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CLINICAL

Cutter Japan, Ltd.

MEMORANDUM

COPIES TO
W. Ewald
K. Kawahara
A. Imai
Y. Sato
K. Nakamura

TO K. Juelicher
FROM T. Minaga TM-378
DATE March 14, 1985
SUBJECT Trip Report for March 2 - 13, 1985

(1) 1st Clinical International Meeting

Participants - R. Rousell, R. Schwartz, T. Nixt, (E. Greene), (S. Chuang), (P. DeHart) from the U. S.
P. Bedogni from Europe
T. Minaga and K. Nakamura from Japan

The clinical studies for IGIV (pH 6.8, R/A), IGIV (pH 5.25 R/A), IGIV (pH 4.25), Hyperimmune (CMV/Ps), Koate-HT, Konyne-HT and α1-PI, which are now on going and is scheduled for 1985 were discussed. The minutes of this meeting was prepared by R. Rousell and will be distributed shortly. Brief summary is as follows.

(A) In the section of IGIV, Japanese ITP studies (Green Cross, Kaketsuken and Sandoz) are presented for the discussion. Since U. S. ITP Data for our product (6.8 R/A) were shown, I will report you "How our strategy for ITP should be, considering data-comparisons with our competitors." This report will be prepared separately.

(B) In the U. S., Immuno initiated the clinical studies for Kawasaki Disease at Harvard Medical School (Dr. Fred Rosen), but Cutter does not so far.

(C) In Europe, Clinical Study of IGIV was initiated to R.A. and SLE but looks not so successful.

(D) Allergic asthma was discussed for another candidate of future IGIV study. Preliminal data showed that low dose (100mg/kg) looks fine, however, the clinical approach must be carefully initiated because of high incidence (i.e. requires more than 300 cases).

(E) To get high titer CMV or Ps lot, it was suggested periodical constant requests from CJL to US (R. Rousell/ C. Patric) would be preferable. I will take this action to enable to get these lots.

(F) For the initiation of Konyne-HT clinical study, U.S. suggested they will start after they receive sibling lot (i.e. not-HT and HT from the same lot), because lot to lot differences of Konyne are common. However, I think sibling lot must have potency differences due to heat inactivation of the Factor IX potency. From this point, sibling lots have disadvantage. But hepatitis studies in virgin cases should work better in sibling lot study.

lost hepatitis-safe

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(2) Factor VIII-HT Meeting

Participants - K. Fernandez, E. Greene, M. Mozen, S. Ojara, M. Sternberg, R. Rousell, P. Bedogni, T.Minaga

(A) The world-wide situations are explained for Factor-VIII-HT products. Virtually, England, West Germany, Italy and Ireland approved Factor VIII-HT without any clinical studies (prohibited to import non-heated one- this may be much better expression for this situation). Some other countries are going to follow. On the other hand, Cutter, U. S. speculates FDA does not allow to produce not-heated Factor-VIII shortly (but nobody knows when). I suggested to have immediate contact with CJL to check the inventory and ship out non-heated Koate at least for CJL to survive till the end of this year - but U. S. inventory situation looks bad. I must suggest you to investiage how many units CJL needs more during 1985 and take immediate actions to keep those, carefully watching MHW's decision for this matter.

(B) I called to Prof. Abe to check if he knows these world-wide storm. He said "I know but Japan is Japan." Prof. Abe looks so rush to submit the clinical data of Factor VIII-HT to MHW. He said "Cutter Japan is far behind compared with all other competitors." But this is definitely not right, because we know CJL should be the fastest one considering the starting date of this clinical study. I think Dr. Abe asked to our competitors to prepare the data even though those do not reach to a half year check point to catch up CJL and organized the final general assembly by all clinical investigators prior to CJL's schedule (April 26). His strange action like this (not scientific at all)should be understood because he has known the world wide changes described in (2)(A). Our competitors must not have half a year clinical study like CJL but I think Dr. Abe was afraid that all his efforts may become meaningless for many companies, if MHW approved Factor VIII-HT without any clinical studies like Europe. Dr. Abe may be unpleasant by realizing that we know this fact. He may not have any good justifications for this rush actions against original protocol - It is anticipated that Dr. Abe will become offensive to CJL to protect himself (remember he took similar actions to Travenol to let them wait till all competitors "ready to go"). But Dr. Abe kindly said to me over telephone "I will wait Cutter Japan and allow all companies to submit PLA at almost same time." How smart he is !

Dr. Abe

(3) Factor VIII by r-DNA

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(4) MHW-Minimum Requirement Change

Participants - K. Fernandez, J. Cherry, J. Huxsoll, E. Greene, T. Minaga

2nd Draft prepared by MHW was reviewed. Several points were discussed for the future chance to revise it. Karen will send disirable Minimum Requirements for Cutter after incorporation of her comment, which will be utilized for CJL to give the comments to MHW on next earliest chance.

