CONFIDENTIAL

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

# REPORT ON CLINICAL TRIALS TO ASSESS THE EFFICACY AND TOLERABILITY OF A NEW HIGH PURITY FACTOR VIII CONCENTRATE (LIBERATE) IN PATIENTS WITH HAEMOPHILIA A

SNBTS PRODUCT SERVICES DEPARTMENT

# INDEX





SBTS0003795_062_0002

## ABBREVIATIONS/DEFINITIONS

| | |
|---|---|
| **Z8** | Intermediate purity factor VIII concentrate manufactured by SNBTS. |
| **LIBERATE** | Trial product. New high purity factor VIII concentrate produced by SNBTS. |
| **HPVIII** | High purity factor VIII produced by CRTS, Lille from Scottish plasma. |
| **HP014** | Clinical trial comparing a high potency factor VIII (Liberate) with an intermediate purity factor VIII concentrate (Z8) in the treatment of patients with Hamophilia A. |
| **HP012** | Clinical trial to assess the tolerability of high potency factor VIII (Liberate) in non-HIV infected patients with Haemophilia A. The patients on this study are 'previously untransfused patients' (PUPs). |
| **HP013** | Clinical trial to assess the tolerability of high potency factor VIII (Liberate) in patients with Haemophilia A who possess antibodies to HIV. |
| **HP016** | Clinical trial to assess the tolerability of high potency factor VIII (Liberate) in patients with Haemophilia A. |

# DRAFT FINAL REPORT FOR SNBTS CLINICAL TRIAL HP014

**CONFIDENTIAL**

**SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE**

# HP014

# CLINICAL TRIAL COMPARING HIGH POTENCY FACTOR VIII CONCENTRATE (LIBERATE) WITH AN INTERMEDIATE PURITY FACTOR VIII CONCENTRATE (Z8) IN THE TREATMENT OF BLEEDING IN PATIENTS WITH HAEMOPHILIA A

# DRAFT FINAL REPORT

**SNBTS Product Services Department**

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| | |
|---|---|
| **SNBTS Monitor :** | Dr R R C Stewart, Product Services Manager (succeeded by Miss J Pelly, Product Services Manager 1/12/93) |
| **Principal Investigators:** | Dr B E S Gibson Glasgow (Paediatrics)<br>Prof G D O Lowe Glasgow<br>Dr C A Ludlam Edinburgh<br>Dr E Mayne Belfast |
| **Report Author:** | Miss E McIntosh, Clinical Research Associate |
| **Date:** | 2 February, 1995 |

## SUMMARY

This study is designed to prove that the new High Purity Factor VIII (Liberate) produced by the SNBTS is effective in the treatment of bleeding in patients with Haemophilia A.

This study examined 110 spontaneous bleeds in 8 patients and also assessed the level of haemostasis achieved in 17 patients undergoing surgery.

All patients showed satisfactory results.

Patients were recruited to the study by the Haemophilia Directors at Royal Infirmary Edinburgh, Glasgow Royal Infirmary, Royal Hospital for Sick Children, Glasgow and Royal Victoria Hospital, Belfast.

To preserve patient confidentiality, patients were identified by subject number. This number identifies the trial centre, trial number and patient number:- eg E-14-01 is the first patient from Edinburgh on HP014.



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## STUDY PERSONNEL

| | |
|---|---|
| **SNBTS Monitor:** | Dr R R C Stewart, BSc, PhD<br>Product Services Manager |
| **Medical Adviser:** | Professor J D Cash, BSc, MBChB, PhD, FRCPath, [illegible], FRCP (Glas), FRCP (Edin) |

**Investigators**

| | |
|---|---|
| **Belfast:** | Dr E E Mayne MBChB, BaO, MD, FRCP(Glas), FRCPath<br>Dr O McNulty MBChB, BaO |
| **Edinburgh:** | Dr C A Ludlam, BSc(hons), MBChB, PhD, FRCP(Edinb), FRCPath<br>SN S Trainer, RGN |
| **Glasgow:**<br>Royal hospital for Sick Children | Dr B E S Gibson, MBChB, MRCPath, FRCP(Glas) Dip in Forensic Med.<br>Dr R Ahmed MBChB, MRCP |
| Glasgow Royal Infirmary | Prof G D O Lowe, MBChB, JCHMT (General Medicine) MD, FRCP(Edinb & Glas), FRCP (Lond) |



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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 time 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 impurities in 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. One such product is HPVIII prepared by the SNBTS Protein Fractionation Centre in Edinburgh. This product is prepared from plasma collected by the SNBTS and NIBTS.

## 2. OBJECTIVE

The aim of this study is to demonstrate that Liberate is effective in the treatment of bleeding in patients with Haemophilia A.

## 3. METHODOLOGY

### 3.1 *Study Design*

Patients with spontaneous bleeds will be assessed for 24 hours after each infusion or until it ceases if this is longer.

Patient will be monitored for 4 months on Z8 and thereafter on Liberate.

The study will continue until production of Z8 ceases and the protocol becomes obsolete.

### 3.2 *Patient Selection*

There is no intended upper limit to the number of patients enrolled. Patients will be hospital in-patients and those on home therapy.

#### 3.2.1 Inclusion Criteria

1. Patients with Haemophilia A.
2. Patients over 12 years of age.
3. Patients with an active bleed.
4. Patients who require Factor VIII to cover surgery or dental extraction.



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3.2.2 Exclusion Criteria

1. Patients whose bleed is potentially life threatening
2. Patients with a history of severe reactions to blood products
3. Any patient with Factor VIII inhibitors.
4. Any patient deemed unsuitable by an investigator.

3.3 ***Treatment***

The products used in the study are:

*Liberate*: Factor VIII in vials of approximately 250 IU with a specific activity of about 150 IU/mg protein.

*Z8*: Factor VIII in vials of approximately 200 IU containing anti-haemophilic factor A at a specific activity of 0.5 - 1.0 IU/mg protein.

The dose of Factor VIII given to each patient will be individualised to achieve blood levels appropriate for their clinical condition. For a minor bleed, initial treatment should be with 500 IU. More severe bleeds will require increased doses.

3.4 ***Measurement of Efficacy***

3.4.1 Hospital In-Patients

Joint or muscle bleeds will be assessed by the following measurements.

1. Severity of pain (pain scale is given in Appendix 1).
2. Circumference of the joint or muscle - pre-infusion
   5/6 hours post-infusion.
3. Use of Analgesia.
4. Goneometry pre-infusion
   5/6 hours post-infusion
5. Patients personal assessment
6. Recurrence of bleeding.

Open bleeds will be assessed by:

1. Cessation of bleeding
2. Recurrence of bleeding
3. Patients personal assessment.



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3.4.2 Home Therapy

Joint or muscle bleeds will be measured by

1. Severity of pain
2. Use of analgesia
3. Recurrence of bleeding
4. Patients personal assessment

Open bleeds will be measured by:

1. Recurrence of bleeding
2. Cessation of bleeding
3. Patients personal assessment

3.4.3 Cover for Surgery or Dental Extraction

This will be assessed by noting the extent, if any, of bleeding during and after the procedure.

3.4.4 Safety Monitoring

All infusions will initially be given in hospital on an out-patient basis.

When the patient is treated in hospital, temperature, blood pressure and pulse rate shall be noted prior to the commencement of each infusion and 30 minutes, 1 hour and 2 hourly thereafter until the patient leaves the unit or until 7 hours post infusion.

## 4. ETHICAL APPROVAL

The trial was approved by the Ethics Committee of each of the Haemophilia Centres which supplied the volunteers informed consent was obtained from all volunteers prior to the study commencement. The Trial was performed under the Clinical Trials Exemption (CTX) Scheme, and conformed to the recommendations of the Declaration of Helsinki as adopted at the 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.



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# 5. RESULTS

## 5.1 *Enrolment*

12 patients from Edinburgh were initially enrolled on the trial. 8 patients received infusions on the trial and 4 patients did not require treatment. 17 patients who required surgery or dental extraction were included. Demographic data is given in Appendix 2.

## 5.2 *Medication*

All infusions were carried out as per protocol.

## 5.3 *Efficacy*

110 spontaneous bleeds were assessed. There is serial data for 60 of these bleeds. These data show a small, variable improvement in joint mobility (Appendix 3). Pain was also noted to improve (Appendix 4).

The patients' own assessment of efficacy was also positive (82% of patients felt Liberate to be 'very helpful' or 'helpful') (Appendix 5).

4 bleeds were noted to either continue beyond or recur within 24 hours.

E-14-01 reported 2 separate joint bleeds which recurred in under 24 hours, the second lasted over 48 hours

E-14-09 reported a muscle bleed lasting more than 48 hours

E-14-11 reported a joint bleed lasting more than 48 hours

Liberate was thought to be effective in all surgical patients, although one patient G-14-07 was noted to have some 'oozing' post-surgery (Appendix 6).

## 5.4 *Safety*

All vital signs were within normal limits where done.

## 5.5 *Adverse Events*

There were no adverse events reported.

## 5.6 *Conclusion*

The trial data would suggest that Liberate is an effective high purity Factor VIII concentrate.



