APPENDIX X

# SNBTS HEAT TREATED FACTOR VIII

## PRELIMINARY CLINICAL EVALUATION STUDIES

(Introductory Note)

February 1985

JDC/SHHD/6/84/1

## INTRODUCTION

There has been worldwide interest in the development of techniques designed to reduce the infectivity of pooled blood products and the option currently seen as the most appropriate for the SNBTS is heat treatment.

Methods have been introduced in which sugars are added to protect factor VIII from the effects of heat. In vitro virological studies have demonstrated that in the sugar medium selected (sorbitol) the traditional wet pasteurisation process (60°C for 10 hours) is less than optimal and an additional period at 70°C has now been included.

Preliminary in vivo and in vitro studies (carried out in Edinburgh and Glasgow), using a 60°C for 10 hours wet heating procedure demonstrated that the sugar appeared to prevent heat denaturisation of factor VIII. The proposed new studies will be performed using products exposed to dry heat (68°C for 24 hours) and wet heat (as described above) and are designed to assess biological acceptability, clinical efficacy and residual infectivity. The need to assess both dry and wet heat arises because the former is less costly and subject to lower yield penalties. However the wet heat is likely to be more virocidally effective.

## GENERAL STRATEGY

### BIOACCEPTABILITY STUDIES (In vivo recovery and ½ life)

It is proposed that detailed studies are performed on a maximum of 12 stable (not bleeding) severe multi-transfused haemophilia A patients and 6 Von Willebrand Disease patients. The suggested protocols are included in the Annex I and II. Particular emphasis is required for the VWD studies because we need to know whether, in the event of withdrawal of intermediate VIII, we have concentrates which are of value to VWD patients.

## CLINICAL EFFICACY STUDIES

It is important, for licensing purposes, that we obtain as much information as possible on the clinical efficiency of the products.

A suggested protocol is included in Annex III. It is unclear, at the present time, as to the number of patients required to complete this study. Certainly it will be important to include patients undergoing both minor and major surgery in which clinical evidence of hemostatis is more easily ascertained.

## RESIDUAL INFECTIVITY STUDIES

These difficult but vital studies require access to patients who, ideally, have not been previously exposed to blood and blood products. The model protocol (see Annex IV) is based upon the work at the Oxford Haemophilia Centre and it should be noted that a prolonged period of study is required. It is suggested that a total of 15 patients should be studied, that as many batches as possible should be used and that the previous Oxford study using BPL intermediate VIII will be used as controls.

# SPECIFIC STRATEGY

## PRIORITY OF STUDIES

It is proposed that the first priority for the product currently available should be the bioacceptability study and that the two other studies are not commenced until this is completed and the data examined by the SHS BTS/Haemophilia Director W.P.

## PRODUCT RELEASE/STUDY CO-ORDINATES

Clinical colleagues who wish to contribute to these studies, will obtain their supplies of this material through their local Regional

Transfusion Centre. Release of product for clinical evaluation will be made on a named patient basis only.

It is recognised that because of the pressure of work in Hospital Haematology Departments it would be helpful if senior consultant staff of the SNBTS gave some assistance with regard to the co-ordination of these studies. It is proposed that when product is released the RTC staff involved will inform Dr F E Boulton (SEBTS) when studies on in vivo recovery and ½ life and/or clinical efficacy are initiated. Dr R J Crawford (WBTS) will be informed when product is released for residual infectivity studies. Drs Boulton and Crawford will give every assistance possible and report back to the Haemophilia/BTS Directors W.P.

No publication of these studies will be undertaken without consultation with the Haemophilia/BTS Directors W.P.

## FUTURE STUDIES

1. Long term repeat exposure

   Consideration will be given as soon as possible to the selection of specific patients that will be exposed exclusively to heat treated products. The main purpose of this study will be to investigate the occurrence of immune complexes, inhibitors and allergic reactions.

2. Inhibitor Patients

   It is suggested that these patients should be a low priority for future study, not least because of the likely quantities required. However, it is of some importance that these studies are undertaken in due course.

