# Cutter

MILES

Ref: JB 85-152

TO: Dr. Sternberg

DATE: March 15, 1985

FROM: Ralph K. Rousell

SUBJECT: Report of Trip to Europe
February 16 - 27, 1985

COPIES TO:

P. Bedogni
K. Brandau
B. Dyos
B. Elliott
W. Ewald
R. Froitzheim/
R. Neumann
E. Greene
V. Shalson
J. Wood

ACTION INFORMATION

I. Visit to Miles/Cutter Stoke Court, Stoke Poges, United Kingdom
February 18, 1985

At Miles UK discussions were held with Dr. Brian Elliott, Ms. Marie Tatt, and Brian Dyos concerning ongoing problems in the UK relating to clinical investigations.

Koate®-HT

The United Kingdom license has been approved, although Cutter UK is still waiting for a formal approval letter from the Committee on Safety of Medicines. Despite this, only Koate®-HT is being used. This is being done on a named-patient basis. It is intended that postmarketing surveillance will be carried out on Koate®-HT. This will include assaying for HTLV-III antibodies. At the present time they are considering doing the postmarketing surveillance at three of four centers. The four centers are Professor A.L. Bloom in Cardiff (recent publication Lancet, February 9, 1985, page 336, who will contribute 100 patients), Dr. Peter Jones in Newcastle who will contribute data on 150 patients, and then either Dr. C. R. Rizza at Oxford or Dr. A. Aronstam at Alton in Hampshire. One of the latter two will contribute 150 patients. Subsequent to my meeting, Dr. Aronstam was recruited to the group. Dr. Elliott will let Dr. Rousell have copies of the postmarketing surveillance protocols.

B. Elliott

Konyne®-HT

E. Greene

At the present time Cutter UK does not have a license for Konyne®. However, they are considering filing a license. We discussed Factor VIII inhibitor bypass activity of Konyne® and also the thrombogenic potential of Konyne® and Konyne®-HT. I confirmed that we did not as yet have any data and that we did not have the inhibitor indication for Konyne®-HT. Similarly we do not have any marketing information on thrombotic complications relating to Konyne®-HT as in the past such problems with conventional Konyne® were related to prolonged high dosage.

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EXHIBIT 79

MIL 082370

| ACTION | INFORMATION |
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| | Gamimune®-pH 4.25, CMV-IGIV,pH 4.25, and Pseudomonas-IGIV,pH 4.25 |
| Done March 15, 1985 | It was agreed that we would send Dr. Elliott the appropriate forms for the laboratory use of CMV-IGIV,pH 4.25 and Pseudomonas IGIV,pH 4.25. He would also assess the number of vials that Professor Hobbs would require for his in vitro work. He would also assess whether Professor Hobbs would wish to do any in vitro work on the conventional Gamimune®,pH 4.25. |
| R.H.Rousell/ R.S.Schwartz | At the present time they do not have any studies underway on ITP. They will reserve judgment on doing studies on ITP with the pH 4.25. We discussed how it might be possible to allay the concerns of the British investigators concerning the possibility of transmission of AIDS by IGIV. I agreed that I would discuss with Dr. Schwartz in the United States the possibility of following our ITP cases up to see if there has been any sero conversion to positive antibodies against HTLV-III. Dr. Elliott confirmed that the United Kingdom did not have any interest in the studies in either Greece or Italy and would only accept data from such studies if it had been approved by the FDA. |
| | All other clinical studies on IGIV,pH 4.25 presently underway in the U.S.A. were discussed. It was agreed that we would keep the U.K. informed of the progress of our studies in burns. We also mentioned our interest in conducting studies in surgical sepsis and surgery. |

II. Participation at the International Symposium on Hemostatic Experiences in the Clinic. Coordinated by the German Workshop on Blood Coagulation Research and the German Society for Thrombosis and Hemostasis.