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# APPENDIX 1

# PAIN ASSESSMENT CHART FOR SNBTS CLINICAL TRIAL HP014

PAIN SEVERITY RATING SCALE
WORST PAIN IMAGINABLE
EXTREMELY PAINFUL
VERY PAINFUL
PAINFUL
COMPLETELY FREE OF PAIN
0 .5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

# APPENDIX 2

# DEMOGRAPHIC DATA FOR SNBTS CLINICAL TRIAL HP014

# HP014 DEMOGRAPHIC DATA PLUS NUMBER OF INFUSIONS FOR TRIAL PATIENTS WHO HAD SPONTANEOUS BLEEDS

| STUDY NUMBER | PATIENT INITIALS | DATE OF BIR | INFUSION LIBERATE | INUSION Z8 |
|---|---|---|---|---|
| E-14-01 | AC | 27.06.52 | 18 | - |
| E-14-02 | JB | 2.10.62 | 14 | 15 |
| E-14-03 | SU | 22.07.56 | - | - |
| E-14-04 | JB | 24.09.51 | - | - |
| E-14-05 | MM | 14.02.65 | 2 | 1 |
| E-14-06 | AW | 20.05.66 | - | - |
| E-14-07 | SM | 16.05.78 | 3 | 2 |
| E-14-08 | JR | 01.11.35 | 7 | 4 |
| E-14-09 | KM | 16.03.51 | 30 | 10 |
| E-14-10 | AD | 16.10.63 | - | - |
| E-14-11 | AS | 16.01.61 | 18 | 3 |
| E-14-12 | DB | 25.06.82 | 8 | 3 |



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# APPENDIX 3

# JOINT MOBILITY (GONEOMETRY) RESULTS FOR SNBTS CLINICAL TRIAL HP014



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HP014: - JOINT MOBILITY AS MEASURED BY GONEOMETRY IN HAEMOPHILIA A PATIENTS BEFORE AND AFTER TREATMENT WITH H8. ALSO SHOWN IS THE DOSE OF H8 U

| PATIENT | BLEED | TIME 0 | | 6 HOURS | | 24 HOURS | | DOSE1 | DOSE2 | DOSE3 | DOSE4 | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No | MIN | MAX | MIN | MAX | MIN | MAX | | | | | |
| E-14-01 | 1 | 10 | 90 | | | 10 | 90 | | | | | |
| E-14-01 | 2 | 25 | 50 | 25 | 50 | 15 | 90 | | | | | |
| E-14-01 | 3 | 3 | 90 | 3 | 90 | 3 | 90 | | | | | |
| E-14-01 | 4 | 5 | 110 | 5 | 110 | 5 | 110 | | | | | |
| E-14-01 | 5 | 30 | 105 | 30 | 105 | 30 | 105 | 660 | | | | 660 |
| E-14-01 | 6 | 7 | 110 | | | 5 | 110 | 720 | | | | 720 |
| E-14-01 | 7 | 15 | 93 | | | 7 | 95 | 720 | | | | 720 |
| E-14-01 | 8 | 7 | 95 | 7 | 95 | 7 | 95 | 720 | | | | 720 |
| E-14-01 | 9 | 5 | 95 | 5 | 95 | 5 | 100 | 735 | | | | 735 |
| E-14-01 | 10 | 10 | 90 | 10 | 90 | 10 | 90 | 735 | | | | 735 |
| E-14-01 | 11 | 5 | 110 | 5 | 110 | 5 | 100 | 735 | | | | 735 |
| E-14-01 | 12 | 5 | 110 | 5 | 110 | 5 | 110 | 750 | | | | 750 |
| E-14-01 | 13 | 7 | 95 | 7 | 95 | 7 | 95 | 795 | | | | 795 |
| E-14-01 | 14 | 10 | 90 | 7 | 93 | 7 | 95 | 880 | | | | 880 |
| E-14-01 | 15 | 3 | 100 | 3 | 100 | 3 | 100 | 880 | | | | 880 |
| E-14-01 | 16 | 7 | 110 | | | 5 | 110 | 980 | | | | 980 |
| E-14-01 | 17 | 20 | 95 | 20 | 95 | 10 | 95 | 9804 | | | | 9804 |
| E-14-01 | 18 | 7 | 105 | 7 | 105 | 5 | 110 | 9804 | | | | 9804 |
| E-14-02 | 1 | 75 | 100 | 75 | 100 | 70 | 120 | 1100 | | | | 1100 |
| E-14-02 | 2 | 55 | 105 | 55 | 100 | 60 | 95 | 1100 | 1100 | | | 2200 |
| E-14-02 | 3 | 90 | 100 | 90 | 110 | 75 | 120 | 1200 | | | | 1200 |
| E-14-02 | 4 | 75 | 95 | 75 | 105 | 70 | 120 | 1225 | | | | 1225 |
| E-14-02 | 5 | 70 | 110 | 70 | 110 | 60 | 130 | 1250 | | | | 1250 |
| E-14-02 | 6 | 90 | 95 | 90 | 95 | 90 | 95 | 1320 | | | | 1320 |
| E-14-02 | 7 | 85 | 100 | 95 | 95 | 90 | 105 | 1320 | 1800 | | | 3120 |
| E-14-02 | 8 | 80 | 100 | 80 | 110 | 70 | 115 | 1350 | | | | 1350 |
| E-14-02 | 9 | 87 | 100 | 87 | 107 | 80 | 115 | 1350 | | | | 1350 |
| E-14-02 | 10 | 85 | 85 | 80 | 85 | 80 | 100 | 1440 | | | | 1440 |
| E-14-02 | 11 | 20 | 40 | 20 | 40 | 20 | 50 | 1470 | | | | 1470 |
| E-14-02 | 12 | 75 | 95 | 75 | 95 | 75 | 95 | 1470 | | | | 1470 |
| E-14-02 | 13 | 90 | 90 | 75 | 80 | 70 | 110 | 1470 | | | | 1470 |
| E-14-02 | 14 | 90 | 100 | 80 | 105 | 70 | 115 | 1470 | | | | 1470 |
| E-14-02 | 15 | 22 | 60 | 22 | 60 | 22 | 60 | 1500 | | | | 1500 |
| E-14-02 | 16 | 55 | 115 | 52 | 118 | 52 | 118 | 1500 | | | | 1500 |
| E-14-02 | 17 | 70 | 120 | 70 | 120 | 80 | 110 | 1500 | | | | 1500 |
| E-14-02 | 18 | 25 | 60 | 25 | 60 | 22 | 65 | 1500 | | | | 1500 |
| E-14-02 | 19 | 50 | 110 | 52 | 113 | 50 | 115 | 1500 | | | | 1500 |
| E-14-02 | 20 | 80 | 110 | 83 | 120 | 75 | 125 | 1500 | | | | 1500 |
| E-14-02 | 21 | 77 | 115 | 80 | 110 | 84 | 110 | 1500 | | | | 1500 |
| E-14-02 | 22 | 80 | 90 | 80 | 85 | 80 | 115 | 1500 | | | | 1500 |
| E-14-02 | 23 | 75 | 90 | 80 | 90 | 73 | 115 | 1500 | 2000 | | | 3500 |
| E-14-02 | 24 | 80 | 100 | 80 | 105 | 75 | 115 | 1800 | | | | 1800 |
| E-14-02 | 25 | 80 | 120 | 75 | 125 | 75 | 130 | 1800 | | | | 1800 |
| E-14-02 | 26 | 90 | 95 | 90 | 95 | 80 | 100 | 1800 | | | | 1800 |
| E-14-02 | 27 | 25 | 65 | 25 | 65 | 25 | 70 | 960 | | | | 960 |



