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PLEASE DELIVER THESE 5 PAGE(S)

TO:

NAME: Mrs. Joyce Boult

COMPANY: Bayer U.K.

LOCATION: Newbury, U.K.

FROM:

NAME: Elias L. Greene

LOCATION: Cutter Biological

SUBJECT: Koate HS - Hepatitis B

Enclosed is the report from Dr. F[illegible] concerning a [illegible] case following use of Koate HS (L[illegible]). [illegible] establish a baseline half life against which [illegible] be compared. I will update you as [illegible]

Best Regards,

GRO-C

Elias L. Greene

FROM CUTTER B[illegible] 08.03.1989 [illegible]
5 AUG '89 THU 22:22 16509115 415 420[illegible]

Koate HS
Hepatitis
for D. Kep...

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PRODUCT SURVEILLANCE

TELEFAX

Total of four pages (incl. flg.)

To: Cutter Biological
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From: J.P. Fallise

Date: 28th July 1989

Re: Trip Report to UK
26 + 27 July 1989

1. Visit to the Royal Free Hospital

Meeting with Dr. Kernoff, Dr. Giangrande, and Sister Ext...

a. Obviously Dr. Kernoff's concern about GRO-A's liver status has not decreased since my last visit in May 89. In fact this problem represents a true matter of conscience for him in an extend which may be considered surprising from a pure medical point of view, considering the medical past history of this patient, but perhaps understandable from his point of view as he is involved in several civil lawsuits investigating responsibilities for the contamination of haemophiliacs with HIV (this was a confidential remark made by Dr. Giangrande after this meeting and the previous one in May).

Since my last visit, Dr. Kernoff has consulted other hepatologists (who have been requested to deliver a written and detailed comment on all possible hypotheses, comments which will be forwarded to us immediately upon receipt) and debated this question in detail with Professor Bloom whose first reaction when he heard about GRO-A's problems for the first time, had been to suspect Koate HS of being a possible HBV contaminant.

Hepatitis exposure 3-4 months previously i.e. about June-July 1988

This "hepatitis B" hypothesis was reinforced when it appeared recently that GRO-A's hepatitis serology had changed some time before the beginning of the trial. On 2 October 1988, when baseline investigations were performed, GRO-A's hepatitis serology was shown to be anti-HBs negative,

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anti-HBe negative, and anti-HBc positive (this status remained unmodified after initiation of the clinical trial as shown by the laboratory results of 15 February 89 and 22 March 89). Only recently GRO-A's anti-HBs status was discovered positive at a period preceding clearly our first investigations for the rFVIII trial. This finding raised the possibility that GRO-A would have become susceptible to hepatitis B, after loss of his anti-HBs antibodies (a phenomenon occuring frequently in anti-HIV positive patients), and would have developed a true hepatitis B. Dr. Kernoff feels that the GOT and GPT profiles would fit better with an hepatitis B than with a recurrent non-A, non-B hepatitis. If this "hepatitis B" hypothesis was correct, one would need to look for a source of contamination or reactivation: either a previous compound alone or Koate HS itself (as source of "re-contamination"). Two reasons argues against Koate HS: first, pasteurized products have recently induced some hepatitis B (Dr. Kernoff is aware of the recent withdrawal of some batches of Koate HS in Japan), and, second, the lapse of time between the treatment with Koate-HS (20 Sept. 1988) and the appearance of pathological liver enzymes (mid-Jan. 1989) may suggest that both events could be causally related.

ELEVATION USUALLY MAXIMAL 2½-4 MONTHS AFTER EXPOSURE, I.E., EXPOSURE EARLY SEPTEMBER TO MIDDLE NOVEMBER.

Dr. Kernoff who is disappointed not to have been informed about the problems of Koate HS in Japan, is asking now for a written report on the Japanese cases of hepatitis B.

GRO-A was tested on hepatitis delta virus (HDV) at the Royal Free. Results were negative.

b. Even if Koate HS has now become the suspect number 1, Dr. Kernoff would like to interrupt GRO-A's treatment with rFVIII for some months before resuming it later, provided the liver enzymes have been normal for a sufficient lapse of time. He repeated what he had already told at our last meeting, namely, that without commitment from our side to re-enrol GRO-A he could not convince him to come back to a plasma-derived product.

c. Whether GRO-A treatment can be interrupted or not, he would like to put aside a certain quantity of PR 3133 with the aim at re-administering it after normalization of GOT and GPT. The problems with this policy are, first, that GOT and GPT behaved similarly under PR 3135, and, second, that PR 3133 will expire in October 1989. If we may not re-use that batch after that date, we could loose up to 80 vials of PR 3133 at once.

d. In a few days Chiron anti-HCV assay will be available at the Royal Free. Serial sera of both patients will be tested.

e. A diagram showing GRO-A's GOTs and GPTs since the beginning of the trial with the batches administered follows this message. Dr. Kernoff has prepared a similar diagram of his own which he will show in Tokyo if a debate on liver problems arises.

f. Dr. Kernoff is interested in recruiting some stage-III patients (mild haemophiliacs needing factor VIII only for operations). We will be called on time if such a cases come up.

g. Several CRFs of patients GRO-A and GRO-A with diaries were remitted.

2. <u>Visit to the University Hospital of Wales</u>

Meeting with Dr. Harrison.

a. Dr. Harrison is optimistic concerning the lecture supposed to be given by Prof. Bloom. There is a good correlation between his results (FVIII:C) and those of Cutter. The draft of the lecture has already been prepared and will have to be completed with numerical data. On next Monday, the pharmacology department will analyze Cutter results. If there is no discrepancy, Prof. Bloom will be able to speak as requested.

b. Several CRFs were remitted to me after review and discussion.

GRO-C

J.P.F. 8/1/89 RHR Comments.

Koate-HS given Sept. 20 1988. On Oct. 2 1988 subject was [illegible] positive. This is an almost impossibly short period (12 days) [illegible] the development of antibodies against core antigen. They usually take [illegible] 3 to 4 months to appear. We really need full details [illegible] possible exposure prior to September [illegible] use of blood and/or blood products [illegible] especially [illegible] going back two or three years.

<u>ONE FIGURE ENTITLED "TRANSAMINASES IN PATIENT GRO-A" FOLLOWS.</u>