EXHIBIT 1
Part 2 of 14

THE UNIVERSITY OF CHICAGO
THE DIVISION OF THE BIOLOGICAL SCIENCES
AND
THE PRITZKER SCHOOL OF MEDICINE
BOX 420
950 EAST 59TH STREET
CHICAGO • ILLINOIS 60637

Telephone (312) 962-6114

Department of Medicine
Section of Hematology/Oncology

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Section of Gastroenterology

February 6, 1984

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

Attn: Document Control
Room 16B-45

RE: IND 16,234
Clinical Investigatation of
Human Erythropoietin

Progress Report

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

JMB/ajt

IND 16,234

Joseph M. Baron, M.D.
Section of Hematology/Oncology
Department of Medicine
The University of Chicago
The Division of the Biological Sciences
and the Pritzker School of Medicine
Box 420
950 East 59th Street
Chicago, IL 60637

SEP 21 1983

Dear Dr. Baron:

Please refer to your notice of claimed investigational exemption for Human Erythropoietin.

The sponsor of an IND is required to forward progress reports for clinical investigations at reasonable intervals not exceeding a year. These reports aid us in the evaluation of the safety and effectiveness of the drug with respect to the plan of study. Your IND does not contain this information.

If your study was discontinued, we should have been notified promptly. Notification of discontinuance should include the reason, assurance that investigators have been informed and steps taken with respect to the unused supplies of the drug.

We request that you send within thirty (30) days either a report or a notice of discontinuance and your final progress report in triplicate identified with IND number 16,234 to the following address:

National Center for Drugs and Biologics, HFN-110
Attention: DOCUMENT CONTROL ROOM #16B-45
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Natalia 9/20/83
Natalia A. Morgenstern
Supervisory Consumer Safety Officer
Division of Cardio-Renal Drug Products
Office of New Drug Evaluation
National Center for Drugs and Biologics

cc:
~~Original~~ IND
HFN-110
HFN-110/CSO
HFN-110/AParsons
HFN-110/NMorgenstern/9/14/83
sb/9/19/83/1320c

REPORT REQUEST

HMR 935325

AM670221959

AM-ITC 01006626

PROGRESS REPORT

ORIGINAL

THE UNIVERSITY OF CHICAGO
THE DIVISION OF THE BIOLOGICAL SCIENCES
AND
THE PRITZKER SCHOOL OF MEDICINE
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Section of Hematology/Oncology

Telephone
(312) 947- 5013

VAI
AAS

July 7, 1980

Ms. Natalia A. Morgenstern
Supervisory Consumer Safety Officer
Division of Cardio-Renal
Drug Products
Bureau of Drugs
Department of Health, Education & Welfare
Public Health Service
Food and Drug Administration
Rockville, Maryland 20857

RE: IND 16,234

Dear Ms. Morgenstern:

Thank you for your letter of June 26, 1980 regarding the above-named IND status report. Since approval of this IND, three patients with chronic renal failure have received Human Erythropoietin. Two male patients received the drug as outlined in detail in the approved protocol in 1979 and one female patient has just completed a trial of the medication, using a slightly altered protocol in which the drug was administered three times per week rather than every twelve hours over a three to four week period in an effort to increased the observed biological efficacy. There has been no detected acute, subacute, or chronic adverse reaction to this drug.

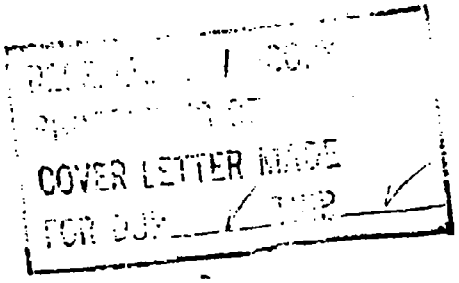
Because of the limited supplies of the drug available and the need to prepare more in a prolonged painstaking course, the pace of study of this agent is necessarily slow. At present we are awaiting preparation of more material to enter additional patients into this study. Detailed information on efficacy in the three patients studied to-date is being prepared at the present time. We intend to study additional patients as more drug becomes available to us. We have been gratified by the lack of apparent toxicity to-date. Each of the patients showed some evidence of stimulation of erythropoiesis by one or more of these study parameters, but our tentative conclusion at this point is that one needs to give larger doses than initially anticipated and for more prolonged periods of time to achieve the substantial and lasting stimulation of red cell production in patients with chronic renal failure.