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| PATIENT | BLEED | TIME 0 | | 6 HOURS | | 24 HOURS | | DOSE1 | DOSE2 | DOSE3 | DOSE4 | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No | MIN | MAX | MIN | MAX | MIN | MAX | | | | | |
| E-14-05 | 1 | 50 | 135 | | | | | | | | | |
| E-14-05 | 2 | 60 | 110 | 60 | 110 | 50 | 130 | 1250 | | | | 1250 |
| E-14-07 | 1 | | | | | | | 500 | 500 | | | 1000 |
| E-14-07 | 2 | 85 | 105 | 82 | 125 | 82 | 130 | 780 | 780 | 780 | | 1560 |
| E-14-07 | 3 | | | | | | | 880 | 880 | 880 | | 1760 |
| E-14-08 | 1 | 52 | 108 | 45 | 109 | 36 | 100 | 540 | | | | 540 |
| E-14-08 | 2 | | | | | | | 540 | | | | 540 |
| E-14-08 | 3 | 49 | 102 | 40 | 108 | 50 | 109 | 5405 | | | | 5405 |
| E-14-08 | 4 | 30 | 110 | 29 | 112 | 28 | 111 | 600 | | | | 600 |
| E-14-08 | 5 | 50 | 111 | 50 | 115 | 40 | 103 | 600 | | | | 600 |
| E-14-08 | 6 | 44 | 104 | 39 | 96 | 42 | 102 | 600 | | | | 600 |
| E-14-08 | 7 | 54 | 107 | 55 | 100 | 55 | 112 | 600 | | | | 600 |
| E-14-08 | 8 | | | | | | | 735 | 735 | 735 | 735 | 2940 |
| E-14-09 | 1 | | | | | | | 440 | | | | 440 |
| E-14-09 | 2 | 75 | 130 | 75 | 130 | 75 | 130 | 440 | | | | 440 |
| E-14-09 | 3 | | | | | | | 440 | | | | 440 |
| E-14-09 | 4 | | | | | | | 440 | 440 | | | 880 |
| E-14-09 | 5 | | | | | | | 440 | 440 | | | 880 |
| E-14-09 | 6 | | | | | | | 440 | 440 | 440 | | 1320 |
| E-14-09 | 7 | | | | | | | 460 | | | | 460 |
| E-14-09 | 8 | | | | | | | 480 | | | | 480 |
| E-14-09 | 9 | | | | | | | 480 | | | | 480 |
| E-14-09 | 10 | | | | | | | 480 | | | | 480 |
| E-14-09 | 11 | | | | | | | 480 | | | | 480 |
| E-14-09 | 12 | | | | | | | 480 | 480 | | | 960 |
| E-14-09 | 13 | | | | | | | 480 | 480 | 480 | | 1440 |
| E-14-09 | 14 | | | | | | | 480 | 480 | 480 | 480 | 1920 |
| E-14-09 | 15 | | | | | | | 500 | | | | 500 |
| E-14-09 | 16 | | | | | | | 500 | | | | 500 |
| E-14-09 | 17 | | | | | | | 690 | | | | 690 |
| E-14-09 | 18 | | | | | | | 690 | | | | 690 |
| E-14-09 | 19 | | | | | | | 720 | 720 | | | 1440 |
| E-14-09 | 20 | | | | | | | 745 | | | | 745 |
| E-14-09 | 21 | | | | | | | 745 | 745 | 745 | | 2235 |
| E-14-09 | 22 | | | | | | | 750 | | | | 750 |
| E-14-09 | 23 | | | | | | | 750 | | | | 750 |
| E-14-09 | 24 | | | | | | | 750 | | | | 750 |
| E-14-11 | 1 | 10 | 107 | | | 10 | 110 | 1000 | 800 | | | 1800 |
| E-14-11 | 2 | | | | | | | 1175 | 1175 | | | 2350 |
| E-14-11 | 3 | 60 | 110 | 60 | 110 | 60 | 110 | 1200 | | | | 1200 |
| E-14-11 | 4 | | | | | | | 1200 | 1200 | | | 2400 |
| E-14-11 | 5 | | | | | | | 1250 | 750 | 750 | | 2750 |
| E-14-11 | 6 | | | | | | | 1325 | | | | 1325 |
| E-14-11 | 7 | | | | | | | 1450 | 1450 | 1175 | | 4075 |
| E-14-11 | 8 | | | | | | | 1590 | | | | 1590 |
| E-14-11 | 9 | 10 | 110 | 10 | 110 | | | 400 | | | | 400 |
| E-14-11 | 10 | | | | | | | 630 | 630 | | | 1260 |
| E-14-11 | 11 | | | | | | | 630 | 630 | 840 | | 2100 |



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| PATIENT | BLEED | TIME 0 | | 6 HOURS | | 24 HOURS | | DOSE1 | DOSE2 | DOSE3 | DOSE4 | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No | MIN | MAX | MIN | MAX | MIN | MAX | | | | | |
| E-14-11 | 12 | 55 | 111 | | | | | 720 | | | | 720 |
| E-14-11 | 13 | | | | | | | 720 | | | | 720 |
| E-14-11 | 14 | | | | | | | 720 | 720 | | | 1440 |
| E-14-11 | 15 | | | | | | | 750 | 750 | 750 | | 2250 |
| E-14-11 | 16 | | | | | | | 795 | | | | 795 |
| E-14-11 | 17 | | | | | | | 795 | 795 | | | 1590 |
| E-14-11 | 18 | | | | | | | 900 | | | | 900 |
| E-14-11 | 19 | | | | | | | 900 | 900 | | | 1800 |
| E-14-12 | 1 | 30 | 80 | 10 | 105 | 5 | 115 | | | | | |
| E-14-12 | 2 | 30 | 110 | 30 | 110 | 20 | 115 | 660 | 660 | 660 | | 1980 |
| E-14-12 | 3 | 30 | 70 | 30 | 75 | 25 | 80 | 660 | 880 | 880 | | 2420 |
| E-14-12 | 4 | 25 | 65 | 10 | 120 | -5 | 125 | 750 | | | | 750 |
| E-14-12 | 5 | 35 | 120 | 15 | 140 | 8 | 140 | 750 | | | | 750 |
| E-14-12 | 6 | 40 | 140 | 27 | 140 | 25 | 140 | 775 | | | | 775 |
| E-14-12 | 7 | 45 | 105 | 10 | 110 | 7 | 120 | 795 | 795 | | | 1590 |
| E-14-12 | 8 | 45 | 105 | 10 | 115 | 7 | 120 | 795 | 795 | | | 1590 |
| E-14-12 | 9 | 15 | 110 | 5 | 125 | 5 | 135 | 795 | 795 | | | 1590 |
| MEAN | | 44.6 | 99.6 | 44.1 | 102 | 39.11 | 107.1 | 1132 | 830.5 | 721.4 | 607.5 | 1468 |



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# APPENDIX 4

## PAIN ASSESSMENT RESULTS FOR SNBTS CLINICAL TRIAL HP014

HP014:- Personal assessment of the severity of joint pain before and after treatment with H8
Patients assessed severity of pain by reference to a rating scale from 0 to 10.

| PATIENT | BLEED NO. | TIME (HOURS) | | |
|---|---|---|---|---|
| | | 0 | 6 | 12 |
| E-14-01 | 1 | | | |
| E-14-01 | 2 | | | |
| E-14-01 | 3 | 0 | 0 | 0 |
| E-14-01 | 4 | 2 | 0 | 0 |
| E-14-01 | 5 | 0 | 0 | 0 |
| E-14-01 | 6 | | | |
| E-14-01 | 7 | | | |
| E-14-01 | 8 | | | |
| E-14-01 | 9 | | | |
| E-14-01 | 10 | 0 | 0 | 0 |
| E-14-01 | 11 | 0 | 0 | 0 |
| E-14-01 | 12 | | | |
| E-14-01 | 13 | | | |
| E-14-01 | 14 | | | |
| E-14-01 | 15 | 0 | 0 | 0 |
| E-14-01 | 16 | | | |
| E-14-01 | 17 | | | |
| E-14-01 | 18 | | | |
| E-14-02 | 1 | 2.5 | 2.5 | 0 |
| E-14-02 | 2 | 2.5 | 2.5 | 4 |
| E-14-02 | 3 | 4 | 4 | 2.5 |
| E-14-02 | 4 | 4 | 2.5 | 1 |
| E-14-02 | 5 | 4.5 | 3.5 | 3.5 |
| E-14-02 | 6 | 7.5 | 7.5 | 5.5 |
| E-14-02 | 7 | 7.5 | 7.5 | 5 |
| E-14-02 | 8 | 4 | 3 | 1 |
| E-14-02 | 9 | 4 | 2.5 | 1 |
| E-14-02 | 10 | 7.75 | 7.5 | 5 |
| E-14-02 | 11 | | | |
| E-14-02 | 12 | 5 | 5 | 5 |
| E-14-02 | 13 | 5 | 5 | 2.5 |
| E-14-02 | 14 | 7.5 | 7.5 | 5 |
| E-14-02 | 15 | 1 | 1 | 0 |
| E-14-02 | 16 | 1 | 0 | 0 |
| E-14-02 | 17 | 1 | 1 | 2.5 |
| E-14-02 | 18 | 2 | 1 | 1 |
| E-14-02 | 19 | 4 | 4 | 1 |
| E-14-02 | 20 | 4 | | |
| E-14-02 | 21 | 5 | 5 | 4 |



