EXHIBIT I

CERA (Continuous Erythropoiesis Receptor Activator), an innovative erythropoietic agent: dose-dependent response in phase I studies

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Abstract

CERA (Continuous Erythropoiesis Receptor Activator), an innovative erythropoietic agent with an extended serum half-life, promotes a greater erythropoietic response than epoetin in animal models. In these two phase I studies, healthy male volunteers were randomized to receive IV single doses of CERA 0.4, 0.8, 1.6 or 3.2 µg/kg or placebo (n=40) or SC single doses of CERA 0.1, 0.2, 0.4, 0.8, 1.6, 2.4 or 3.2 µg/kg or placebo (n=70). A potent dose-dependent erythropoietic response was observed with both IV and SC administration. Response to CERA was rapid with peak increases in reticulocytes occurring within 10 days and levels returning to baseline after 20 days. After IV administration, mean (± SD) reticulocyte response to CERA 0.4 µg/kg was an increase of 115% (± 47%) over baseline, indicating that the minimum threshold dose for erythropoiesis was possibly less than the lowest study dose used. The maximum erythropoietic effect did not appear to have been reached with the highest study dose of 3.2 µg/kg, which produced a mean reticulocyte increase of 334% (± 100%). Threshold minimum dose for stimulation of erythropoiesis after SC administration of CERA was 0.8 µg/kg. At the highest SC dose, mean increase in reticulocytes was 252% (± 83%). Soluble transferrin receptor levels also increased in a dose-dependent manner after IV or SC injection while serum ferritin and serum iron levels decreased, reaching a nadir 5–10 days after administration before returning to baseline. CERA was very well tolerated following both routes of administration. In conclusion, IV and SC CERA has a potent, prolonged dose-dependent erythropoietic activity. Phase II studies of CERA administered every 3 weeks to patients with cancer are ongoing.

Background

- Anemia is very common in patients with cancer with a prevalence of approximately 50%.[1]
- Anemia worsens prognosis in cancer patients,[1-4] and is associated with impaired quality of life (QoL).[2]
- Consequently, treatment of anemia is considered to be an integral part of cancer management.
- Recombinant human erythropoietin (rHuEPO, epoetin) is effective in the management of anemia in cancer patients, and has been shown to increase hemoglobin (Hb) levels, reduce need for blood transfusions and improve QoL.[4]
- Recent evidence suggests that treatment with epoetin improves tumor control and may improve survival in patients with cancer.[5-7]
- CERA (Continuous Erythropoiesis Receptor Activator) is an innovative erythropoietic agent that promotes a greater erythropoietic response than epoetin in animal models.[8]
- Data also indicate that CERA has a prolonged elimination half-life that may allow less frequent clinical dosing (e.g. every 3 or 4 weeks).
- The greater erythropoietic response with CERA and the prolonged half-life may therefore provide an important advance in the treatment of cancer-related anemia.

Purpose

- To assess the dose-response pharmacodynamics of CERA, administered intravenously (IV) and subcutaneously (SC), in healthy subjects.
- To determine the safety and tolerability profile of CERA in these subjects.

Methods

- Healthy male subjects (n=110) were enrolled into two single-center, single-blind, placebo-controlled studies.
- Study 1 involved a total of 38 subjects (18–50 years), who received a single IV dose of CERA (0.4–3.2 µg/kg) or placebo.
- Study 2 involved a total of 70 subjects (18–45 years), who received a single SC dose of CERA (0.1–3.2 µg/kg) or placebo.
- Reticulocyte counts, red blood cell (RBC) counts, hematocrit (Hct), Hb, ferritin and soluble transferrin receptor levels were used as markers of pharmacodynamic response to CERA.
- Safety and tolerability measures were assessed in subjects receiving CERA and placebo; tests were also performed for the presence of anti-erythropoietin antibodies.

Results

- CERA induced a dose-dependent increase in reticulocyte counts with IV and SC administration (Figures 1 and 2); reticulocyte counts peaked at day 10, and had returned to baseline by day 20.