Venue: Saarbrucken, Germany
February 20-23, 1985

The meeting was held entirely in German. It was attended by all the leading hematologists in Germany and Austria. A copy of the program is attached for information, as well as a selection of the abstracts in English and a more detailed abstract in German. Copies of any of the other abstracts which might be of interest to anyone based upon the title in the program can be supplied on request. The following were the major items to come out of this meeting:

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MIL 082371

ACTION

INFORMATION

1. The session on virus inactivation of plasma products and the biochemistry of Factor VIII complexes had three of the seven papers by Biotest, one by Immuno, and one by Alpha Pharmaceuticals (Green Cross). Cutter was not represented. The paper from the Green Cross on the inactivation of HTLV-III/LAV virus in Factor VIII and Factor IX concentrates was presented by Dr. C. M. Heldebrant on behalf of S. McDougal and O. Dittmann. This actually dealt with the work that Alpha and Cutter had done in collaboration with the Center for Disease Control in Atlanta Georgia. However Dr. Heldebrant did not present any of the Cutter data. As a result of this immediately following Dr. Heldebrant's presentation in the discussion section I mentioned that like Dr. Heldebrant Cutter had also conducted studies on the inactivation of the HTLV-III/LAV in our Koate® and Konyne® preparations also done in collaboration with the Center for Disease Control. I mentioned the fact that we heated in the lyophilized stated at 68°C for 72 hours and the fact that no active virus could be detected after 12 hours of heating, which equated with a destruction of 4.3 logs of virus in 12 hours. I also mentioned that the full details would be presented by Dr. McDougal in a paper at the International Conference on AIDS in Atlanta in mid-April, 1985.

2. Throughout the meeting it was very apparent that dry heat treatment of coagulation factor concentrates is not viewed with favor by the German hematologists. They are unanimously in the support of wet heat treatment (pasteurization). In fact in summarizing one session, Professor Egli of Bonn went so far as to state that even though dry heat treatment might inactivate the AIDS virus, it did not inactivate non-A non-B hepatitis virus/viruses nor hepatitis B viruses. He went on to indicate that heat treatment of coagulation factor concentrates in a wet state was, however, effective in inactivating the viruses of non-A non-B hepatitis and hepatitis B. He stated that non-A non-B hepatitis had been transmitted by the dry-heat treated preparations.

   The session on adverse reactions in substituition therapy with plasma derivatives was also of great interest. The paper which received the most interest here was the study by Manucci and his colleagues dealing with the dry Factor VIII heat treat preparation of Hyland in virgin hemophilics. This has also been published in The Lancet.

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ACTION INFORMATION

Essentially Hyland/Travenol had recruited 18 virgin hemophilics in Europe (seven severe, five moderate, and six mild). These patients were treated exclusively with their Factor VIII HT preparations. They were compared with a control group of 29 virgin hemophilics treated with non-heat-treated Factor VIII concentrates. They showed that over a 12-month period, none of the patients receiving the heat treated preparations showed seroconversion to positive antibody against HTLV-III, while in the control group five patients demonstrated seroconversion. None of the patients had other risk factors for developing AIDS and non of the patients involved in the study had developed either AIDS or pre-AIDS syndrome up to the present time.

4. Professor Schallers of Heidelberg suggested that because of the presence of other proteins in Factor VIII concentrates, e.g., fibronectin, etc., viruses can be immobilized, bound, and protected from inactivation. Following infusion they could be transported to the liver, where they would be released by the reticuloendothelial system. They suggested that hepatitis B might be one such virus. Obviously they were making a strong case for production of a highly purified Factor VIII concentrate.

III. Discussions with Professor Scharrer Concerning a Cutter Study of Koate®-HT (wet) in Virgin Hemophilics

R. Neumann/
R. H. Rousell

At a separate meeting attended by Dr. R. Neumann, Mr. R. Froitzheim, Professor Scharrer of Frankfurt, and myself, we discussed the possible study of Cutter's new wet heat treated Factor VIII concentrate in virgin hemophilics. Professor Scharrer is quite agreeable to representing us in this context, but in view of the scarcity of virgin hemophilics, strongly recommended that we agree to a joint study with Behringwerke and Immuno which would be controlled by Professor Schimpf. I indicated that we were quite agreeable to this and that I would immediately on return to the U.S.A. set into motion the processes necessary for obtaining 1,200 vials each of 1,000 I.U. Koate®-HT (wet) prepared in accordance with the specifications which have been previously laid down by Professor Scharrer.

