chronic renal failure and erythropoietin deficiency resulted in a dose-dependent increase in mean hemoglobin. No such increase was observed in animals treated with epoetin. Dose- and time-dependent increases in hemoglobin levels and the duration of response were also observed following treatment with CERA. These findings were consistent with those seen in studies of non-rodent species.

Conclusions

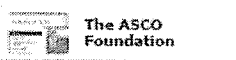
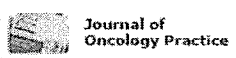
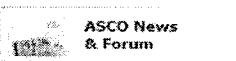
- CERA is an innovative new erythropoietic agent with a lower systemic clearance and an increased serum half-life compared with epoetin.
- In animal studies, CERA appears to be a more potent stimulator of erythropoiesis than epoetin, both with regard to magnitude and duration of response.
- The observed erythropoietic effect of CERA is dose-dependent and specific.
- Erythropoietic response is comparable after both SC and IV administration of CERA.
- The unique pharmacodynamic and pharmacokinetic properties of CERA suggest that it may represent a significant development in the treatment of anemia, offering enhanced erythropoietic activity and the opportunity of increased dosing intervals for greater flexibility and convenience.

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Pre-clinical and phase I pharmacokinetic and mode-of-action studies of CERA (continuous erythropoiesis receptor activator), a novel erythropoietic agent with an extended serum half-life

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Abstract No: 3006

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Abstract: CERA is a novel erythropoietic agent for the treatment of anemia. Pharmacokinetic properties of CERA were investigated in animal models and in 2 placebo-controlled studies of healthy male volunteers randomized to receive single doses of CERA 0.4-3.2 µg/kg by intravenous (IV) injection or CERA 0.1-3.2 µg/kg by subcutaneous (SC) injection. In addition, the erythropoietic activity of CERA was compared with that of epoetin using a normocythemic mouse model and *in vitro* using a UT-7 (human myeloid leukemia cell line) proliferation assay. Binding to the erythropoietin (EPO) receptor was compared *in vitro* using a soluble EPO receptor-binding assay. Median serum half-life of CERA was 7-fold greater than that of epoetin following IV injection in dogs (49.0 vs 6.4 h). In healthy volunteers, mean serum half-life for CERA ranged between 70-122 h after IV and 102-146 h after SC administration depending on dose. AUC and Cmax increased more than proportionally with dose. In the receptor-binding assay, association rates of CERA and epoetin with soluble EPO receptor were similar whereas the dissociation rate of CERA was higher than that of epoetin. CERA had greater erythropoietic activity than epoetin in the normocythemic mouse but not *in vitro* (dose range 0.003-3 U/ml). Taken together, these data suggest that CERA binds less tightly to the EPO receptor and dissociates more quickly compared with epoetin. A novel mode of action is proposed by which rapid dissociation from the erythropoietin receptor together with an extended serum half-life result in an enhanced and sustained erythropoietic effect through continuous modulated stimulation of erythropoiesis. These pharmacokinetics may lead to enhanced erythropoietic activity, less frequent dosing and optimal patient outcomes.

Associated Presentation(s):

1. **Pre-clinical and phase I pharmacokinetic and mode-of-action studies of CERA (continuous erythropoiesis receptor activator), a novel erythropoietic agent with an extended serum half-life**

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