SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

CONFIDENTIAL

A PHARMACOKINETIC STUDY TO

COMPARE A NEW HIGH POTENCY FACTOR VIII PRODUCT WITH AN ESTABLISHED

INTERMEDIATE PURITY FACTOR VIII PRODUCT IN HAEMOPHILIA PATIENTS

(HP 011)

PROTOCOL
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Protocol dated .....

Clinical Investigator

Name .....

Title .....

Address .....

.....

.....

Signed .....

Date .....

Monitor

Dr R R C Stewart
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Medical Unit
Livingstone House
39 Cowgate
Edinburgh
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Signed .....

Date .....

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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 apparent immune disturbance has not been unequivocably 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 (PFC) has taken the development of such a product as a major objective and has entered a collaborative arrangement with CRTS (Lille).

This study is a comparative pharmacokinetic study in which HPVIII will be compared with Z8, according to the published guidelines of the Factor VIII/Factor IX Scientific and Standardisation Committee of the International Society for Thrombosis and Haemostasis (2)

The products used will be material manufactured at the Protein Fractionation Centre, Edinburgh from plasma collected by the SNBTS and NIBTS.

The aim of the study is to demonstrate that the processing required of the new product:

1. does not alter the active molecule in such a way as to reduce its in vivo recovery.
2. does not alter the in vivo half life of the active molecule.

2. METHODS

2.1 Patients

Twelve stable non-bleeding patients with haemophilia A (WHO disease classification number 286.0) will be entered. They should have a baseline Factor VIII of less than 2% (ie normally classed as 'severe') and preferably should be anti-HIV negative.
The volunteers will be hospital outpatients and will be recruited by the Haemophilia Directors of Scotland and Northern Ireland.

2.2 Exclusion criteria

The following will be excluded from the study:

1. Volunteers who have received Factor VIII concentrate, cryoprecipitate or fresh frozen plasma in the previous 7 days.
2. Volunteers who are considered unlikely to attend for the full 48 hour session.
3. Patients with an active bleed.
4. Patients who are less than 16 years of age.
5. Patients with inhibitors to Factor VIII

2.3 Location of study

The study shall take place at Inveresk Clinical Research Ltd, Riccarton, Edinburgh.

2.4 Trial Design

The study will be a randomised crossover study in which each volunteer will receive both HP VIII and Z8. Patients will be randomised as to which treatment is received first using randomisation lists prepared before the study commences by Dr R Stewart and a period of at least 7 days will be allowed between the two infusions.

3. TRIAL MEDICATION

3.1 Description

The products to be used in the study are Z8 : Factor VIII in vials of approximately 200IU containing anti-haemophilic factor A at a specific activity of 0.5-1.0 IU/mg of protein.
HPVIII: Factor VIII in vials of approximately 250IU containing anti-haemophilic factor A at a specific activity of greater than 50IU/mg of protein.
These products are produced by the Protein Fractionation Centre from plasma collected by the SNBTS and Northern Ireland BTS and will be supplied gratis by the SNBTS.
Two different batches of each product will be used.

3.2 Storage

Factor VIII concentrate should be stored in the dark at temperatures between +2°C and +8°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. Z8 may take up to 20 minutes to dissolve.

4. **DOSE OF FACTOR VIII**

The dose of Factor VIII given to each patient will be individualised to attempt to achieve a peak plasma level of 1.0 IU/ml. This will require that each patient receives 50 IU/kg of Factor VIII. The dose of Factor VIII, and the corresponding volumes of the two products are given in Appendix I.

5. **RECRUITMENT OF VOLUNTEERS**

The purpose and procedures of the study will be explained to prospective participants 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 Pre-infusion samples

Prior to the start of the infusion a 9ml sample of blood shall be taken into a 10ml tube containing 1ml of citrate anticoagulant solution (consisting of 3.1% sodium citrate dihydrate with 5% Hepes). In addition, a 10ml sample shall be taken for local laboratory safety monitoring.

6.2 Clinical monitoring

The volunteers' temperature, recumbent blood pressure and pulse rate shall be noted prior to the commencement of the infusion and 30 mins, 1h, 2h, 4h, 8h, 12h, 18h, 24h, 36 and 48h thereafter (see Appendix II).

6.3 Infusion of trial medication

The material should be infused as soon as practicable after dissolution is complete. The infusions, however, should be completed within 30 minutes.

6.4 Sampling schedule

Nine millilitre samples should be taken into a 10ml tube containing 1ml of citrate anti-coagulant solution (consisting of 3.1% sodium citrate dihydrate with 5% HEPES).

These tubes will be supplied by the Coagulation Laboratory of the Edinburgh and South East of Scotland Blood Transfusion Service. A sample will be taken before the infusion commences and at the following times after the start of the infusion: 15 mins, 30 mins, 1h, 2h, 3h, 4h, 6h, 8h, 12h, 16h, 24h, 30h,36h and 48h. In addition, a 10ml sample shall be taken for local laboratory safety monitoring. This is detailed in Appendix III.

6.5 Sample handling

Each sample for Factor VIII assay should be placed on ice immediately after collection and centrifuged as soon as possible at 2000 to 3000 x g for 15 to 30 min at 0 to +20°C.

The supernatant shall be split into 1ml aliquots, and snap frozen in ethanol: dry ice and stored at -20°C. Tubes will be identified by a code number to allow the laboratory performing the analysis of samples to be 'blind' to the patient and timing of the sample.