Suggestions with regard to these studies would be welcome

PATIENT'S NAME.....

HOSPITAL.....D.O.B.....

BODY WEIGHT.....Kg. HEIGHT.....cms

CONSULTANT.....

PARTICULARS OF INFUSION: Batch No.....

No. of Vials..... Volume infused.....mls. Total dose.....u.

If local VIII C assay on infusate was performed please give value and also value & source of standard.....

Solubility time.....minutes. Infusion time.....minutes

| | Before | 10 min. | 20 min. | 30 min. | 40 min. | 50 min. | 60 min | 180 min. | 360 min. | 24 hrs. | 10 days |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TEMPERATURE | | | | | | | | | | | |
| BLOOD PRESSURE | | | | | | | | | | | |
| PULSE | | | | | | | | | | | |
| Factor VIII C | | | | | | | | | | | |
| Factor VIII Cag | | | | | | | | | | | |
| Factor VIII Rag | | | | | | | | | | | |
| Anti HB (titre) | | | | | | | | | | | |
| 10 mls plasma stored at -30°C | | | | | | | | | | | |

NOTES: (1) Dose should be infused in 20 minutes.

(2) 10 mls plasma should be aliquoted (1 ml) and stored for future studies.

(3) Patients selected for this study should be haemostatically stable.

(4) PLEASE RETURN COMPLETED FORM TO DR F BOULTON, EDINBURGH & SOUTH EAST BLOOD TRANSFUSION SERVICE, ROYAL INFIRMARY, EDINBURGH.

Clinical Comments

Appendix X
Annex 1

## [illegible] IN VIVO RECOVERY AND T LIFE STUDIES VON WILLEBRAND'S DISEASE

PATIENT'S NAME..... ...

HOSPITAL.....D.O.B.....

BODY WEIGHT.....Kg. HEIGHT.....cms

CONSULTANT.....

PARTICULARS OF INFUSION: [illegible]atch No.....

No. of Vials..... Volume infused.....mls. Total dose.....u

If local VIII C assay on infusate was performed please give value and also value & source of standard.....

Solubility time.....minutes. Infusion time.....minutes

| | Before | 10 min. | 20 min. | 30 min. | 40 min. | 50 min. | 60 min | 180 min. | 360 min. | 24 hrs. | 10 days |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TEMPERATURE | | | | | | | | | | | |
| BLOOD PRESSURE | | | | | | | | | | | |
| PULSE | | | | | | | | | | | |
| Factor VIII C | | | | | | | | | | | |
| Factor VIII Cag | | | | | | | | | | | |
| Factor VIII Rag | | | | | | | | | | | |
| Anti HB (titre) | | | | | | | | | | | |
| 10 mls plasma stored at -30°C | | | | | | | | | | | |

NOTES: (1) Dose should be infused in 20 minutes.

(2) 10 mls plasma should be aliquoted (1 ml) and stored for future studies.

(3) Patients selected for this study should be haemostatically stable.

(4) PLEASE RETURN COMPLETED FORM TO DR F BOULTON, EDINBURGH & SOUTH EAST BLOOD TRANSFUSION SERVICE, ROYAL INFIRMARY, EDINBURGH.

Clinical Comments

Appendix X
Annex 2

~~[illegible] FACTOR VIII: CLINICAL EFFICACY STUDY~~

PATIENT'S NAME.....

HOSPITAL.....

CONSULTANT.....

CLINICAL CONDITION/SURGERY etc.....

.....

.....

Body Weight.....

Dose Schedule: Day (1).....Day (2).....

Day (3).....Day (4).....Day (5).....

.....

Batch Nos.....

Date Treatement Initiated.....

CLINICAL NOTES

(1) Was Haemostasis satisfactorily controlled?

.....

(2) Was amount of Factor VIII used similar to anticipated use of non-heated VIII product?

.....

(3) Were there any untoward reactions? (If so, please specify)

.....

