Hirsut Appt 2

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

CONFIDENTIAL

SCOTLAND/NORTHERN IRELAND HAEMOPHILIA DIRECTORS CLINICAL TRIAL TO ASSESS THE TOLERABILITY OF HIGH POTENCY FACTOR VIII CONCENTRATE (HPVIII) MANUFACTURED BY SNBTS IN PATIENTS WITH HAEMOPHILIA A (HP 016)

PROTOCOL
14 SEPTEMBER 1992

R R C STEWART

GRO-C

GRO-C (Fax)

SCOTLAND/NATIONAL BLOOD TRANSFUSION SERVICE

CLINICAL TRIAL TO ASSESS THE TOLERABILITY OF HIGH POTENCY FACTOR VIII CONCENTRATE (HPVIII) MANUFACTURED BY SNBTS IN PATIENTS WITH HAEMOPHILIA A (HP016)

Protocol dated .....

Clinical Investigator

Name .....

Title .....

Address .....

.....

.....

Signed .....

Date .....

Monitor

Dr R R C Stewart
SNBTS Headquarters Medical Unit
Medical Unit
Livingston House
39 Cowgate
Edinburgh
EH1 1JR

Signed .....

Date .....

INDEX PAGE

APPENDICES

I Sampling Schedule
II Information for Patients/Consent to Participate Form
III Declaration of Helsinki

1. INTRODUCTION

The treatment of patients with haemophilia A was revolutionised in 1964 following the observation by Poole et al (1) who demonstrated that a fraction of plasma precipitated on thawing (cryoprecipitate) was effective in reducing bleeding in such patients. For many years, cryoprecipitate was the mainstay of treatment of haemophilia patients, until purified Factor VIII concentrates became available.

While this further improved the treatment of haemophilia patients, it was not without its drawbacks, notably virus transmission (HIV, hepatitis B and non-A, non-B hepatitis agents) and an apparent immune disturbance in non-HIV infected individuals. The cause of this immune disturbance has not been unequivocally identified, and many contaminants of the Factor VIII concentrate have been implicated, including immunoglobulin and total protein load.

This suggestion has led most manufacturers to develop Factor VIII products which have less contaminating protein in them. The Protein Fractionation Centre, Edinburgh has developed such a product in collaboration with French colleagues.

This surveillance study is designed to assess the tolerability of HPVIII in patients with Haemophilia A, particularly in respect to evidence of viral transmission.

The aim of this study is to assess the tolerability of HPVIII. This will consist of the following elements.

i. Immediate (allergic-type) reactions.

ii. To assess effects of HPVIII on immune function, by measurement of lymphocyte subset numbers.

iii. To assess the development of inhibitors to Factor VIII in patients on HPVIII.

iv. To monitor liver function in patients on HPVIII.

2. METHODS

2.1 Patients

The patients will be hospital in patients and outpatients and will be recruited by the Haemophilia Directors of Scotland and Northern Ireland.

2.2 Inclusion Criteria

Patients of either sex and any age whom the physician believes requires Factor VIII concentrate. All patients shall be diagnosed as suffering from Haemophilia A. Patients who have not been previously treated with a Factor VIII concentrate (Previously untreated patients) should be included in the PUP Study (HP012).

2.3 Exclusion Criterion

The only exclusion criterion is intolerance to Factor VIII concentrates.

2.4 Number of Patients

Patients who fulfil the entry criteria and who, in the opinionm of the Haemophilia Director, require treatment with HPVIII will be enrolled. This will be limited to 250 patients.

3. TRIAL MEDICATION

3.1 Description

The product to be used in the study is:
HPVIII: Factor VIII in vials of approximately 250 IU with a specific activity of greater than 50 IU/mg protein. This product is produced by the Protein Fractionation Centre and will be supplied gratis by the SNBTS.

3.2 Storage

Factor VIII concentrate should be stored in the dark at temperatures between +2^{o}C and +8^{o}C.

3.3 Resolution from the dry state

The vial of Factor VIII Concentrate and the sterile water for injections (Ph Eur) should be brought to room temperature before reconstitution. Remove the plastic caps from the Factor VIII Concentrate and the sterile water for injections (Ph Eur) and clean the stoppers with a spirit swab. Using a syringe, gently add the sterile water for injections (Ph Eur) to the dried Factor VIII. The contents of the vial should be mixed gently to ensure resolution. DO NOT SHAKE THE SOLUTION. The solution should then be allowed to stand without further agitation.

Performed in this way the reconstitution is generally instantaneous and should be complete within 5 minutes in the case of HPVIII.

4. DOSE OF HPVIII

The dose of HPVIII given to each patient will be individualised to attempt to achieve blood levels appropriate for their clinical condition.

5. RECRUITMENT OF PATIENTS

The purpose and procedures of the study will be explained to prospective subjects and their unforced written consent obtained prior to their taking part in the study. It must be emphasised to each prospective subject that, if they wish to withdraw their participation in the study, they are free to do so without prejudicing their clinical care.