Figure 1. Mean reticulocyte count over time following IV administration of CERA

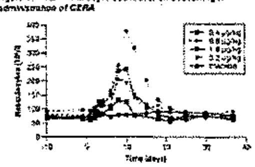
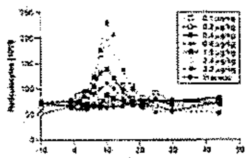
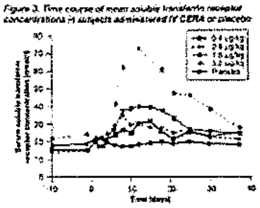


Figure 2. Mean reticulocyte count over time following SC administration of CERA



- The minimum study dose with IV administration (0.4 µg/kg) produced a mean (± SD) increase in reticulocyte count of 115% (± 47%) over baseline; this indicates that the minimum threshold dose may be even lower.
- With SC administration, the minimum threshold dose for stimulation of erythropoiesis was 0.8 µg/kg, inducing an increase in reticulocyte count of 91% (± 34%) over baseline.

Figure 3. Time course of mean soluble transferrin receptor concentrations in subjects administered IV CERA or placebo



A dose-dependent increase in soluble transferrin receptor concentration was also seen with SC CERA administration (data not shown).

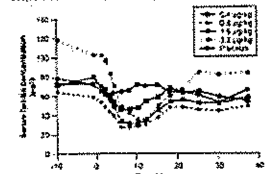
- The mean (± SD) increases in reticulocyte counts observed with the highest study dose (3.2 µg/kg) were 334% (± 100%) and 252% (± 83%) with IV and SC administration, respectively.

Table 1. Baseline-corrected mean (± SD) AUECs for hematologic parameters after IV and SC administration of CERA

CERA dose (µg/kg)	Hct (%·day)	Hb (g·day/dl)	RBC (10^{12}·day/l)
Study 1 (IV)			
Placebo	-3.7 ± 50.7	-6.9 ± 12.8	-1.5 ± 5.4
0.4	18.8 ± 31.9	9.6 ± 14.7	-3.3 ± 3.6
0.8	40.0 ± 39.1	2.4 ± 12.8	1.3 ± 3.8
1.6	72.8 ± 51.9	10.6 ± 14.3	3.5 ± 4.3
3.2	72.4 ± 49.2	14.9 ± 10.6	4.4 ± 4.8
Study 2 (SC)			
Placebo	-34.3 ± 43.9	-7.5 ± 13.4	-2.8 ± 4.6
0.1	1.4 ± 31.9	3.1 ± 11.6	-2.0 ± 2.9
0.2	-20.6 ± 33.7	-10.1 ± 15.2	-3.8 ± 4.6
0.4	-41.7 ± 48.5	-17.8 ± 12.6	-4.5 ± 4.5
0.8	10.5 ± 27.4	-2.1 ± 13.6	1.6 ± 3.8
1.6	15.2 ± 50.0	5.8 ± 18.7	1.5 ± 5.3
2.4	81.4 ± 54.5	25.6 ± 12.8	11.2 ± 7.2
3.2	56.6 ± 54.7	22.8 ± 19.6	7.4 ± 5.0

- The mean baseline-corrected areas under the effect curve (AUECs) from day 1–27 for the hematologic parameters are shown in Table 1. Increases in Hct, Hb and RBC counts were observed with increasing dose of CERA in both the IV and SC groups. Inter-subject variability in these parameters was higher in the SC group, possibly due to the influence of dose, volume and injection site.
- An increase in soluble transferrin receptor concentration was observed with increasing doses of IV CERA (Figure 3). A decrease in serum ferritin concentration was seen with increasing IV CERA dose (Figure 4). These reached a nadir 5–10 days post-administration before returning to baseline. Similar data were observed following SC administration (not shown).
- CERA was well tolerated in all enrolled subjects who received it (n=[illegible]). No serious adverse events were reported in subjects receiving CERA in either study, and there were no relevant differences in the number of adverse events between active and placebo groups.
- No anti-erythropoietin antibodies were detected in any of the subjects receiving CERA.

Figure 4. Time course of mean serum ferritin concentrations in subjects administered IV CERA or placebo



A dose-dependent decrease in serum ferritin concentration was also seen with SC CERA administration (data not shown).

Conclusion

- In phase I studies, CERA induced potent, prolonged, dose-dependent stimulation of erythropoiesis following IV and SC administration.
- The potent and sustained erythropoietic response to CERA may represent a significant development in the management of anemia in cancer patients, enabling longer intervals between doses.
- Phase II trials with CERA are currently ongoing, and are designed to establish effective dosages and dosing intervals for Hb correction and maintenance in cancer patients.

References

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