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| | | | | |
|---|---|---|---|---|
| E-14-02 | 22 | | | |
| E-14-02 | 23 | 7.5 | 5 | 1 |
| E-14-02 | 24 | 2.5 | 2.5 | 1 |
| E-14-02 | 25 | 4 | 2.5 | 1 |
| E-14-02 | 26 | 5 | 5 | 2.5 |
| E-14-02 | 27 | 2.5 | 2.5 | 1 |
| E-14-05 | 1 | 6.5 | | |
| E-14-05 | 2 | 5 | 3.5 | 2 |
| E-14-07 | 1 | 0.5 | 0.5 | 0 |
| E-14-07 | 2 | 1 | 0.5 | 0.5 |
| E-14-07 | 3 | 2.5 | 2.5 | 2.5 |
| E-14-08 | 1 | 0.9 | 0.7 | 0.3 |
| E-14-08 | 2 | 1 | 0.5 | 0 |
| E-14-08 | 3 | 2.5 | 2 | 0.5 |
| E-14-08 | 4 | 1.5 | 1 | 0.5 |
| E-14-08 | 5 | 2 | 1 | 0 |
| E-14-08 | 6 | 2.5 | 1 | 0 |
| E-14-08 | 7 | 2.5 | 2 | 1.5 |
| E-14-08 | 8 | | | |
| E-14-09 | 1 | 0.8 | 0.5 | 0.2 |
| E-14-09 | 2 | 1.25 | 0.5 | 0 |
| E-14-09 | 3 | 0.5 | 0 | 0 |
| E-14-09 | 4 | 0.5 | 0.5 | 0.5 |
| E-14-09 | 5 | 0.5 | 0 | 0 |
| E-14-09 | 6 | 0.5 | 0 | 0 |
| E-14-09 | 7 | 2.75 | 2.75 | 2.75 |
| E-14-09 | 8 | 0.5 | 0 | 0 |
| E-14-09 | 9 | | | |
| E-14-09 | 10 | 1.5 | 0.25 | |
| E-14-09 | 11 | 1.5 | 0.5 | |
| E-14-09 | 12 | 1.5 | 0.5 | 0.1 |
| E-14-09 | 13 | 1.5 | 0.75 | |
| E-14-09 | 14 | 0.5 | 0.5 | 0.5 |
| E-14-09 | 15 | 1.5 | 1.5 | 1.5 |
| E-14-09 | 16 | 1.5 | 1.5 | 1.5 |
| E-14-09 | 17 | 0.8 | 0.2 | |
| E-14-09 | 18 | 0.25 | | |
| E-14-09 | 19 | | | |
| E-14-09 | 20 | | | |
| E-14-09 | 21 | 4 | 2.5 | 0 |
| E-14-09 | 22 | | | |
| E-14-09 | 23 | | | |
| E-14-09 | 24 | 0.4 | | |
| E-14-09 | 25 | 0.8 | 0.5 | |
| E-14-09 | 26 | 1.4 | 0.8 | 0.2 |
| E-14-11 | 1 | 2.5 | 2 | 0.55 |
| E-14-11 | 2 | 2.5 | 1.5 | 0 |



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| | | | | |
|---|---|---|---|---|
| E-14-11 | 3 | 5 | 2.5 | 1 |
| E-14-11 | 4 | 2.5 | 2.5 | 0 |
| E-14-11 | 5 | 2.5 | 2 | 0 |
| E-14-11 | 6 | 2.5 | 2.25 | 1.5 |
| E-14-11 | 7 | 2.5 | 2 | 1 |
| E-14-11 | 8 | 2.5 | | 0 |
| E-14-11 | 9 | 1.5 | 0 | 0 |
| E-14-11 | 10 | 1.5 | 0.55 | 0 |
| E-14-11 | 11 | | | |
| E-14-11 | 12 | 2 | 0 | 0 |
| E-14-11 | 13 | 2.5 | 0.5 | 0 |
| E-14-11 | 14 | 2.5 | 1.5 | 0 |
| E-14-11 | 15 | 0.5 | 0.5 | 0 |
| E-14-11 | 16 | 0.5 | 0.5 | 0 |
| E-14-11 | 17 | 2 | 2 | 2 |
| E-14-11 | 18 | 2.5 | 2 | 1 |
| E-14-11 | 19 | 4 | 2.5 | 0 |
| E-14-12 | 1 | 4.5 | 3 | 2.5 |
| E-14-12 | 2 | 5.5 | 1.5 | 0.5 |
| E-14-12 | 3 | 6 | 3.5 | 2 |
| E-14-12 | 4 | 6 | 4.5 | 2.5 |
| E-14-12 | 5 | 3.5 | 1 | 0 |
| E-14-12 | 6 | 2.5 | 1 | 0 |
| E-14-12 | 7 | 3.5 | 2.5 | 2 |
| E-14-12 | 8 | 2.5 | 1 | 0.5 |
| E-14-12 | 9 | 2.5 | 1 | 0.5 |
| E-14-12 | 10 | 4 | 4 | 2.5 |
| MEAN | | 2.70 | 1.96 | 1.10 |
| 95% CI | | 2.29 | 1.56 | 0.83 |



SBTS0003795_062_0023

# APPENDIX 5

## PATIENTS ASSESSMENT OF EFFICACY FOR SNBTS CLINICAL TRIAL HP014

Patient personal assessment of efficacy of H8 in treating bleeding episodes

| TOTAL NUMBER OF BLEEDS | 111 |
|---|---|
| Extremely helpful | 7 |
| Very helpful | 35 |
| Helpful | 56 |
| Only helped a bit | 11 |
| Did not help at all | 2 |

82% of the treatment episodes were assessed as 'helpful' or 'very helpful' and 6% as 'extremely helpful'. The balance (12%) were assessed as 'only helped a bit' or 'did not help at all'.



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# APPENDIX 6

# EFFICACY IN SURGICAL PROCEDURES FOR SNBTS CLINICAL TRIAL HP014

# EFFICACY IN SURGICAL PROCEDURES
# (N = 17)

| CENTRE | PROCEDURE | HAEMOSTASIS |
|---|---|---|
| Y1 | Left knew synovectomy | Effective |
| Y2 | Correction of club foot | Effective |
| Y3 | Appendicectomy | Effective |
| B1 | Dental extraction | Satisfactory |
| B2 | Dental extraction | Satisfactory |
| B3 | Dental extraction | Satisfactory |
| B4 | Cataract removal | Satisfactory |
| B5 | Removal of basal cell carcinoma from bac | Satisfactory |
| B6 | Pinning of fractured and femure | Satisfactory |
| G1 | Arthroscopy | Satisfactory |
| G2 | Shoulder replacement | Satisfactory |
| G3 | Cyst removal | Satisfactory |
| G4 | Knee surgery | No excess bleeding |
| G5 | Hip surgery | Satisfactory |
| G6 | Mastoidectomy | Satisfactory |
| G7 | Knee replacement | Some oozing |
| G8 | Abcess drainage | Satisfactory |



SBTS0003795_062_0027

Telephone
041-339 8888 Ext GRO-C

Yorkhill
Glasgow G3 8S

RA/SJG

DEPARTMENT OF HAEMATOLOGY

29th November 1993

Vicki Miller
Clinical Trials Monitor
SNBTS
Livingstone House
39 Cowgate
EDINBURGH EH1 1JR

Dear Ms Miller

Re: CLINICAL TRIAL OF HPVIII

The following patients who are on trial for HPVIII have had surgery which was covered with HPVIII and no bleeding problems were encountered.

Patient No. 1 GRO-A - He had correction of bilateral club feet on GRO-A 1992. He was covered with HPVIII. There was no excessive bleeding. He was continued on post-operative treatment for 11 days after which it was stopped. He had further manipulation and change of plaster on GRO-A again with cover and without any problem.

Patient No. 2 GRO-A had orthoscopic synovectomy of his left knee of GRO-A 1993. He was covered with HPVIII. No bleeding problem was encountered.

Patient No. 3 GRO-A had emergency appendicectomy under cover with HPVIII. He also did not have any bleeding problem both during the operation and post-operatively.

You will have the batch number of all these infusions in your records. If you need any further information please do not hesitate to contact me.

Yours sincerely

GRO-C

R AHMED
REGISTRAR IN HAEMATOLOGY

The ROYAL HOSPITALS

Department of Haematology
Royal Victoria Hospital
Grosvenor Road.
Belfast.

16th September 1993.

Dear Dr Shanahan,

Enclosed please find the list of our patients who underwent surgery under cover of HP VIII. If you require any further detail please contact me.

Yours sincerely,

GRO-C



SBTS0003795_062_0029

The ROYAL HOSPITALS

USE OF HP VIII IN PATIENTS UNDERGOING SURGI

NUMBER OF PATIENTS : 6

Procedures covered : - 3 patients had dental extraction
- 1 patient had cataract removal
- 1 patient had basal cell carcino removed from head
- 1 patient had excision of pun lip & arm and skin

All achieved haemostasis satisfactorily



SBTS0003795_062_0030

Co-Directors:
Dr. G. D. O. Lowe
Dr. I. D. Walker

Sister I. M. McDougall

Haemophilia Centre
Wards 2 & 3

ROYAL INFIRMARY
GLASGOW
G4 0SF
TELEPHONE: 041-552 3535

Ext. GRO-C
Direct Line: GRO-C



November 23, 1993

Vicki Miller
Clinical Research Associate
SNBTS
Livingstone House
39 Cowgate, EDINBURGH

Dear Ms. Miller:

re; SNBTS HPVIII Clinical Trials

The following patients have received High Purity factor VIII as haemostatic cover for surgery.

1) GRO-A - arthroscopy. Haemostasis satisfactory.
2) GRO-A - shoulder replacement. Haemostasis satisfactory.
3) GRO-A - removal of epidydimal cyst. Bruising only.
4) GRO-A - (a) removal of infected knee prosthesis; (b) knee fusion. Surgeon queried excessive bleeding during surgery on both occasions, but no excessive post-operative bleeding.
5) GRO-A - (a) hip replacement for hip fracture (Inverness); (b) re-operation for dislocation (Glasgow). Haemostasis satisfactory.
6) GRO-A - Mastoidectomy. Haemostasis satsifactory.
7) GRO-A - Knee replacement. Early wound infection causing wound breakdown with recurrent oozing despite satisfactory VIIIc levels. Thought mostly due to infection.
8) GRO-A - Axillary abscess drainage. Haemostasis satisfactory.

On the whole, haemostasis following these procedures has been in general satisfactory and consistent with our previous haemophilic surgery experience.