6. TRIAL SCHEDULE

6.1 Infusion of trial medication

The material should be infused as soon as practicable after dissolution is complete. The infusion rate should be such to permit the infusion to be completed within 30 minutes.

6.2 Sample Collection Arrangements

6.2.1 Prior to Therapy

See Appendix I

1. For emergency treatment take a single blood sample immediately before infusion of HPVIII concentrate.

2. For an elective procedure, if possible an additional pre-treatment blood sample should be collected some time before entry.

Blood Samples

All samples will be analysed locally on entry:

1. Lymphocyte subsets
2. Liver function test (including ALT or AST)
3. Viral serology: Test for anti-HAV, HBsAg, anti-HBc, anti-HCV, anti-parvovirus B_{19}
4. Serum stored (5ml, for children < 5 year - 1ml) at -40^{o}C

6.2.2 Follow Up Samples

THREE MONTHLY SAMPLES

1. T cell subset numbers shall be determined
2. Liver function test (including ALT or AST)
3. Viral serology: Test for anti-HAV, HBsAg, anti-HBs, anti-HCV, anti-parvovirus B_{19}
4. Serum sample stored

These sampling schedules are summarised in Appendix I.

6.3 Detection of Inhibitors to Factor VIII(c)

Samples shall be tested for the presence of inhibitors to Factor VIII(c) before the first infusion and three monthly intervals thereafter. Any factor VIII inhibitor activity detected will be reported in Bethesda units.

6.4 Documentation

1. Entry Registration Form (Form A) should be completed as soon as a potentially suitable patient is identified and sent to the Co-ordinating Centre. The Co-ordinating Centre will issue a letter of confirmation of receipt which will include a patient study number.

2. Blood Product Usage Report Form (Form B) should be completed to keep a record of blood product usage by patients in the study. If it is more convenient, a computer printout of usage may be attached to Form B.

3. A quarterly laboratory reportform shall be completed for each patient, on which the results of those tests required by the protocol shall be recorded.

6.5 Adverse Events

Acute adverse events in the use of Factor VIII concentrates are rare. Some patients experience slight irritation at the site of injection. A transitory headache or nausea following the administration of Factor VIII concentrate also has been reported and for individual patients, this appears to be batch related.

In the event of any patient experiencing a reaction to the infusion, the infusion should be stopped immediately and appropriate medical action taken. The infusion should be restarted in such case only when, in the opinion of the attending physician, it is justifiable to do so.

6.6 Analysis of Data

As this is an open study without a control group, the data will be presented descriptively. The data will be subject to analysis to determine whether there are any trends associated with time on HPVIII.

7. ADMINISTRATION

7.1 Ethical Review

The protocol will be approved by the ethics committee of each of the Haemophilia Centres which supplies the haemophilia patients. No individual, whose respective ethics committee has not consented to the study, will be entered.

7.2 Declaration of Helsinki

The trial shall conform to the recommendations of the Declaration of Helsinki as adopted at 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by the 41st World Medical Assembly, Hong Kong 1989. A copy is appended (Appendix IV).

7.3 Legal Category

The trial will be performed under the terms of the Clinical Trials Exemption (CTX) Scheme. It will not take place until authorisation to proceed has been received from the Medicines Control Agency.

7.4 Compliance with protocol and permitted deviations

The final protocol of the study will be agreed by the clinical investigators and the SNBTS and will be signed in confirmation of such agreement. The protocol will be approved by the SHHD and the local Ethics Committee. Any variations to this protocol must be agreed in advance by the clinical investigators and approved by the SNBTS and SHHD. The Medicines Control Agency and the local Ethics Committee will be informed of any such variations. While in normal circumstances the protocol should be adhered to, in any emergency situation, the clinical investigator(s) shall exercise their clinical judgement and safeguard the patient's interests. In such cases, deviations from the protocol shall not require the prior approval of the SNBTS and the SHHD, nor the local Ethics Committee. Any such deviations from the protocol, along with full details of the reasons for their occurrence should be reported to the SNBTS in writing as soon as possible.

7.5 Confidentiality

Volunteers taking part in the study will be issued with a study number, and this number and initials will be used to identify samples and in the handling of data. Patients taking part in the study may thus be assured that their identity will be known to as few people as possible.

7.6 Maintenance of Records

The Case Report Forms of each patient shall be retained by the SNBTS for a period of at least 15 years and shall be made available for the inspection of members of the Regulatory Authorities, or other authorised individuals only.

7.7 Indemnity of Investigators/Haemophilia Doctors

Trials of SNBTS Factor VIII products are covered by a Scottish Home and Health Department Compensation Scheme which is based on ABPI Healthy Volunteer Study Guidelines. One copy of this letter should be signed by the Investigator in agreement with the terms of the letter and returned to Dr R Stewart. In addition each major investigator will be required to sign an Investigator's Agreement.

