EXHIBIT 7
Part 1 of 2

MEMORANDUM

DATE: December 3, 1984

TO:

G. Binder	P. Lai	D. Tajiri
J. Browne	F. K. Lin	D. Vapnek
M. Caruthers	G. Rathmann	R. Weist
A. Cohen	R. Smalling	P. Whitcome
T. Kaneko (Kirin)	N. Stebbing	J. Zimmerman
J. Koumegawa (Kirin)	T. Strickland	

FROM: Joan Egrie and Jim Fenno

SUBJECT: SUMMARY OF ERYTHROPOIETIN CLINICAL PANEL MEETING

On November 5 at the invitation of Amgen, a meeting of U.S. clinical and erythropoietin (EPO) experts met with Amgen and Kirin staff to discuss strategies for U.S. EPO clinical trials. A list of attendees is appended. A discussion of the meeting follows.

I. END STAGE RENAL DISEASE PATIENTS IN THE U.S.

A. Patient Population

The most straight forward indication for erythropoietin is for the treatment of patients with end stage renal disease (ESRD). Since this patient population is so large and available, and the potential for erythropoietin therapy clear, the concensus was that ESRD patients and not normal adult male volunteers be used for initial clinical testing.

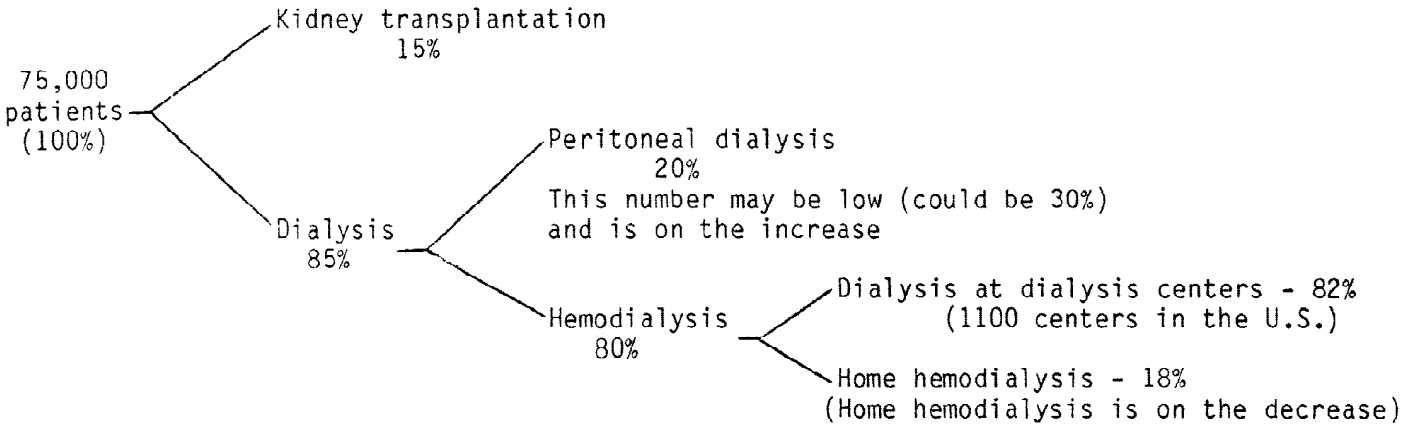
The renal dialysis patient population is currently 75,000 in the U.S and is estimated to be 100,000 by 1990. The patient population has a skewed age distribution with over 70% of chronic renal failure (CRF) patients being older than 50 years of age. Among the patient population:

54% are male
46% are female

66% are Caucasion
30% are Black
4% are other

Factors which contribute to the anemia of end stage renal disease include decreased erythropoiesis, decreased RBC survival, and inhibition of erythropoiesis due to the accumulation of toxic metabolites resulting from the uremic condition.

B. Management of ESRD Patients in U.S.



Dialysis center hemodialysis patients are dialyzed and seen by medical personnel 2-3x/week which would make them an easy group to monitor clinically. Although some dialysis centers target home dialysis patients as well, these patients are usually seen only every 1-2 months. Children, in general, receive peritoneal dialysis if possible. Hemodialysis patients are generally more anemic than the patients receiving peritoneal dialysis.

II. PATIENT SELECTION FOR THE INITIAL CLINICAL TRIAL

A. Inclusion Criteria:

- CRF patients who are undergoing hemodialysis at dialysis centers
- Life expectancy greater than 3 months
- Age 18-55 years
- Males and postmenopausal or surgically sterile females
- Ambulatory
- Hematocrit 25 or below (no lower limit)
- Clinically stable based on documented patient history. Requires monitoring patients for 3 months prior to the start of the test to establish a constant baseline. There should be no changes in the patients general health, no changes in medication which s/he's receiving, no requirement for emergency care, no need for transfusion if this has not been part of patient's prior requirements, and no subjective or medically-defined "ups or downs" in patient's clinical status.