Yours sincerely,

GRO-C

Professor Gordon D.O. Lowe
CONSULTANT PHYSICIAN
am/wrd/protocol/hp8/report

FVIII REPORT 01/02/95

cc: Dr.I.D.Walker

# APPENDIX 7

## PROTOCOL
## FOR SNBTS CLINICAL TRIAL HP014

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

CONFIDENTIAL

# CLINICAL TRIAL OF COMPARING HIGH POTENCY FACTOR VIII CONCENTRATE (HPVIII) WITH AN INTERMEDIATE PURITY FACTOR VIII CONCENTRATE (Z8) IN THE TREATMENT OF BLEEDING IN PATIENTS WITH HAEMOPHILIA A

(HP014)

PROTOCOL

28 NOVEMBER 1991

Dr R R C STEWART

Tel No
Fax No GRO-C

SNBTS Headquarters
Medical Unit
Livingstone House
39 Cowgate
Edinburgh

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

# CLINICAL TRIAL TO ASSESS THE TOLERABILITY OF HIGH POTENCY FACTOR VIII CONCENTRATE (HPVIII) WITH AN INTERMEDIATE PURITY FACTOR VIII CONCENTRATE (Z8) IN THE TREATMENT OF BLEEDING IN PATIENTS WITH HAEMOPHILIA A

## (HP014)

Protocol dated .....

Clinical Investigator

Name .....

Title .....

Address .....

.....

.....

Signed .....

Date .....

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

Signed .....

Date .....



SBTS0003795_062_0034

## 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 time 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. One such product is HPVIII prepared by the Protein Fractionation Centre of the SNBTS. This product is prepared from plasma collected by the SNBTS and NIBTS.

The aim of this study is to demonstrate that HPVIII is effective in the treatment of bleeding in patients with haemophilia A.

## 2. METHODS

### 2.1 Study Design

The study shall be an open controlled study.

## 2.2 Patients

There will be no limit to the number of patients entered into the study. All patient who fulfil the entry criteria below and who, in the opinion of the Haemophilia Directors require to be treated with Factor VIII should be enrolled.

### 2.2.1 Inclusion Criteria

Patients should satisfy the following criteria:

1. be suffering from haemophilia A (WHO Disease Classification Number 286.0)

2. are at least 12 years of age.

3. have an active bleed, or require factor VIII replacement to cover surgery or dental extraction.

In the early phases of the study, patients will be hospital outpatients who present at the local Haemophilia Centre with acute bleed, which may be of the following type, haemarthrosis, post dental treatment. As experience with HPVIII increases, patients who are 'self administering' at home will be included in the study.

### 2.2.2 Exclusion Criteria

The following will be excluded from the study:

1. Patients whose bleed is considered to be potentially life threatening.

2. Patients with a history of severe reactions to blood products.

3. Patients who possess inhibitors to Factor VIII.

4. Any other patient whom the physician thinks is unsuitable for inclusion in the study.

2.3 Location of Study

The study shall take place at the Haemophilia Centre, Royal Infirmary, Edinburgh, the Department of Medicine, Royal Infirmary Glasgow, Department of Haematology, Royal Hospital for Sick Childrem, Glasgow and the Department of Haematology, Royal Victoria Hospital, Belfast.

**3. TRIAL MEDICATION**

3.1 Description

The products to be used in the study are:

HPVIII: Factor VIII in vials of approximately 250 IU with a specific activity of about 150 IU/mg protein.

Z8: Factor VIII in vials of approximately 200IU containing anti-haemophilic factor A at a specific activity of 0.5-1.0 IU/mg protein.

These products are produced by the Protein Fractionation Centre, Edinburgh from plasma collected by the SNBTS and NIBTS and will be supplied gratis by the SNBTS.

3.2 Storage

Factor VIII concentrate should be stored in the dark at temperatures between +2°C and +8°C.



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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) to the dried Factor VIII. The contents of the vial should be mixed gently to ensure resulution. 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 CONCENTRATE.**

The dose of Factor VIII given to each patient will be individualised to achieve blood levels appropriate for their clinical condition. For a minor bleed, initial treatment should be with 500 IU. More severe bleeds will require increased doses.

**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

Patients will be monitored for a 4 month period while being treated with Z8 and the efficacy of Z8 in treating any bleeds which occur in this time will be recorded. Thereafter the pateint will be switched to HPVIII and the efficacy of this product in treating bleeds will be recorded.

### 6.1 Clinical monitoring

When the patient is being treated in hospital, temperature, blood pressure and pulse rate shall be noted prior to the commencement of each infusion and 30, min, 1hr and 2 hourly thereafter until the patient leaves the unit or until 7 hours post infusion. (See Appendix I)

### 6.2 Infusion of trial medication

The material should be infused as soon as practicable after dissolution is complete. The rate of infusion should be such to permit infusion to be completed within 30 minutes. Continuous infusion over a long period is to be avoided.

### 6.3 Measurement of efficacy

This is outlined in Appendix II.

#### 6.3.1 Inpatients

The efficacy of the Factor VIII concentrates in treating bleeds in inpatients will be assessed as follows:

1. Severity of pain (assessed by rating scale, see Appendix I) at time zero and 5-6 hours (if appropriate).
2. Quantity and nature of analgesics required.
3. Circummference of muscle or joint at time zero and 5-6 hours (if appropriate).

4. Personal assessment of efficacy by the patien by selecting the one from the list which best described the outcome.

i. Extremely helpful
ii. Very helpful
iii. Helpful
iv. Only helped a bit
v. Did not help at all

5. Degree of restriction of joint mobility (assessedd by goneometry) at time zero and 5-6 hours.
6. Cessation of opening bleeding (if appropriate).
7. Failure of bleed to recurr within 48 hours (if appropriate).

6.3.2 Patients on Home Therapy

The efficacy of the Factor VIII concentrates in treating bleeds in patients on home therapy will be assessed as follows:

1. Severity of pain (assessed by rating scale, see Appendix III) at time zero and 5-6 hours (if appropriate).
2. Quantity and nature of analgesics required.
3. Personal assessment of efficacy by the patient by selection the one from the list which best described the outcome.

i. Extremely helpful
ii. Very helpful
iii. Helpful
iv. Only helped a bit
v. Did not help at all

4. Failure of bleed to recurr within 48 hours (if appropriate).

6.3.3 Patients requiring dental or other surgery

The efficacy of the Factor VIII to conncentrates in control of bleeding inpatients requiring dental or other surgery will be assessed by noting whether bleeding occurred and, if so, the extent of bleeding.



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## 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 volunteers. 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 II).

### 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.



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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 confirmationof 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 clonical 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. Volunteers 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. 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.

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 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 event 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 whatever cause, of any patient in the study, 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 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.

**8. REFERENCE**

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

**APPENDIX I**

**INPATIENT CLINICAL MONITORING SCHEDULE**

| | PRE-INFUSION | 30 MIN | 1 H | 3 H* |
|---|---|---|---|---|
| TEMPERATURE | X | X | X | X |
| BLOOD PRESSURE | X | X | X | X |
| PULSE RATE | X | X | X | X |

* Repeat at 2 hourly intervals until patient leaves unit, or until 7 hours post-infusion whichever is shorter.

## APPENDIX II

### GUIDE TO EFFICACY ASSESSMENT PARAMETERS

| | Pain Severity Rating Scale | Circumference of joint or muscle | Goneometry | Analgesic Usage | Personal assessment | Cessation of open bleed | Bleed recurrence |
|---|---|---|---|---|---|---|---|
| INPATIENTS | | | | | | | |
| Joint or muscle bleed | X | X | X | X | X | | X |
| Open Bleed | | | | | X | X | X |
| PATIENTS ON HOME THERAPY | | | | | | | |
| Joint or muscle bleed | X | | | X | X | | X |
| Open bleed | | | | | X | X | X |

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APPENDIX IV

# DECLARATION OF HELSINKI

## Recommendations Guiding Physicians in Biomedical Research involving Human Subjects

Adopted by the 18th World Medical Assembly,
Helsinki, Finland, 1964
and ammended by the 29th World Medical Assembly,
Tokyo, Japan, October 1975
35th World Medical Assembly,
Venice, Italy, October 1983
and the
41st World Medical Assembly,
Hong Kong, September 1989

### Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge annd conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, 'The health of my patient will be my first consideration', and the International code of Medical Ethics declares that, 'A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient'.

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedureds involve hazaards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving hujman subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.



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Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

**I BASIC PRINCIPLES**

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design annd performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically coompetent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportioon to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessmment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of sciencce and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians



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should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should bot be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of theis official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are compiled with.

**II MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)**

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic methods.



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4. The refusal of the patient to participate in a study must never interfere witn the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1,2).

6. The physician can combine medical research with professsional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

## III NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interests of science and society should never take precedence over considerations related to the wellbeing of the subject.