NOTE: Since my return this has been done and we have placed an order for 1,200 x 1000 U. vials, all of which are to be manufactured from HTLV-III antibody negative plasma. Tropon has been informed that these could be shipped to them in early September.

U.S. 0581

MIL 082373

ACTION INFORMATION

IV. Meetings at Bayer, Wuppertal, and Tropon, Koln on February 25th and 26th.

Meeting at Bayer Clinical Department.
Participants: Dr. K. Brandau, Dr. F. Schumann, Dr. J. P. Fallise, Dr. R. Neumann, Dr. P. Bedogni, Dr. E. Greene, and Dr. R. H. Rousell.

Dr. Brandau opened the meeting by introducing himself and his position within the Bayer organization. He will have the responsibility for maintaining an ongoing watch on Cutter's medical monitor in Europe.

R.H. Rousell/ W. Ewald/ V. Shalson

Dr. P. Bedogni supplied an overview of the research in Europe. It was generally agreed that it would be extremely useful for those involved in the Cutter studies in Europe to supply a matrix of our ongoing plans for various new products in various European markets. This would be coordinated by Dr. Rousell and supplied to Dr. Brandau.

R. H. Rousell has returned a corrected copy to Dr. Bedogni.

France
The French Transfusion Service, Behringwerke, and Travenol are all doing their own Factor VIII-HT studies under the direction of Dr. J. P. Allain. Dr. Bedogni has supplied a protocol to Dr. Allain for considerattion. A copy was also supplied to Dr. Rousell for comments and corrections. This has been done. Dr. Bedogni will keep Dr. Rousell informed and supply a final protocol in due course.

Germany
CMV-IGIV
The name Cytoglobin has so far been rejected by the trademark licensing authority as being too close to the generic name.

Dr. Neumann presented data on the progress of the clinical studies. She indicated that in kidney transplantation the overall incidence of CMV infection has been extremely low. They are seeing CMV infections occurring in the controls, however, comparison with the treated group will need to await completion of the studies. They will combine the first four centers and analyze seronegative patients. In Bone Marrow Transplant they would look at both seropositive and seronegative patients, and they are not doing control studies in bone marrow transplantation. Dr. Neumann reported that Biotest had just started a study in renal transplantation.

The study in leukemic children has been delayed because of staffing problems at the centers. Both studies already include routine prophylaxis using a VZ immune globulin, which may make results of the study difficult to interpret.

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MIL 082374

ACTION

INFORMATION

Pseudomonas IGIV

The name Psomaglobin has been registered in Germany. Both Biotest and Sandoz have studies underway. Professor Bauenfiend compared titers against Pseudomonas in Cutter IGIV, Biotest, and Sandoz. He found that the Cutter preparation was superior to the other two. The majority of the studies in this area concern the use of Pseudomonas IGIV in the treatment of infections in patients on respiratory support. They're on schedule for application for a license about mid-year, and anticipate approval toward the end of 1985.

Polyglobin

Professor Goebel in Dusseldorf has a two-year ongoing study comparing Intraglobin and Polyglobin in the prevention of infection in leukemic children. No data are yet available.

Koate®-HT (wet)

The proposed study by Professor Scharrer was discussed. Details of this have been mentioned previously in the report. They stressed that laboratory tests have not yet been performed at the Paul Ehrlich Institute and thus there would only be a decision on this license application by about November, 1985.

In this context, it was agreed that they would then attempt to alter the CMV-IGIV license to the pH 4.25 configuration. It was estimated that they would submit this in about December, 1985, and that a license decision could be expected about April, 1986. The change from the Pseudomonas IGIV,pH 6.8 to the pH.4.25 configuration would be submitted at the same time.

GRO-C

RHR:jb



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