6.6 Sample analysis

The samples for Factor VIII assay will be transported to the Coagulation Laboratory of the Edinburgh and South East of Scotland Blood Transfusion Service, where the Factor VIII activity will be measured by a one stage Factor VIII assay using a calibrated International Plasma Factor VIII standard.

6.7 Laboratory Safety Monitoring

The samples taken prior to infusion and at 48 hours will be used to perform a full blood count and a clinical chemistry screen at the Pathology Laboratory of Inveresk Research International.

Samples at the Coagulation Laboratory also will be analysed for von Willibrand Factor antigen levels and, for Factor VIIIc antigen levels.

Additional aliquots should be stored at the Edinburgh South East of Scotland BTS Coagulation Laboratory in case other assays are considered necessary.

7. CLINICAL PERSONNEL

The study will be run by the medical and nursing staff of Inveresk Clinical Research Ltd.

8. 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 severe reaction to the infusion, the infusion should be stopped immediately and appropriate medical action taken. The infusion should be restarted in such cases only when, in the opinion of the attending physician, it is justifiable to do so.

9. STATISTICAL DESIGN

9.1 Null hypothesis

That the preparative handling of the HPVIII causes such a change in the molecule as to markedly reduce the in vivo recovery and half life compared with Z8.

9.2 End points

The mean half lives infusion/distribution phase and elimination phase of the products will be calculated.
The mean peak serum level of the products will be calculated.
Recovery will be calculated using the formula:

$$\text{Percentage Recovery} = \frac{\text{plasma volume} \times \text{observed rise in Factor VIII level}}{\text{dose of Factor VIII given}}$$

Plasma volume will be calculated from the formula:

Plasma volume (ml) = 41 x weight (kg)

The half-life will be calculated using Software as recommended by the Factor VIII/Factor IX Scientific and Standardisation Committee of the International Society of Thrombosis and Haemostasis (2).

9.3 Data Collection

A case report form will be completed for each subject, recording the results of the clinical monitoring of the volunteers. In addition laboratory report forms will be completed recording the results of the tests performed on the samples.

These should be completed in blue or black ink. Any errors should be crossed out with a single line and the correct value entered alongside. The change should be dated and initialled by the person making the correction. The original entry should still be legible. Snopake, Liquid Paper etc must not be used.
The original of the Case Report Form will be collected by Dr R Stewart on his routine visits to the Trial Centre.

9.4 Data handling

While the samples will be assayed at the Coagulation Laboratory of the Edinburgh and South East of Scotland Blood Transfusion Centre copies of the raw data from these will be returned to Inveresk Clinical Research Ltd for compilation into a pharmacokinetic report.

10. ADMINISTRATION

10.1 Ethical review

The protocol will be approved by the ethics committee of each of the Haemophilia Centres which supplies the haemophiliac volunteers. No individual, whose respective ethics committee has not consented to the study, will be entered. In addition, this protocol will be reviewed by the Ethics Committee as arranged by Inveresk Clinical Research Ltd.
The unpressured written informed consent of the patients should be collected prior to the start of the study. An information for patients document is appended to this protocol (Appendix IV)

10.2 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 35th World Medical Assembly, Venice 1983 and the 41st World Medical Assembly, Hong Kong 1989. A copy is appended. (Appendix V).

10.3 Legal category

This 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 Department of Health.

10.4 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 occurence should be reported to the SNBTS in writing as soon as possible.

10.5 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. Volunteers taking part in the study may thus be assured that their identity will be known to as few people as possible.
Information from the study may be published in the scientific literature. Patient confidentiality will be maintained in any such reports.

10.6 Maintenance of Records

The Laboratory Report Form of each volunteer 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.

10.7 Indemnity of Haemophilia Doctors/Patient Compensation

Trials of SNBTS Factor VIII products are covered by a Scottish Home and Health Department Compensation Scheme. This is based largely on the ABPI Guidelines for Healthy Volunteer Studies. The Department requires to review each trial before it can proceed. They will issue a letter of indemnity to each major clinical investigator. Also, clinical investigators are indemnified against claims arising from their participation in the study.

In addition each major investigator will be required to sign an Investigator's Agreement.

10.8 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 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 investigators.

10.9 Monitoring Responsibility

Monitoring of the trial will be the responsibility of Dr R Stewart who will visit the Centre during the study to assess progress.

10.10 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.

10.11 Early Cessation of Trial

The SNBTS reserve the right to stop the trial if:

a. Evidence is gained that patients are being edposed to an unacceptable risk.

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

c. Advances in therapy make the protocol obsolete.

10.12 Publications

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.

11. REFERENCES

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

2. Morfini M, Lee M, Messori A, 1991, Thrombosis and Haemostasis, 66, 384-6.

3. Guidelines for Medical Experiments in Non-Patient Human Volunteers. Association of the British Pharmaceutical Industry 1988.

APPENDIX I

DOSE	50 IU/KG	POTENCY	28	10 IU/ml
			HPVIII	25 IU/ml
WEIGHT	28		HPVIII	
	IU ml	IU	ml	
50	2500 250	2500	100	
52	2600 260	2600	104	
54	2700 270	2700	108	
56	2800 280	2800	112	
58	2900 290	2900	116	
60	3000 300	3000	120	
62	3100 310	3100	124	
64	3200 320	3200	128	
66	3300 330	3300	132	
68	3400 340	3400	136	
70	3500 350	3500	140	
72	3600 360	3600	144	
74	3700 370	3700	148	
76	3800 380	3800	152	
78	3900 390	3900	156	
80	4000 400	4000	160	