7.8 Prestudy Documentation

The study will be conducted under the Clinical Trial (Exemption) Scheme (CTX) of the Medicines Control Agency. Trial medication will not be issued to a trial centre until Dr R Stewart receives the following:

1. Approval of the study by Medicines Control Agency by the issue of CTX.

2. A copy of the Local Ethics Committee's letter of approval.

3. A copy of the laboratory normal ranges for the tests required by the protocol.

4. A specimen copy of the informed consent form.

5. An up-to-date copy of the curriculum vitae of each of the clinical investigators.

6. A copy of the letter of indemnity signed by the major investigator in that centre.

7.9 Monitoring Responsibility

Monitoring of the trial will be the responsibility of Dr R Stewart who will visit the Centre to review progress at least every three months. During the early phases of the trial these visits will be more frequent to ensure that any misunderstandings are cleared up quickly.

7.10 Adverse Event Reporting

Any serious adverse events which occurs subsequent to the infusion of HPVIII should be reported immediately by telephone to Dr R Stewart or his deputy (Tel No 031 220 4590). A serious adverse event includes the death of any patient in the study of whatever causes, even if apparently unrelated to the trial medication. This is necessary as the SNBTS must report such reactions to the Medicines Control Agency promptly. Minor adverse events would be reported at the next regular monitoring meeting.

7.11 Early Cessation of the Trial

The SNBTS reserve the right to stop the trial if:

a. Recruitment is too slow to allow accrual of an adequate number of patients in a reasonable length of time.

b. Evidence is gained that patients are being exposed to an unacceptable risk.

c. For any reason, it is not possible to continue to supply the trial material.

d. Advances in therapy make the protocol obsolete.

7.12 Publication

Without prejudice of the intention to publish the results of this study, the SNBTS reserve the right to review any written or oral presentation of the data prior to publication. This is to ensure that no information with potentially commercial application is disclosed prematurely.

8. REFERENCES

1. Poole J, Hershgold EG, Pappenhagen AR, 1964 Nature, 203, 312.

APPENDIX I

SAMPLING SCHEDULE

	Prior to Therapy	Month 3	Month 6	Month 12
Liver Function Tests	X	X	X	X
Serum Stored (5ml)	X	X	X	X
Lymphocyte Subsets	X	X	X	X
Factor VIII Inhibitors	X	X	X	X

APPENDIX II

INFORMATION FOR PATIENTS
Clinical Trial of High Potency
Factor VIII

Trial Number: HP 016

You are invited to take part in a clinical trial of a new preparation of Factor VIII. This product is prepared by the Protein Fractionation Centre made from plasma collected by the SNBTS and NIBTS from unpaid Scottish and Northern Irish blood donors. These donors are all tested for the presence of antibodies to HIV, and for the presence of Hepatitis B surface antigen. The factor VIII concentrate is of a higher potency than that currently produced by the Scottish National Blood Transfusion Service (having a specific activity of over 50 IU per milligramme of protein). It has been suggested that such higher potency factor VIII concentrates may enhance patient care. The most noticeable difference which you as a patient will detect is that the product is made up in a smaller volume and it is likely to go into solution more quickly than other products which you have used.

A similar product (made from plasma from French blood donors) is in routine use in France and there is considerable experience with it. However, as this product has not been widely used within the UK, the Haemophilia Directors and the Scottish National Blood Transfusion Service have agreed that, in the meantime, it should only be used on a clinical trial basis.

The purpose of the trial is to closely monitor recipients of the high potency factor VIII concentrate to ensure that the use of the product is not associated with any unexpected side effects. This will require that samples are taken at specified times for specified tests. This will mean that you will have to attend the Haemophilia Centre more frequently than at present. Travelling expenses for such additional visits will be re-imbursed. The data gained will be very valuable and will assist in the improvement of haemophilia care in Scotland and Northern Ireland.

If you have any questions about the purpose or procedures of the trial, your Haemophilia Director will attempt to answer them.

You are invited to take part in this trial, but should be clear that you may choose not to do so. Having agreed to take part in the study, you may withdraw at any time without being required to give a reason. You may be assured that refusal to take part or withdrawal will not prejudice your medical care in any way, although, obviously, you will not be able to continue to receive the high potency factor VIII concentrate. The Haemophilia Director and the staff of the centre will take responsibility for your clinical care during the study. They will halt your participation if it is felt that continued participation would be detrimental to your well-being.

The Scottish Home and Health Department has agreed to offer compensation to patients who take part in trials of SNBTS products in the unlikely event of their suffering any significant deterioration in health or well-being as a result of their taking part in the trial.

All efforts will be made to ensure that information that is obtained with this study which can be identified with you will remain confidential. In any written reports and publications, you will be referred to by a code number only.

It however is possible that representatives of the Scottish National Blood Transfusion Service or of governmental regulatory agencies may wish to examine your records and in signing this consent you give permission for such examination. Some insurers treat participation in medical studies as a material fact which should be mentioned when making any proposal for health-related insurance and that accordingly participation in the study should be disclosed of the patient is in the process of seeking or renewing any such insurance and the patient should check that participation does not affect any existing policies (including endowment mortgages) held by the patient. A form to send to our insurers will be supplied.

This information for patients is intended to assist the patient in deciding whether to take part in the clinical trial. If the patient agrees to do so, they should sign the consent form which should be presented along with this document.