(4) Any other comments?

.....

(5) On how many occasions has this patient received heat treated factor VIII concentrate?
(include information on the use of other haemostatics)

.....

NOTE: Please return to Dr F Boulton, Edinburgh & South East Scotland Blood Transfusion Service, Royal Infirmary, Edinburgh, along with any laboratory assay values.

Signed.....

(Medical Practitioner)

Appendix X
Annex 3

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Appendix X
Annex 4

# RESIDUAL INEFECTIVITY STUDIES ON SNBTS HEAT TREATED FACTOR VIII CONCENTRATE

## INTRODUCTION

The recent introductiont of factor VIII preparations, where attempts have been made to reduce the infectivity of concentrates by pasteurisation, -propriolactone, UV light and chemical treatment, has made it important to obtain objective evidence as to their safety with regard to (1) residual of infectivity, (2) the in vivo recovery and survival of factor VIII and (3) tests to exclude the presence of immune complexes and other factors which might cause allergic reactions.

Studies which cover (2) and (3) can be carried out by evaluating the use of concentrates in severe haemophiliacs on regular factor VIII therapy. The assessment of residual infectivity of concentrates can only be carried out satistactorily in prospective studies. In a preliminary study, South of the border, on 30 patients each given one or two batches of factor VIII to cover an operative procedure or other treatment requiring concentrate, showed that all 9 patients who had not received blood concentrates before contracted non-B hepatitis after receiving their first transfusion of either US commercial factor VIII or NHS factor VIII (Fletcher et al 1983), as assessed by liver function tests.

It is proposed to assess the residual infectivity of heat treated SNBTS factor VIII by means of a clinical trial in patients who have only minimally been exposed to large pool factor VIII concentrates, based on the protocol developed in Oxford.

## METHODS

Subjects will be selected from infrequently treated patient groups (haemophilia A and VWD) who have not previously been treated with large pool factor VIII concentrates. Ideally, they should not have received any blood products in the 6 months prior to entry into the trial, and preferably have received less than 50 donor units (total) of cryoprecipitate in the past. They should be HBsAg, anti-HBs and anti-HBc negative. They should also have had no previous hepatitis. A record of their transfusion history and past hepatitis should be included in the case notes for the trial.

## PROCEDURE

Patients attending any of the collaborating Haemophilia Centres during the course of the project who fulfil the criteria given will be admitted to the study. The aims of the study will be explained to them, and their consent or that of their parents obtained, if under 16 years of age.

Prior to the start of treatment each patient will undergo a full clinical examination, with special reference to liver disease, and blood will be taken for serological analysis, a full blood count and liver function tests, before treatment is started. A record should be made of their detailed transfusion history and past attacks of hepatitis. If the patient is seen as an emergency, then as many tests will be performed as is compatible with the situation. Blood samples for liver function tests must be separated and frozen within 1 hour of withdrawal.

Patients will be followed up for 12 months following their treatment episode in the absence of any transfusion hepatitis. Liver function tests and tests for hepatitis A and B markers, CMV and EBV should be carried out at appropriate intervals (see below). Blood will be collected before treatment and at weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 40 and 52 weeks post-transfusion. Follow-up after the 52 week study will be 3 monthly for a further 2 years. If a patient develops evidence of acute hepatitis, his liver function tests and hepatitis B serology will be followed fortnightly until his condition resolves, or for 3 months after the onset, and if his condition has not resolved, then monthly for six months.

## DEFINITION OF HEPATITIS

A patient will be considered to be suffering from acute hepatitis if he develops relevant clinical symptoms and signs, or shows an increase of at least two and a half times the upper limit of normal serum aminotransferase levels, having had normal values previously.

Hepatitis will be classified (1) as acute icteric (raised serum bilirubin
or (2) .. anicteric
or (3) .. symptomless

Hepatitis A, cytomegalovirus infection, glandular fever will be excluded by appropriate laboratory tests.

