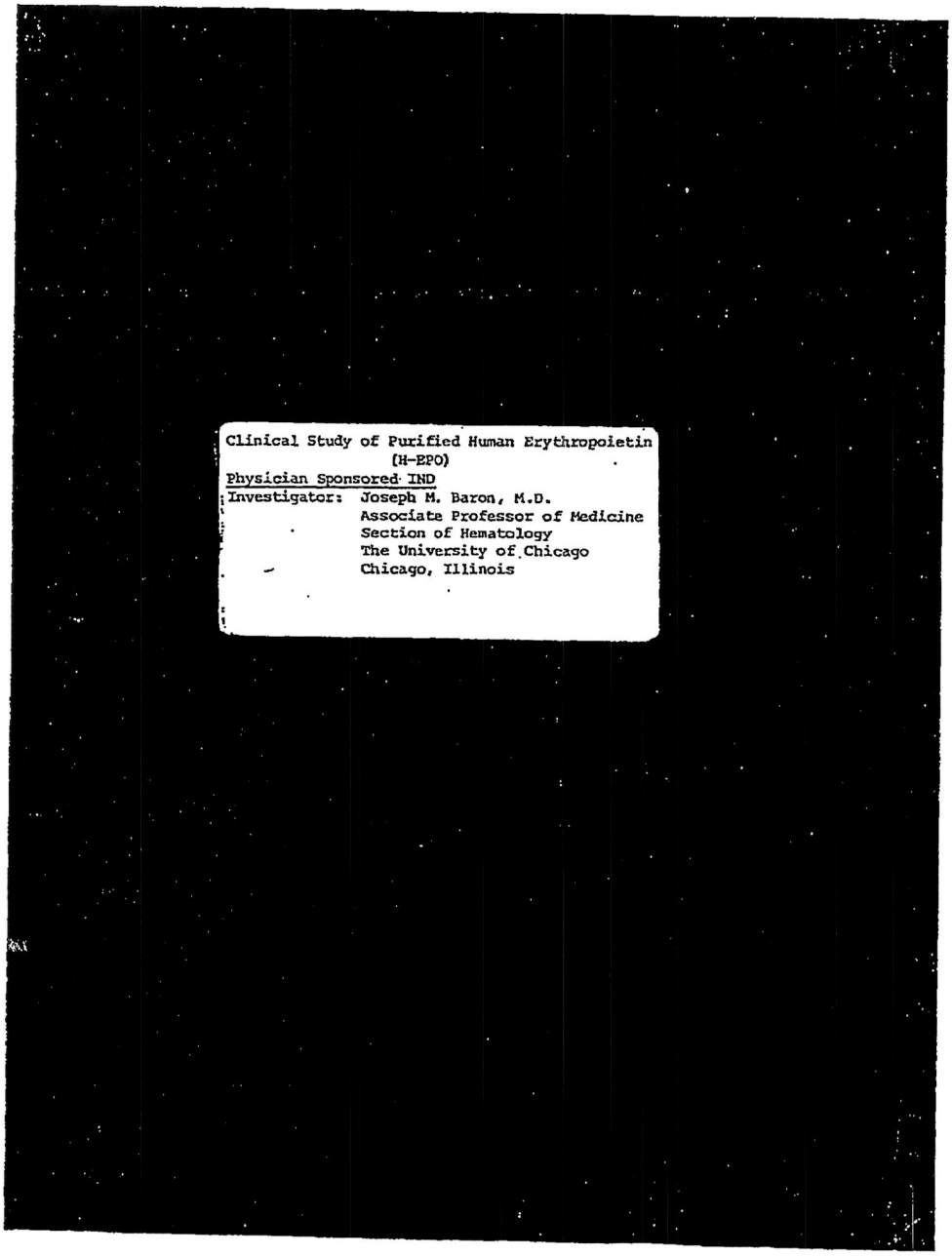
Exhibit 2050
05-12237-WGY



BARON 00036

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February 6, 1984

National Center for Drugs and
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HFN-110
5600 Fishers Lane
Rockville, MD 20857

RE: IND 16,234
Clinical Investigatation of
Human Erythropoietin

Progress Report

Attn: Document Control
Room 16B-45

Dear Sir:

Purified human erythropoietin (H-EPO) has been administered intravenously to 5 individuals since inception of our studies. Three patients with a chronic renal failure on hemodialysis were the first to receive the hormone in 1979 and 1980. Most recently, two normal volunteers received single injections of the hormone (June and July, 1983) to assess pharmacokinetics in comparison with the renal failure patients. The first two patients with chronic renal failure received 20 intravenous doses of the hormone (q 12 hrs for a 10 day period) in the Clinical Research Center at the University of Chicago. The third individual received initial doses as an inpatient and then follow-up injections every 2-3 days immediately following outpatient dialysis over the subsequent three-week period. The two normal individuals received their injections of the hormone in the Clinical Research Center and were monitored as per protocol.