(5) Vacuum of Koate

Participents - J. Huxsoll, C. Mintz, T. Minaga

Some confusions were existed for the definition of acceptable vacuum values for Koate. Although it was defined not more than 15 inch Hg in CJL-QC protocol, vacuum is changed as a function of the time after Koate was took out from refrigerator storage condition. Therefore, we realize a little scientific data are necessary to know the appropriate testing timing. Berkeley will initiate such experiment by which we can know it. It was agreed that we will discuss again over FAX MESSAGE for this matter after they generate the basic data. I know we have faced the product shortage due to no availability of non vacuum type.

* From our clinical studies of Koate-HT (vacuum-type), we have not heard any complains through our clinical investigators. Considering the difficulty to program the manufacturings of non-vacuum special lots just for Japan, CJL-Marketing should analyze how real the impact is for Koate if it becomes vacuum type. It is my personal opinion/impression that CJL should not have any impact at the market even though it is changed to vacuum type. This decision will help CJL itself.

** (Discussed over telephone with K. Muragishi)

(6) Hyperimmune Screening Program

Participants - Dr. Dopkins, S. Chuang, T. Minaga

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We discussed how Cutter Japan can get special lots of V.Z., CMV and Ps. It is essential for CJL-sales promotion to cover no ITP indication for Polyglobin. To reinforce the screening program for those, they need budget approval for the additional manpower at Berkeley. Therefore, possible strategy was discussed to make it realistic. We should discuss the following possible action plans.

[STRATEGY]

Action-I by S. Chuang

Steve will initiate the proposal for the budget approval or whatever, through his supervisor (V. Shalson), to reinforce the screening program for VZ, CMV and Ps, emphasizing that those special lots are really required for CJL to accomplish sale targets (126,000 vials) among heavy competitions. Even though the proposed program will not be in time for the supply in this year, this action surely help for CJL to take available special lots produced by the present program.

Action-II by T. Minaga

Minaga will initiate the proposal through K. Juelicher to W. Ewald, i.e., CJL asks to provide lot to lot special pathogens titers for usual Polyglobin - many hospitals are asking the titers. In order to get sales target, data supply for each lot to CJL will reinforce CJL - potential sales powers against competitors. About 10-12 pathogens will be listed up and will be reported for this data supply requirement. They will surely need additional manpowers, however, those are re-utilizable for the propose discribed in Action-I.

Reciprocal Effects to be Expected

Two independent proposals through two different V.P. (Shalson/Ewald) should have much stronger powers for the agreement at the top management.

(7) Meeting with World-wide Marketing Department

(A) Participants - V. Shalson, S. Chuang, T. Minaga

General discussions were done for the understanding of Japanese heavy competitions for IGIV. Steve did excellent presentation for the high titer special lots of Polyglobin and emphasized the real needs of those to Japanese market.

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(B) Participants - V. Shalson, B. Diver, S. Chuang, T. Minaga

How the defence study should be published was discussed. Actually the study was originally designed for products defence, however, present situations of world-wide Cutter are complicated in terms of IGIV (i.e., R/A 6.8 in Japan, R/A 5.25 in U.S. and Europe, pH 4.25 just field in U.S.-PLA). Moreover, the data which are not accepted for CJL are PKA or monomer values in the study. CJL is utilizing some publication's data for PKA as an advantage for Polyglobin, compared with Venoglobulin-I. However, the data in our defence study shows the differences of PKA between two products are much less, which is not good for us and CJL is utilizing data of monomer values by the ultra-centrifuge (low resolution), which is roughly 95 %, however, data in defence study roughly 85 % of monomer by other method, which is again not good for CJL (may cause confusion in the market). Therefore, at least, complete elimination of data for R/A 6.8 product and complete eliminations of data for Japanese competitors products in the study for R/A 5.25 and pH 4.25 IGIV were recommended in order to avoid all possible involvement of CJL in this publication. However these data became very valuable for CJL to set up our justification for pH 4.25 IGIV registration. Data itself scientifically very valuable for us but some of them should not be published at the present moment.

(8) IGIV Task Force Meeting

Participants - M. Boyce, R. Hein, B. Diver, Dr. Dopkins, P. Marsh, S. Chuang, J. Huxsoll, T. Minaga and some others

Minutes will be distributed shortly as we receive every time. One interesting discussion for Ps-hyperimmune was going on. This is for Germany clinical trials, however, it is lower titer than expected. If Germany cannot accept this lot for their clinical trials, it may be possible for CJL to take it. S. Chuang will watch what will happen for this lot.

(9) Customer Claim and Mixing Test of Polyglobin

Participants - J. Cherry, G. Nakamura, (K. Fernandez), T. Minaga

(A) They required Customer Claim Report from Japanese market. Actually three systems presently exist. One is Q.C. report by Y. Sato, another is Manufacturing Department report by H. Tsukashita, and the other is regarding adverse reactions by T. Minaga. The newly required one more report to Berkeley should be done by H. Fukumoto, who has filed all claims of the products from Japanese market.