## LABORATORY TESTING

It is important that aliquots of sera obtained from patients in this project are retainedd for use when tests for non-A, non-B hepatitis etc become available.

While the basic laboratory tests may be carried out at the Microbiology Laboratory serving the local Haemophilia Centre, aliquots of each specimen (2 x 1 ml serum) obtained from all patients during the

period of follow-up and stored at -20°C, should be retained andsent to Dr R J Crawford at the Glasgow and West of Scotland Blood Transfusion Centre, Law Hospital, Carluke, Lanarkshire on the completion of each patient study. These archive samples will be retained securely by Dr Crawford and will not be subject to analysis without consultation of all investigators.

## CENTRAL RECORDING SYSTEM

Detailed records will be kept for all patients followed in the project. Dr Crawford will be informed when patients are entered into the study and copies of the completed follow-up form should be sent to him at the end of each patient study.

## ANALYSIS OF RESULTS

At appropriate intervals in the project, the incidence of acute hepatitis, both B and non-A, non-B, will be assessed by the Haemophilia/BTS Directors W.P.in relation to:-

(1) The transfusion history of each patient

(2) The disease category and severity of coagulation defect of each patient

(3) The ratio of symptomatic to symptomless cases of hepatitis for hepatitis B and non-A, non-B hepatitis

(4) The age of the patient

(5) The amount of factor VIII transfused to each patient

(6) The attack rate

(7) The incidence of chronic sequelae and the type of hepatitis.

It is the intention of the SNBTS to make the data from the studies available to the UK Haemophilia Centre Hepatitis Working Party.

## REFERENCE

Fletcher, M L, Trowell, J M, Craske, J, Pavier, K and Rizza, C R. Non-A, non-B hepatitis after transfusion of factor VIII in infrequently treated patients. BMJ, 287, 1754 (1983).

ASSESSMENT OF RESIDUAL INFECTIVITY OF SNBTS "HEPATITIS REDUCED" FACTOR VIII CONCENTRATES FOR NON-A, NON-B OR HEPATITIS B VIRUSES

## VIRAL HEPATITIS FOLLOW-UP*

| | | |
|---|---|---|
| tient | SURNAME: | PRODUCT UNDER TRIAL |
| | FORENAME(S): | HAEMOPHILIA CENTRE |
| | D.O.B. | FACTOR VIII LEVEL |
| | DIAGNOSIS: | |
| evious history of hepatitis<br>te of last treatment | | Previous Exposure to Blood Products (Type/Quantity/Dates) |
| aso or current treatment<br>ce of current treatment | | Batch No. of concentrate<br>Amount (Factor VIII Units) |

| ST ENQUIRY | | PRE-TREATMENT SAMPLE DATE | FOLLOW-UP DATES | | | | |
|---|---|---|---|---|---|---|---|
| | | | Week 1 | Week 2 | Week 4 | Week 6 | Week 8 |
| irubin (μmol/l) | | | | | | | |
| nine amino-nsferase (iu/l) | | | | | | | |
| artate amino-nsferase (iu/l) | | | | | | | |
| aline phosphatase | | | | | | | |
| Ag** | RIA | | | | | | |
| i-HBc | RIA | | | | | | |
| i-HBs | | | | | | | |
| i-HAV | | | | | | | |
| -HAV IgM | | | | | | | |
| -CMV | | | | | | | |
| i-HTLV-III | | | | | | | |
| ptoms/Signs of hepatitis ce last seen. ter Yes/No) | | | | | | | |
| toms /Signs of AIDS since t seen (Enter Yes/No) | | | | | | | |
| tory of transfusion since t seen. (Enter Yes/No) es Product, Batch Nos Date | | | | | | | |