# DRAFT INTERIM REPORT FOR SNBTS CLINICAL TRIAL HP012

CONFIDENTIAL

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

# HP012

# SCOTLAND/NORTHERN IRELAND HAEMOPHILIA DIRECTORS CLINICAL TRIAL TO ASSESS THE TOLERABILITY OF HIGH POTENCY FACTOR VIII/CONCENTRATE (LIBERATE) MANUFACTURED BY SNBTS IN NON-HIV INFECTED PATIENTS WITH HAEMOPHILIA A

# DRAFT INTERIM REPORT

**SNBTS Product Services Department**

**Tel: 0131 220 4590**
**Fax: 0131 220 3105**

| | |
|---|---|
| **SNBTS Monitor :** | Dr R R C Stewart, Product Services Manager (succeeded by Miss J Pelly, Product Services Manager 1/12/93) |
| **Principal Investigators:** | Dr A Dawson — Aberdeen<br>Prof GDO Lowe — Glasgow<br>Dr C A Ludlum — Edinburgh<br>Dr E Mayne — Belfast<br>Dr A Stark — Dumfries |
| **Report Author:** | Miss E McIntosh, Clinical Research Associate |
| **Date .** | 26 January 1995 |

## SUMMARY

Liberate is a refined product developed by SNBTS in response to worries about viral transmission and an apparent immune disturbance in non-HIV infected patients.

This is a surveillance study to determine the virological safety of Liberate. The protocol is based on the International Committee of Thrombosis and Haemostasis recommendations but with broadened entry criteria and more prolonged follow-up in certain circumstances.

The study assesses the immediate reactions, virolgical safety, the effect of Liberate on immune function and the development of inhibitors to Liberate.

Ideally a study such as this should be undertaken only in previously untransfused patients (PUPs) but the number of such individuals in Scotland is likely to be small within any one year and therefore individuals who have only been transfused with single donation products, and those patients who were entered in the Z8 PUP study and were closely monitored and shown not to have contracted hepatitis are included

All the Haemophilia Centres for Scotland and Northern Ireland were asked to identify suitable patients for inclusion in this trial for the purposes of this report only those centres/investigators whose patients are included in the trial have been listed.

To preserve patient confidentiality, patients were referred to by subject number. This number identifies the trial centre, trial number and the patient number:- eg E-12-01 is the first patient from Edinburgh enrolled on HP012.

## STUDY PERSONNEL

**SNBTS Monitor:** Dr R R C Stewart BSc, PhD
Product Sevices Manager until Nov 93
Miss Jane Pelly, GRSC
Product Services Manager from 1/12/93

**Medical Advisor:** Professor J D Cash, BSc, MBChB, PhD, FRCPath, FRCPE, FRCP(Glas), FRCS(Edin)

**Investigators**

**Belfast:** Dr E Mayne, MBChB, BaO MD, FRCP(Glas), FRCPath
Dr O McNulty, MBChB, BaO

**Edinburgh:** Dr C A Ludlam, BSc(Hons), MBChB, PhD, FRCP(Edin), FRCPath
SN S Trainer, RGN

**Glasgow:**
**Royal Infirmary:** Professor G D O Lowe, MBChB, JCHMT (General Medicine), MD
Dr B Shaw, MBChB, FRCP (Edin & Glas), FRCP(Lond), DRCOG
Dr I Walker, MD, FRCP, FRCPath

**Yorkhill:** Dr B E S Gibson, MBChB, MRCPath, FRCP(Glas), Dip in Forensic Medicine
Dr R Ahmed, MBChB, MRCP



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# INDEX



APPENDICES





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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 immune disturbance has not been unequivocally identified, and many impurities in 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 in Edinburgh, in collaboration with French colleagues, have developed such a product (Liberate).

This surveillance study is designed to assess the safety of Liberate with respect to transmission of potentially infectious viruses. The protocol is based on the International Committee of Thrombosis and Haemostasis recommendations but entry criteria have been broadened and follow up more prolonged in certain circumstances.

## 2. OBJECTIVES

The aim of this study is to assess the tolerability of Liberate. This will be done by measuring the following:

i. Immediate (allergic-type) reactions.

ii. Virological safety - to assess HIV, non-A, non-B hepatitis and parvovirus transmission by Liberate.

iii. To assess effect of Liberate on immune function, by measurement of lymphocyte subset numbers.

iv. To assess the development of inhibitors to Factor VIII in patients on Liberate.

## 3. METHODOLOGY

This is an open labelled study, involving up to 40 patients, recruited by the Haemophilia Directors of Scotland & Northern Ireland.

## 4. INCLUSION CRITERIA

1. Previously untransfused patients (PUPs)
2. Z8 PUPs
3. Partial PUPs
4. Patients with Haemophilia A and von Willebrands Disease
5. Patients whom the physician believes requires Factor VIII.
6. Patients of either sex.
7. Patients of any age.



SBTS0003795_062_0059

## 5. EXCLUSION CRITERIA

1. Patients who have previously been transfused with fractionated pooled plasma products, other than those who were part of the Z8 PUP study.

2. Patients who are known to have liver dysfunction ie to have abnormality of liver function on routine testing at entry or clinical evidence of chronic liver disease.

3. Patients who are serologically positive for anti-HIV, anti-HCV, HBsAg, anti-HBc or anti-HBs (unless due to vaccination).

4. Patients at risk of HIV infection other than from blood products.

5 Patients with a known history of alcohol abuse.

## 6. CLINICAL MONITORING

The patients temperature, recumbent blood pressure and pulse rate shall be noted prior to the commencement of the infusion and 15 min, 30 min and 1h thereafter.

Blood Samples

All samples will be analysed locally

Pre-infusion

1. LFTs including ALT (or AST if ALT not available) and GGT

2. Serum stored 5ml, (for children < 5 years - 1ml) at -40°C

3. Virology (HAV, HBV, HCV, EBV, CMV, HIV and parvovirus)

4. Lymphocyte subsets

5. Full blood count

Follow Up Samples

a) Fortnightly Samples:

Samples will be procured fortnightly until 16 weeks after the last infusion. For patients who took part in the Z8 PUP study, monthly sampling is acceptable.

Follow up samples:

1. LFTs including ALT and GGT. (If ALT not available locally measure AST immediately and store aliquot at -70°C for ALT measurement later if required).

2. Full blood count.

3. Serum stored at -40°C 5ml, (for children < 5 years - 1ml)

b) Three Months, Six Months the six monthly up to 2 Years Post First Infusion

In addition to those required in a) above,.

i) Lymphocyte subsets

ii) Viral Serology (HAV, HBV, HCV, EBV, CMV, HIV, parvovirus)

## 7. DETECTION OF INHIBITORS TO FACTOR VIII(C)

Samples should be taken to test for the presence of inhibitors to Factor VIII(c) before the first infusion and three monthly thereafter. Factor VIII inhibitor activity will be measured in Bethesda units.

## 8. ETHICAL APPROVAL

The trial was approved by the Ethics Committee of each of the Haemophilia Centres which supplied the volunteers informed consent was obtained from all volunteers prior to the study commencement. The Trial was performed under the Clinical Trials Exemption (CTX) Scheme, and conformed to the recommendations of the Declaration of Helsinki as adopted at the 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.

## 9. RESULTS

27 patients have been enrolled in the trial so far. 12 patients have had one or more infusions, 9 patients have never been treated with blood products and 3 have been previously treated with Z8. Demographic data is given as Appendix 1.

### 9.1 *Liver Function Tests*

All results are within the normal ranges for the Investigating Centre.

### 9.2 *Full Blood Count*

All results were judged normal by the investigator except the 6 month sample for subject Y-12-07 which showed anaemia due to severe haemorrhage.

### 9.3 *Lymphocyte Subsets*

These data are difficult to interpret since the patients are of different ages and many results are not available. Complete data is only available for 13 of the 12 patients and thus it is not possible to draw any conclusions from these results.

### 9.4 *Factor VIII Inhibitors*

None of the patients on this study have developed inhibitors to Factor VIII (Appendix 4).

### 9.5 *Virus Results*

#### 9.5.1 HAV, HBV, HCV

Not all results are available for all subjects. However, there appear to have been no seroconversions noted

#### 9.5.2 EBV, CMV

Much of this data is unavailable but no seroconversions are noted

#### 9.5.3 HIV

There are no seroconversions noted

#### 9.5.4 Parvovirus

2 patients have become positive to parvovirus:

Y-12-01: appears to have converted at 12 months
Y-12-06: appears to have converted at 3 months

It is impossible to know whether this seroconversion is directly attributable to Liberate because of the high seropravalence in the population in general.

9.6 *Adverse Events*

Excepting the 2 patients who seroconverted to Parvovirus (B19) (discussed at 9.5.4) there were no adverse events reported.

## 10. CONCLUSION

Liberate was well tolerated by the study group, and is proved to be a safe high purity Factor VIII concentrate.