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I have discussed this subjects with H. Fukumoto before my departure and have got agreement with him. Report after June 11, 1984 will be reported by him to J. Cherry.

(B) Berkeley-QA is about to start their mixing tests of Polyglobin with other liquid drug. We asked to test first with washed red cells, about which we recently received the occurance of aggregation of red cells from Gunma University. Precise situations were explained how it happened. In addition, CJL will pass information about the mixing tests which we did. We have two different data. One was prepared in CJL-Preclinical Section and the other is under colaboration with Nihon University, Itabashi Hospital, which will be reported shortly to us.

(10) Long Term Stability Programs for Japanese Registrations

Participants - R. Victor, L. Thompson, T. Minaga

(A) CMV-hyperimmune

They have two old lots which still have more than 5 times titers, compared with the usual Polyglobin. We agreed to initiate long term stability study using these lots by setting March 1985 as Zero time at 10°C. One more new lot is about to come in and will be started accordingly.

(B) Ps-hyperimmune

One new lot is about to start for Japanese long term stability program.

(C) pH 4.25 IGIV

Required three lots started in February 1985.

(D) Koate-HT

During this March, CJL can expect one year stability data which is essential part of our Koate-HT PLA. CJL should ask J. Cherry to pass the Berkeley-QA organization chart and C.V. for the persons who were involved for this stability studies. Those are required under GLP regulations.

(11) H_2L_2 Test (Test for the confirmations of Reduced Alkylated) and pH Test

Participants - J. Huxsoll, R. Victor, T. Minaga

(A) Data descrepancies between U.S. and Japan were discussed by reviewing all the historical process. Some more study and the communications are necessary to get final agreements - but now it becomes easy to understand why it went wrong and how we should do for H_2L_2 test.

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(B) I think we should now analyze the accumulated paired data for pH between U.S. and Japanese testing methods for Polyglobin in order to avoid unnecessary advanced samples (cost consuming) any more, if possible. I should ask Y. Sato to analyze the data.

(12) PPF-Stopper

Participants - K. Fischer, J. Cherry, C. Turner, J. Hink, T. Minaga

Experimental data prepared in Berkeley are shown. Data are as follows. Leakage which CJL reported first are quite realistic according to this data.

	old west	new Steveus
(A) Metal tipped plastic spike (frequent use in Japan)		
(i) Set alone	452/200	340/200
(ii) Set with air needle side by side	90 %	90 %
in separate holes	10 %	10 %
(B) Large needle set (Japanese)		
(i) Set alone	1/60	not yet done
(ii) Set with air needle side by side	412/12	not yet done
separate hole	5/12	not yet done
with maximum separation of sets	0/36	not yet done

(13) PPF - PLA

This should be reported separately.

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(14) Meeting with Dr. Tomonaga (UCLA)

Dr. and Mrs. Tomonaga and Dr. Nakahama (UCLA) were invited for dinner. Dr. Tomonaga is a visiting scientist of UCLA from Nagasaki University till the end of this August. CJL-detailman in charge of Nagasaki University tried to let him meet me prior to his departure to U.S., however, I was too busy to get the chance. What we found later is surprisingly he entered the same High School as mine in the same year and then he moved to Hiroshima one year later. He returned to Nagasaki again when he entered Medical School. We did not know each other but could meet at Los Angeles. Many friends of mine are also his friends, we found.

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We now get very strong connection with Nagasaki University on this occasion through him. Available after this September. He is pretty famous Hematologist. Dr. Nakahama spend 2 years at UCLA and he is about to return to his original University (Kawasaki Med. Col., Kurashiki City, Okayama). He is a specialist of Lung Disease. His Japanese Professor is Dr. Soejima. This connection may be utilizable for Polyglobin.

(15) Meeting with Prof. Winston (UCLA - Dept. of Hematology and Oncology)

I met Prof. Winston along with Dr. Budninger (Cutter) as Lunch Time Meeting. Dr. Budninger did her own work with him. What were decided for the lectures were as follows.

(A) Two Special Lectures of His in Japan

June 22 (Sat) at Osaka chaired by Prof. Masaoka
June 29 (Sat) at Tokyo chaired by Prof. Takaku/Miwa

(B) 1 hour lecture with 30 min. discussion time regarding his Gamimmune experiences in the field of CMV/BMT, similar talk which he did at San Diego.

(C) What will be covered by Cutter Japan

* Round trip ticket (L.A⟷Japan) for Prof. Winston
* Hotel charge, June 21, 22 (Osaka) and June 28, 29 (Tokyo) for Prof. and Mrs. Winston (Total 4 nights)
*Shinkansen one way ticket (Kyoto⟶Tokyo) for Prof. and Mrs. Winston

(D) Prof. and Mrs. Winston arrive at Osaka on June 21. T. Minaga will pick them up at Osaka Airport.

Regards,

GRO-C

T. Minaga

TM/fm