| tient | SURNAME: | PRODUCT UNDER TRIAL |
|---|---|---|
| | FORENAME(S) | HAEMOPHILIA CENTRE |

| T ENQUIRY | | FOLLOW-UP DATES | | | | |
|---|---|---|---|---|---|---|
| | | Week 10 | Week 12 | Week 16 | Week 20 | Week 24 |
| irubin (μmol/l) | | | | | | |
| nine amino-nsferase (iu/l) | | | | | | |
| artate amino-nsferase (iu/l) | | | | | | |
| aline phosphatase | | | | | | |
| Ag** | RIA | | | | | |
| i-HBc | RIA | | | | | |
| -HBs | | | | | | |
| -HAV | | | | | | |
| -HAV IgM | | | | | | |
| -CMV | | | | | | |
| -EBV | | | | | | |
| -HTLV-III | | | | | | |
| toms/Signs of hepatitis since seen. (Enter Yes/No) | | | | | | |
| toms/Signs of AIDS since seen. (Enter Yes/No) | | | | | | |
| ory of transfusion since seen. (Enter Yes/No) es Product, Batch Nos and Date) | | | | | | |

Page 3 (Continuation Sheet)

| tient | SURNAME: | PRODUCT UNDER TRIAL |
|---|---|---|
| | FORENAME(S) | HAEMOPHILIA CENTRE |

| ST ENQUIRY | | FOLLOW-UP DATES | | | |
|---|---|---|---|---|---|
| | | Week 28 | Week 32 | Week 40 | Week 52 |
| irubin (μmol/l) | | | | | |
| uni amino-<br>nsferase (iu/l) | | | | | |
| artate amino-<br>nsferase (iu/l) | | | | | |
| aline phosphatase | | | | | |
| Ag** | RIA | | | | |
| i-HBc | RIA | | | | |
| i-HBs | | | | | |
| i-HAV | | | | | |
| i-HAV IgM | | | | | |
| i-C... | | | | | |
| i-EBV | | | | | |
| i-HTLV-III | | | | | |
| ptoms/Signs of hepatitis since<br>t seen. (Enter Yes/No) | | | | | |
| ptoms/Signs of AIDS since<br>t seen. (Enter Yes/No) | | | | | |
| tory of transfusion since<br>t seen. (Enter Yes/No)<br>Yes Product, Batch Nos and Date | | | | | |

Page 4 (Continuation sheet)

| | | |
|---|---|---|
| ;ient | SURNAME: | PRODUCT UNDER TRIAL |
| | FORENAME(S) | HAEMOPHILIA CENTRE |

| ;T ENQUIRY | | FOLLOW-UP DATES | | | | |
|---|---|---|---|---|---|---|
| | | | | | | |
| irubin (μmol/l) | | | | | | |
| nii amino-<br>nsferase (iu/l) | | | | | | |
| artate amino-<br>nsferase (iu/l) | | | | | | |
| aline phosphatase | | | | | | |
| Ag** | RIA | | | | | |
| i-HBc | RIA | | | | | |
| i-HBs | | | | | | |
| i-HAV | | | | | | |
| i-HAV IgM | | | | | | |
| i-CMV | | | | | | |
| .-EBV | | | | | | |
| i-HTLV-III | | | | | | |
| )toms/Signs of hepatitis since<br>: seen. (Enter Yes/No) | | | | | | |
| )toms/Signs of AIDS since<br>: seen. (Enter Yes/No) | | | | | | |
| :ory of transfusion since<br>. seen. (Enter Yes/No)<br>es Product, Batch Nos and Date. | | | | | | |

Signed . . . . . .

Date . . . . . .

# ASSESSMENT OF RESIDUAL INFECTIVITY OF SNBTS HEAT TREATED FACTOR VIII CONCENTRATES (DATA SHEET)

* This form should be used for cumulative recording of results of tests at intervals as indicated in the main protocol for up to nine months after receiving the heat treated factor VIII.

** Serum for hepatitis B antigen and antibody, hepatitis A, CMV, EBV and HTLV-III antibodies should be packed with standard precautions and sent to Dr R J Crawford, Glasgow and West of Scotland Blood Transfusion Centre, Law Hospital, Carluke, Lanarkshire.