I. Safety

No acute, subacute, or chronic adverse reactions have been noted to date. The three patients with chronic renal failure continue in the dialysis program at the University of Chicago at the present time.

II. Pharmacokinetics

The disappearance curves of erythropoietin after single intravenous doses were complex, with an unexpectedly rapid initial T-½ (ranging from .11 to .472 hours in the group of 5 individuals with overlap between the normals and the chronic renal failure patients) and a slower secondary decay following a second small peak. Analysis of the second serum peak detected by the radioimmunoassay

in one of the individuals with chronic renal failure revealed the presence of smaller molecular weight material (?subunits or breakdown products) than injected erythropoietin. These data were not derived from studies in steady state conditions because of lack of sufficient hormone to achieve this by continuous infusion. Of interest was the similar shape of the curves in the renal failure patients and the two normal volunteers. There was insufficient material under the second peak to assay for bioactivity.

Patients with renal failure had minimal urine outputs, thus eliminating urinary excretion of erythropoietin as a factor in analysis of the serum decay curves. In the two normal volunteers with normal urine outputs, the erythropoietin excretion in the urine did not represent more than a trace amount of injected hormone in each subject.

III. Biological Efficacy

Hematologic parameters in the three patients with chronic renal failure were assessed prior to and following erythropoietin administration as outlined in the submitted protocol. There was no significant increase in the hematocrit observed, however, each patient showed a mild to modest increase in reticulocyte number with peaks noted at days 9, 10, and 11, respectively. Two of the three patients showed increased numbers of nucleated red cells/1000 bone marrow cells and the disappearance of radio-iron from plasma was shortened in two of the three individuals. One of the three patients showed an increase in red cell mass following the treatment program.

IV. Summary

Purified erythropoietin has been studied in five individuals to date without adverse effects. Similarly rapid initial disappearance rates followed by slower secondary decay of serum radioimmunoassay detectable erythropoietin levels was seen in two normal volunteers and in three patients with chronic renal failure. In each instance a second peak of radioactivity was seen during the plasma disappearance curve studies and in one individual this was shown to contain material of smaller molecular weight than the initial injected erythropoietin. Definite evidence of erythroid marrow stimulation was detected, but no dramatic hematologic effect could be documented during the relatively short treatment.

V. Comment

In view of the extensive renal osteodystrophic changes seen in the bone marrows of the individuals with chronic renal disease, it is not surprising that no further

stimulatory effect was observed during the short treatment. This observation is consistent with the prolonged time course for erythroid marrow recovery seen with the use of androgens (usually three to five months or more) or following successful renal transplantation (correction of anemia, when it occurs, at 6 to 12 weeks following successful transplantation).

Pending availability of sufficient amounts of purified hormone in preparation, we intend to conduct further studies which would permit steady state estimates of erythropoietin pharmacokinetics and permit the more prolonged therapy needed to adequately assess the potential role of erythropoietin administration in the therapy of anemia of chronic renal disease.

Respectfully submitted,

Joseph M. Baron

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October 2, 1985

Natalia A. Morgenstern
Supervisory Consumer Safety Officer
Division of Cardio-Renal Products
Office of Drug Research and Review
Center for Drugs and Biologics
Department of Health
and Human Services
Food and Drug Administration
Rockville, Maryland 20857

Dear Ms. Morgenstern:

Thank you for your letter of September 12, 1985, regarding IND #16,234. There have been no further studies performed under this claimed investigational exemption since our last report to you. These follow-up studies have been delayed because of lack of availability of sufficient amounts of purified human urinary erythropoietin to permit us to carry out the investigations. We expect that adequate amounts of the hormone will be forthcoming within the next several months and that we will be able to continue studies undertaken as described in earlier reports to you. We have not discontinued our study and we wish to have the IND continued until such time as we will be able to complete the intended investigations.

Thank you very much for your help in this regard.

Sincerely yours,

Joseph M. Baron

Joseph M. Baron, M.D.
Associate Professor of Medicine
Section of Hematology/Oncology

JMB:ss

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