B. Exclusion Criteria:

- Hepatitis B +
- Diabetes
- Diastolic pressure = 100 or higher
- Other systemic illnesses which might interfere such as lupus
- Sickle Cell Anemia
- Drug addicts
- Abnormal liver function
- Low platlet count
- Coombs positive
- GI bleeding (test positive for occult blood)
- Serum erythropoietin of 32 mU/ml or above (normal $\pm$ 2 SD)
- Corticosteriod or immunosuppressant therapy
- Patients part of another clinical experiment
- Androgen therapy

C. Points which arose during the discussion on the choice of patients

1. There was a unanimous decision to start testing immediately in ESRD patients rather than normals. This group is considered to be the major target for EPO therapy. Adamson's experiments on subtotally nephrectomized uremic sheep and Van Stone's work on a similar model in rats suggest that ESRD patients could benefit even from a short term trial of erythropoietin therapy. Since anemia is a major complication for ESRD patients, patient compliance during the testing period is expected to be good. Furthermore, while there might be a risk of EPO administration to both ESRD patients and normals, the normals might have an additional risk by obtaining too high a hematocrit. Dr. Krantz felt that an increased risk of blood clots could occur at a hematocrit of 43-44% and that this risk becomes more pronounced at a hematocrit of $\geq$53%. Furthermore, the metabolism of EPO and the kinetics of an EPO response are likely to be different in normals than in ESRD patients; therefore, more clinically useful information could be obtained by conducting the initial experiments with renal dialysis patients. Dr. Krantz stressed that although the data provided by Adamson and Van Stone suggest that EPO will be efficacious, treatment of ESRD patients is likely to be complicated due to the possible presence of nonspecific inhibitors of erythropoiesis.

2. Although 70% of CRF patients are over 50 years of age, a patient age limit of 55 years was set for the initial EPO study. Two considerations prompted this decision: (1) Since the marrow decreases with age, the capacity for erythropoiesis also can decrease with age, even in healthy individuals; (2) In Dr. Goldwasser's first EPO trial, his one patient over the age of 55 showed no change in marrow or reticulocytosis when given EPO.

3. It is likely that ESRD patients will be receiving one or more of the following treatments - Iron and vitamin supplements, blood transfusions, or androgen (e.g., nandrolone dedanoate) therapy at some time.

   Iron and vitamin supplements are replacement therapy given to the majority of patients for nutritional reasons. Patients should not discontinue these supplements while receiving EPO.

   Transfusions of patients with severe anemia of chronic renal failure is oftern necessary and in some cases may even be desirable. Transfusions are given to selected patients when their hematocrits decrease to very low levels. The frequency with which transfusions are given and the number of patients receiving transfusions seem to vary between different dialysis centers. It is estimated that ~20% of all dialysis patients receive periodic transfusions. There may be a tendency to increase the number of transfusions given to at least part of the CRF patient population who are candidates for receiving a kidney transplant. Until recently, exposure to tissue antigens in the transfused leukocytes and platelets was believed to jeopardize the success of a future kidney transplant. However, the opposite now appears to be the case; transfusions have been found to improve kidney graft survival. The conclusions of the panel was that patients requiring transfusions should not be excluded from the initial trial as long as they meet the 3 month clinical stability criteria.

   Androgens are administered to ~10-30% of CRF patients in an attempt to stimulate RBC production. The mechanism of action of androgens is unclear. They could be working directly or synergistically with EPO in the marrow or they could be working to increase EPO production from extra renal sites or remaining kidney tissue. Steroid treatment is helpful in some, but not all patients and has associated side effects, especially for female patients. The conclusion was that androgens should not be admisistered concomitantly with EPO for the initial studies since they may alter the patient's dose response to EPO, and are likely to complicate the evaluation of EPO efficacy.

4. No exclusions were felt necessary for concomitant therapy with antihypertensive drugs.

III. ASPECTS OF TREATMENT SCHEDULE

A. Route of Administration

For the initial study, one bolus IV injection will be administered.