I trust this will be a satisfactory interim report and that additional useful data will be forthcoming from our continued study of this material in human beings.

Sincerely yours,

Joseph M. Baron

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



JMB/ajt

IND 16,234

Joseph M. Baron, M.D.
Box 420
950 East 59th Street
Chicago, Illinois 60637

Dear Dr. Baron:

Please refer to your Notice of Claimed Investigational Exemption for Human Erythropoietin (H-EPO).

The sponsor of an IND is required to forward progress reports for clinical investigations at reasonable intervals not exceeding a year. These reports aid us in the evaluation of the safety and effectiveness of the drug with respect to the plan of study. Your IND does not contain this information. We request that you report within 30 days.

If your study was discontinued, we should have been notified promptly. Notification of discontinuance should include the reason, assurance that investigators have been informed and steps taken with respect to the unused supplies of the drug. This information and your final progress report should be in triplicate and directed to the assigned IND number.

Sincerely yours,

6/23/80
Natalia A. Morgenstern
Supervisory Consumer Safety Officer
Division of Cardio-Renal
Drug Products
Bureau of Drugs

cc:
Orig. IND
HFD-110
HFD-110/CSO
HFD-110/ASmith/gp/6/19/80
REPORT REQUEST

HMR 935328

1.1

JAN 16 1980

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
REVIEW AND EVALUATION OF MANUFACTURING CONTROLS DATA
CHEMIST'S REVIEW #2

A. 1. IND#: 16-234 Date Completed: 12-18-79

Sponsor: Joseph M. Baron, M.D.
University of Chicago
Address: The Pritzker School of Medicine
Chicago, Illinois 60637

2. Product Name(s):

Proprietary: None

Non-proprietary: Human Erythropoietin

USAN: None

Compendium: None

Code name and/or number: None

3. Dosage Form(s) and Route(s) of Administration:

Injectable, 276 units per ml

4. Pharmacological Category and/or Principal Indication:

Regulation of normal red blood cells.

B. Amendments: March 28, 1979: Form 1571.
August 6, 1979: Submitted in response to our letter.

C. Remarks:

The sponsor states that the molecular weight of erythropoietin is 40,000. Approximately 40% is protein and 60% is carbohydrate. The amino acid sequence has been determined.

The solution is steriled filled into presterilized vials, closed with a sterile rubber stopper. Storage of the solution at -20°C for up to 2 years has resulted in no loss of activity.

D. Conclusions and/or Recommendations:

The sponsor should have submitted the paper describing the amino acid sequence and stability data. However, it is not worth the time and

effort to request this additional information. The Notice is acceptable from a manufacturing and controls standpoint.

R.J. Wolters 1/14/80

cc:
Orig. IND 16-234
~~HFD-110~~
HFD-110/CSO
HFD-110/RJWolters/ccp/1/14/80
R/D init. by: AJThompson 12/19/79

HMR 935330

IND AMENDMENT. 111

ORIGINAL

THE UNIVERSITY OF CHICAGO
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AND
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BOX 420
950 EAST 59TH STREET
CHICAGO · ILLINOIS 60637

Department of Medicine
Section of Hematology/Oncology

Telephone
(312) 947-5013

August 6, 1979

Robert Temple, M.D.
Bureau of Drugs (HFD-110)
Park Lawn Building
5600 Fishers Lane
Rockfield, Maryland 20857

Dear Dr. Temple:

Thanks for your recent letter regarding IND 16,234-Human Erythropoietin (H-EPO). I am responding to the questions raised by that letter.

1. The molecular weight of Erythropoietin is 40,000. Approximately 40% of the molecule is protein and 60% is carbohydrate. The amino acid composition of the molecule has been determined and shows no unusual pattern.

2. The final material was packaged in our University Pharmacy. The vials were closed with rubber seals under metal cover using sterile procedures. No heat sealing was performed. These bottles permit multiple doses to be removed from the solution if needed.

3. Storage of the erythropoietin solution of at -20° has resulted in no loss of activity of the hormone by bioassay for periods of storage up to two years.

Thank you for your attention to this application.

COVER LETTER MADE FOR IND

Sincerely yours,

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

RECEIVED AUG 8 1979 HFD-110 BUREAU OF DRUGS

JMB:ei

HMR 935331

AM670221965

AM-ITC 01006632