# APPENDIX 1

# DEMOGRAPHIC DATA FOR SNBTS CLINICAL TRIAL HP012

# DEMOGRAPHIC DATA

| STUDY NO. | INITIALS | DATE OF BIRTH |
|---|---|---|
| B-12-01 | GRO-A | /59 |
| B-12-02 | | /91 |
| B-12-03 | | /93 |
| E-12-01 | | /88 |
| G-12-01 | | /76 |
| G-12-02 | | /70 |
| Y-12-01 | | /91 |
| Y-12-04 | | /89 |
| Y-12-05 | | /90 |
| Y-12-06 | | /92 |
| Y-12-07 | | /91 |
| Y-12-08 | | /93 |

GRO-A



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# APPENDIX 2

# LIVER FUNCTION TEST RESULTS FOR SNBTS CLINICAL TRIAL HP012

# LIVER FUNCTION TESTS

| STUDY NO | PRE-INFUSI | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| **ALT RESULTS** | | | | | |
| B-12-01 | NT | 26 | 33 | 20 | NT |
| B-12-02 | 24 | 27 | 24 | 21 | 32 |
| B-12-03 | 55 | NT | NT | NT | NT |
| E-12-01 | <5 | NT | 17 | 13 | NT |
| G-12-01 | 17 | 19 | 16 | 11 | NT |
| G-12-02 | 19 | 15 | NT | NT | NT |
| Y-12-01 | 31 | 26 | 17 | 16 | 17 |
| Y-12-04 | 19 | 24 | 24 | 20 | 15 |
| Y-12-05 | 30 | 32 | NT | NT | NT |
| Y-12-06 | 43 | 26 | 34 | NT | NT |
| Y-12-07 | 13 | 26 | 19 | 13 | 15 |
| **GGT RESULTS** | | | | | |
| B-12-01 | NT | 26 | 23 | 24 | NT |
| B-12-02 | 23 | 20 | 19 | 18 | 19 |
| B-12-03 | 23 | NT | NT | NT | NT |
| E-12-01 | NT | NT | 12 | 10 | NT |
| G-12-01 | 16 | 20 | 17 | 15 | NT |
| G-12-02 | 15 | 15 | NT | NT | NT |
| Y-12-01 | 15 | NT | 16 | 15 | 15 |
| Y-12-04 | NT | 18 | NT | 16 | 14 |
| Y-12-05 | 15 | NT | NT | NT | NT |
| Y-12-06 | 16 | 15 | 13 | NT | NT |
| Y-12-07 | NT | NT | 16 | 18 | NT |
| Y-12-08 | 20 | NT | NT | NT | NT |
| **AST RESULTS** | | | | | |
| B-12-01 | 25 | 31 | 33 | 25 | NT |
| B-12-02 | 40 | 41 | 41 | 47 | 71 |
| B-12-03 | 56 | NT | NT | NT | NT |
| E-12-01 | NT | NT | NT | NT | NT |
| G-12-01 | 22 | 24 | 19 | 15 | NT |
| G-12-02 | 31 | 18 | NT | NT | NT |
| Y-12-01 | 53 | 42 | 38 | 54 | 57 |
| Y-12-04 | 39 | 54 | 53 | 41 | 39 |
| Y-12-05 | 52 | 53 | NT | NT | NT |
| Y-12-06 | 62 | 41 | 42 | NT | NT |
| Y-12-07 | 38 | 39 | 36 | 35 | 56 |
| Y-12-08 | 51 | NT | NT | NT | NT |

| STUDY NO | PRE-INFUSI | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| ALKALINE PHOSPHATE RESULTS | | | | | |
| B-12-01 | 108 | 110 | 91 | 24 | NT |
| B-12-02 | 175 | 178 | 165 | 2141 | 174 |
| B-12-03 | 286 | NT | NT | NT | NT |
| E-12-01 | 500 | NT | 159 | 154 | NT |
| G-12-01 | 260 | 260 | 255 | 220 | NT |
| G-12-02 | 265 | 225 | NT | NT | NT |
| Y-12-01 | 218 | 204 | 184 | 185 | 169 |
| Y-12-04 | 120 | 148 | 126 | 139 | 133 |
| Y-12-05 | 246 | 209 | NT | NT | NT |
| Y-12-06 | 174 | 173 | 171 | NT | NT |
| Y-12-07 | 237 | 223 | 201 | 198 | 198 |
| Y-12-08 | 249 | NT | NT | NT | NT |
| BILIRUBIN RESULTS | | | | | |
| B-12-01 | 8 | 8 | 9 | 10 | NT |
| B-12-02 | 7 | 5 | 3 | 1 | 3 |
| B-12-03 | 2 | NT | NT | NT | NT |
| E-12-01 | 13 | NT | 4 | 3 | NT |
| G-12-01 | 9 | 7 | 7 | 9 | NT |
| G-12-02 | 7 | 8 | NT | NT | NT |
| Y-12-01 | 3 | 3 | 6 | 8 | 3 |
| Y-12-04 | 2 | 12 | 17 | 10 | 6 |
| Y-12-05 | 8 | 11 | NT | NT | NT |
| Y-12-06 | 8 | 8 | 8 | NT | NT |
| Y-12-07 | 9 | 4 | 6 | 12 | 8 |
| Y-12-08 | 5 | NT | NT | NT | NT |



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# APPENDIX 3

# LYMPOCYTE SUBSET RESULTS FOR SNBTS CLINICAL TRIAL HP012

## LYMPHOCYTE SUBSET RESULTS

| STUDY N | PRE-INFUSION | | | 3 MONTHS | | | 6 MONTHS | | | 12 MONTHS | | | 18 MONTHS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD |
| B-12-01 | 1.28 | 0.47 | 2.72 | 0.29 | 0.40 | 0.73 | NT | NT | NT | 0.73 | 0.31 | 2.35 | NT | NT | NT |
| B-12-02 | NT | NT | NT | 4.20 | 2.05 | 2.05 | 3.74 | 1.23 | 3.04 | NT | NT | NT | NT | NT | NT |
| B-12-03 | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |
| E-12-01 | 1.22 | 0.77 | 1.58 | 0.75 | 0.59 | 1.27 | 0.69 | 0.47 | 1.47 | 0.95 | 0.54 | 1.76 | NT | NT | NT |
| G-12-01 | NT | NT | NT | 0.59 | 0.32 | 1.81 | 0.75 | 0.40 | 1.85 | NT | NT | NT | NT | NT | NT |
| G-12-02 | NT | NT | NT | 0.73 | 0.35 | 2.09 | NT | NT | NT | 0.59 | 0.26 | 2.24 | NT | NT | NT |
| Y-12-01 | 5.68 | 2.57 | 2.21 | 2.65 | 3.35 | 0.79 | 5.77 | 2.47 | 2.33 | 3.37 | 1.25 | 2.69 | 2.71 | 1.49 | 1.82 |
| Y-12-04 | 1.46 | 0.71 | 2.05 | 1.27 | 0.54 | 2.3 | NT | NT | NT | 1.12 | 0.56 | 2.0 | 0.38 | 0.20 | 1.9 |
| Y-12-05 | NT | NT | NT | 1.26 | 0.41 | 3.12 | 1.19 | 0.34 | 3.43 | NT | NT | NT | NT | NT | NT |
| Y-12-06 | 2.00 | 0.57 | 3.47 | 3.47 | 1.40 | 2.48 | 2.97 | 1.39 | 2.13 | NT | NT | NT | NT | NT | NT |
| Y-12-07 | NT | NT | NT | 2.66 | 1.18 | 2.25 | 3.66 | 1.89 | 1.94 | NT | NT | NT | 0.35 | 0.15 | 2.33 |
| Y-12-08 | 4.09 | 1.52 | 2.69 | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT | NT |



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# APPENDIX 4

# FACTOR VIII INHIBITOR LEVELS FOR SNBTS CLINICAL TRIAL HP012

# FACTOR VIII INHIBITOR LEVELS

| STUDY NUMBER. | PRE-INFUSI | 3 MONTH | 6 MONTH | 12 MONTH | 18 MONTH |
|---|---|---|---|---|---|
| B-12-01 | N | NT | N | N | NT |
| B-12-02 | NT | N | N | N | N |
| B-12-03 | N | NT | NT | NT | NT |
| B-12-01 | N | NT | N | N | NT |
| G-12-01 | N | N | N | N | NT |
| G-12-02 | N | N | NT | NT | NT |
| Y-12-01 | N | N | N | N | N |
| Y-12-04 | N | N | NT | N | N |
| Y-12-05 | N | NT | NT | NT | NT |
| Y-12-06 | NT | N | N | NT | NT |
| Y-12-07 | N | NT | N | N | NT |
| Y-12-08 | N | NT | NT | NT | NT |