An IV route was chosen over IM and SQ since for the hemodialysis patient this route is open and administration convenient. Dr. Cohen's recent pharmacokinetic data suggest that the half life of EPO is greater when it is administered by IM versus an IV injection. An IM injection might also be more convenient for EPO administration to CRF patients not undergoing hemodialysis or to patients with other indications (i.e., chronic inflammatory disease, etc.). Although IM injection has several advantages, it was eliminated from the initial study since it could be associated with bleeding problems in hemodialysis patients and could necessitate an additional ~45 minute stay at the dialysis center for evaluation. SQ injection might be more likely to be associated with an antibody reaction and was therefore eliminated. It was agreed that the effectiveness of EPO probably could be increased if it were given by a slow IV infusion or by subdividing the doses. A bolus IV injection was considered more appropriate for the initial study, however, since it would maximize toxicology data even though it may not optimize biological effectiveness.

B. Dose

For the initial evaluation there will be 5 different groups of 5 patients, with each group receiving one of the following dose levels per injection: 100, 300, 1,000, 3,000 or 10,000 U/70kg. The final dose levels will be subject to reevaluation after reviewing the results of the toxicology study. Patients in each of the 5 different dose level groups will be treated successively. In order to evaluate all safety parameters, at least 2 patients at the lower dose level must complete the study before administering the higher dose to the next group.

We still have no firm data indicating an effective optimum dose level. Furthermore, each patient is likely to require individual optimization of dose due to differences in possible uremic inhibitors of erythropoiesis, age, health, etc. As a guideline, Dr. Goldwasser's clinical EPO trial and Dr. Adamson's sheep model suggest a dose of ~1,000 U/70kg may be efficacious. Since this dose could either already be on a plateau or for ESRD patients be suboptimal, it was decided that doses 10 fold below and 10 fold greater than 1,000 U/70kg should be included. Although a usual Phase I drug evaluation would use an escalating dose schedule, the present design of separate groups for each dose was chosen since it would generate more data for future dose optimization.

C. Injection Schedule

EPO will be administered three times per week at the end of each hemodialysis treatment for a total of 3 weeks (9 total injections).

This was considered the most practical administration schedule since it will merely be an adjunct to the patient's regular treatment routine. Post-dialysis injection is more desirable since it would be difficult to detect any acute reaction to EPO if it were administered during dialysis. Three weeks was considered long enough to evaluate safety parameters and also to obtain an indication of effectiveness, including an increased hematocrit.

D. Wash Out Period

One week post treatment evaluation period for safety and two week (minimum) post treatment evaluation period for efficacy.

Biological effects of EPO including increased circulating reticulocytes and increased hematocrit could require at least 1-2 weeks to be manifest; therefore, patient monitoring will be continued for 2 weeks after the last treatment. Depending on the data collected, monitoring for biological efficacy could be continued past 2 weeks.

E. Drop Out Points

Two conditions were identified that would require a patient to be dropped from various aspects of the initial study.

1. A need for a transfusion due to a very low hematocrit in the middle of the study. In this case, EPO injections could continue in order to obtain data on drug safety; however, the transfusion would eliminate an evaluation of biological efficacy.

2. An increase in hematocrit to ~45-50% coupled with an increase in blood pressure (relevant change on a percentage basis for each individual). This would require an immediate withdrawal from further EPO treatment, but would also indicate efficacy.

F. Pharmacokinetics

Since patients will be hospitalized and monitored for 24 hours after the first EPO injection, this represents an ideal opportunity to obtain serum samples to generate pharmacokinetic data. Pharmacokinetics are anticipated to be different in different patients, since the degree of uremia, etc., may influence the EPO clearance rate. Serum EPO levels can be determined at different times after injection using an RIA. For at least one time point, an evaluation of biologically active EPO should be made in the exhypoxic polycythemic mouse assay.

IV. PATIENT EVALUATION

A. Safety

Test	Interval
History and relevant physical - Exactly what constitutes a relevant history needs to be further defined, but it should include vital signs, complaints and subjective patient evaluation, and all tests for entry and exclusion criteria.	Pre and post study (week 4)
Vital signs	Pre and post each injection. Patients will be hospitalized for 24 hours after the first injection and vital signs will be monitored at 1, 4, 8, and 24 hours post injection.
CBC (including differential, platelet and reticulocyte count, etc.)	Pre and post study for safety (week 3 and week 4) (See later for efficacy)
Ferritin	As for CBC
PT and PTT	As for CBC
Urinalysis (where urine is available)	Pre and post study (week 3 and week 4)
EKG	Pre and post study (week 4)
Chest X-ray	Pre and post study (week 4)
Chemistry panel - including HCO_3 (blood gases)	Prestudy and at the beginning of each week, before dialysis, for a total of 5 weeks
Anti-EPO Antibodies	Pre and post study (week 4)
Anti-media/CHO cell antibodies	Pre and post study (week 4)

B. Efficacy

Test	Interval
CBC	3x/week, predialysis, for at least 5 weeks. Depending on the data collected at the 5 week point, consider continuing for further evaluation of efficacy.