EXHIBIT L

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

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Presented at

The American Society of Hematology

44th Annual Meeting

December 6–10, 2002

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 sustained or improved efficacy should improve the choice and quality of treatment. 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 rodent and non-rodent species. The systemic clearance of CERA was assessed in rats and dogs following injection of single doses. The pharmacodynamic properties of CERA and epoetin were compared in the normocythaemic mouse model, using single doses as well as repeated administration over several weeks. The influence of route of administration on CERA activity was also evaluated. In addition, the erythropoietic activity of CERA was tested in nephrectomized rats treated once weekly over a period of 6 weeks.

Results: [illegible]

Summary: [illegible]

Background

- [illegible]

Purpose and Methods

- The properties of CERA (Continuous Erythropoiesis Receptor Activator) were assessed in several studies in rodent and dog [illegible]

Results

- [illegible]

Table 1. [illegible]

[illegible]	[illegible]	[illegible]

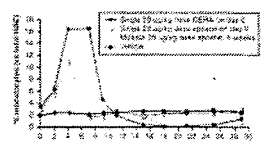

Figure 1. Effect on reticulocytes in mice following SC administration of single dose CERA 20 µg/kg, single dose epoetin 20 µg/kg or multiple dose epoetin 20 µg/kg

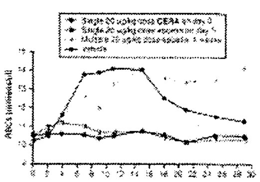

Figure 2. Effect on erythrocytes in mice following SC administration of single dose CERA 20 µg/kg, single dose epoetin 20 µg/kg or multiple dose epoetin 20 µg/kg

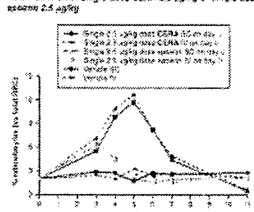

Figure 3. Effect on reticulocytes in mice following SC or IV administration of single dose CERA 2.5 µg/kg or single dose epoetin 2.5 µg/kg

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.

References

1. [illegible]
2. [illegible]
3. [illegible]
4. [illegible]
5. [illegible]
6. [illegible]

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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

Printer Friendly
E-Mail Article

Sub-category: Supportive Care

Category: Patient Care

Meeting: 2003 ASCO Annual Meeting

Abstract No: 3006

Author(s): A. Haselbeck, B. Reigner, P. Jordan, A. Pannier, J. Glaspy; F. Hoffmann-La Roche, Penzberg, Germany; F. Hoffmann-La Roche, Basel, Switzerland; UCLA School of Medicine, Los Angeles, CA

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**

No presentation available
Meeting: 2003 ASCO Annual Meeting
Presenter: Anton Haselbeck, PhD
Session: Palliative, Supportive, and Elderly Care (General Poster Session)

Other Abstracts in this Sub-Category

1. Safety and efficacy evaluation of concurrent dosing of pegfilgrastim with multi-day regimens of etoposide or topotecan in male rats

Meeting: 2003 ASCO Annual Meeting **Abstract No:** 582 **First Author:** A. M. Standeven
Category: Patient Care - Supportive Care

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