# APPENDIX 5

# VIROLOGY RESULTS FOR SNBTS CLINICAL TRIAL HP012

# VIROLOGY RESULTS

| STUDY NO | PRE-INFUSION | 3 MONTH | 6 MONTH | 12 MONTH | 18 MONTH |
|---|---|---|---|---|---|
| **EBV RESULTS** | | | | | |
| E-12-01 | Y | Y | Y | Y | Y |
| G-12-01 | NT | NT | NT | NT | NT |
| G-12-02 | NT | NT | NT | NT | NT |
| Y-12-01 | NT | NT | NT | NT | NT |
| Y-12-04 | NT | NT | NT | NT | NT |
| Y-12-05 | NT | NT | NT | NT | NT |
| Y-12-06 | N | NT | NT | NT | NT |
| Y-12-07 | N | N | NT | NT | NT |
| Y-12-08 | NT | NT | NT | NT | NT |
| **ANTI-CMV RESULTS** | | | | | |
| E-12-01 | N | NT | NT | NT | NT |
| G-12-01 | Y | Y | Y | Y | Y |
| G-12-02 | NT | NT | NT | NT | NT |
| Y-12-01 | NT | NT | NT | NT | NT |
| Y-12-04 | NT | NT | NT | NT | NT |
| Y-12-05 | NT | NT | NT | NT | NT |
| Y-12-06 | N | NT | NT | NT | NT |
| Y-12-07 | N | N | NT | NT | NT |
| Y-12-08 | NT | NT | NT | NT | NT |
| **ANTI-HAV RESULTS** | | | | | |
| E-12-01 | N | N | N | N | N |
| G-12-01 | N | N | N | NT | NT |
| G-12-02 | N | NT | NT | NT | NT |
| Y-12-01 | N | N | N | N | N |
| Y-12-04 | N | N | N | N | N |
| Y-12-05 | N | N | N | N | NT |
| Y-12-06 | N | N | N | N | NT |
| Y-12-07 | N | N | N | N | NT |
| Y-12-08 | N | NT | NT | NT | NT |

| STUDY NO | PRE-INFUSI | 3 MONTHS | 6 MONTHS | 12 MONTH | 18 MONTH |
|---|---|---|---|---|---|
| **ANTI-HBs RESULTS** | | | | | |
| E-12-01 | Y | Y | Y | Y | Y |
| G-12-01 | Y | Y | Y | Y | Y |
| G-12-02 | N* | Y | Y | Y | Y |
| Y-12-01 | Y | Y | Y | Y | Y |
| Y-12-04 | Y | Y | Y | Y | Y |
| Y-12-05 | Y | Y | Y | Y | Y |
| Y-12-06 | NT | Y | Y | Y | Y |
| Y-12-07 | Y | Y | Y | Y | Y |
| Y-12-08 | N | NT | NT | NT | NT |
| **ANTI-HBsAg RESULTS** | | | | | |
| E-12-01 | N | N | N | N | N |
| G-12-01 | N | N | N | NT | NT |
| G-12-02 | N* | Y | Y | Y | Y |
| Y-12-01 | N | N | N | N | N |
| Y-12-04 | N | N | NT | NT | N |
| Y-12-05 | N | N | NT | NT | NT |
| Y-12-06 | N | N | NT | NT | NT |
| Y-12-07 | N | N | N | N | NT |
| Y-12-08 | Y | Y | Y | Y | Y |
| **ANTI-PARVOVIRUS B19 RESULTS** | | | | | |
| E-12-01 | N | N | N | N | NT |
| G-12-01 | N | N | N | NT | NT |
| G-12-02 | N | NT | NT | NT | NT |
| Y-12-01 | N | N | N | Y | NT |
| Y-12-04 | N | N | N | N | NT |
| Y-12-05 | N | N | N | N | NT |
| Y-12-06 | N | Y | Y | Y | NT |
| Y-12-07 | N | N | N | N | NT |
| Y-12-08 | N | NT | NT | NT | NT |
| **ANTI-HIV RESULTS** | | | | | |
| E-12-01 | N | NT | NT | NT | NT |
| G-12-01 | N | N | NT | NT | NT |
| G-12-02 | N | NT | NT | NT | NT |
| Y-12-01 | N | N | N | N | NT |
| Y-12-04 | N | NT | NT | NT | NT |
| Y-12-05 | N | N | NT | NT | NT |
| Y-12-06 | NT | NT | NT | NT | NT |
| Y-12-07 | N | N | NT | NT | NT |
| Y-12-08 | NT | NT | NT | NT | NT |



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| STUDY NO | PRE-INFUSION | 3 MONTH | 6 MONTH | 12 MONTH | 18 MONTH |
|---|---|---|---|---|---|
| ANTI-HCV RESULTS | | | | | |
| E-12-01 | N | N | N | N | N |
| G-12-01 | N | N | N | NT | NT |
| G-12-02 | N | NT | NT | NT | NT |
| Y-12-01 | N | N | N | N | N |
| Y-12-04 | N | N | N | N | N |
| Y-12-05 | N | N | N | N | NT |
| Y-12-06 | N | N | N | NT | NT |
| Y-12-07 | N | N | N | N | NT |
| Y-12-08 | N | NT | NT | NT | NT |

**Key:**

| | | |
|---|---|---|
| N | - | Negative |
| Y | - | Positive |
| NT | - | Not Tested |
| * | - | Vaccinated |

***(NB: No virology results have been received for the 3 Belfast patients enrolled on this study)***



SBTS0003795_062_0076

# APPENDIX 6

# PROTOCOL
# FOR SNBTS CLINICAL TRIAL HP012

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 NON-HIV INFECTED PATIENTS WITH HAEMOPHILIA A

# (HP 012)

Participating Centres
Aberdeen
Belfast
Dundee
Edinburgh
Glasgow (GRI & Yorkhill)
Inverness

PROTOCOL
25 NOVEMBER 1991

R R C STEWART

Telephone Number:
Fax Number: GRO-C

## SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

## SCOTLAND/NORTHERN IRELAND HAEMOPHILLIA DIRECTORS CLINICAL TRIAL TO ASSESS THE TOLERABILITY OF HIGH POTENCY FACTOR VIII/CONCENTRATE (HPVIII) MANUFACTURTED BY SNBTS IN NON-HIV PATIENTS WITH HAEMOPHILIA A
## (HP 012)

**Protocol Dated** .....

**Clinical Investigator**

Name .....

Title .....

Address .....

.....

Signed ..... Date .....

Monitor Miss Jane Pelly
Scottish National Blood Transfusion Service
Product Services Department
Livingstone House
39 Cowgate
Edinburgh
EH1 1JR

Signed ..... Date .....

# CONTENTS

## 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 in Edinburgh, in collaboration with French colleagues, have developed such a product.

This surveillance study is designed to assess the safety of HPVIII with respect to transmission of potentially infectious viruses. The protocol is based on the International Committee of Thrombosis and Haemostasis recommendations but entry criteria have been broadened and follow up more prolonged in certain circumstances.

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. Virological safety - to assess HIV, non-A, non-B hepatitis and parvovirus transmission by HPVIII.

iii. To assess effect of HPVIII on immune function, by measurement of lymphocyte subset numbers.

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

Blood samples will be collected before infusion of HPVIII concentrate and serially thereafter. The frequency of sampling decreases with time but it is envisaged that the patients should be followed up for at least 2 years after the initial infusion. Ideally a study such as this should be undertaken only in previously untransfused patients (PUPs) but the number of such individuals in Scotland is likely to be small within any one year and it is therefore proposed to include individuals who have only been transfused with single donation products, and those patients who were entered in the Z8 PUP study and were closely monitored and shown not to have contracted hepatitis. In addition to analysis of all patients entered, the data will be analysed separately for PUPs (Group 1), those who have previously received unfractionated blood products (Group 2), and those who were Z8 PUP's (Group 3).



SBTS0003795_062_0081

## 2. METHODS

### 2.1 Patients

The patients will be hospital 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 and who belong to one of the following groups:

1 Previously untransfused patients
2. Z8 PUPS
3. Partial PUPs

Both patients with Haemophilia A and von Willibrands Disease will be recruited.

### 2.3 Exclusion Criteria

1. Patients who have previously been transfused with fractionated pooled plasma products, other than those who were part of the Z8 PUP study.

2. Patients who are known to have liver dysfunction ie to have abnormality of liver function on routine testing at entry or clinical evidence of chronic liver disease.

3. Patients who are serologically positive for anti-HIV, anti-HCV, HBsAg, anti-HBc or anti-HBs (unless due to vaccination).

4. Patients at risk of HIV infection other than from blood products.

5 Patients with a known history of alcohol abuse.

### 2.4 Number of Patients

Up to 40 patients will be enrolled.

## 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 prepared by the Protein Fractionation Centre, Edinburgh from plasma collected by the SNBTS and NIBTS and will be supplied gratis by the SNBTS.

### 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) shoud be brought to room temperature before reconsitution. 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 te 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 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 rate of infusion should be such as to allow the infusion to be completed within 30 minutes. Continuous infusion over a long period is to be avoided.

### 6.2 Clinical Monitoring

The patients temperature, recumbent blood pressure and pulse rate shall be noted prior to the commencement of the infusion and 15 min, 30 min and 1h thereafter. This is summarised in Appendix 1.



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## 6.3 Sample Collection Arrangements

### 6.3.1 *Prior to Therapy*

See Appendix II

1. For emergency treatment take a single blood sample immediately before infusion of HPVIII concentrate. If possible an additional pre-treatment blood sample should be collected some time before entry for an elective procedure.

2. Give first injection of vaccine for Hepatitis B if not known to be immune.

Blood Samples

All samples will be analysed locally

At entry:

1. LFTs including ALT (or AST if ALT not available) and GGT

2. Serum stored (5ml, for children < 5 years - 1ml) at -40°C

3. Virology (HAV, HBV, HCV, EBV, CMV, HIV and parvovirus)

4. Lymphocyte subsets

5. Full blood count

### 6.3.2 *Follow Up Samples*

a). ***Fortnightly Samples***

Samples will be procured fortnightly until 16 weeks after the last infusion. For patients who took part in the Z8 PUP study, monthly sampling is acceptable.

Follow up samples:

1. LFTs including ALT and GGT. (If ALT not available locally measure AST immediately and store aliquot at -70°C for ALT measurement later if required).

2. Full blood count.

3. Serum stored at -40°C (5ml, for children < 5 years - 1ml)

b) ***Three Months, Six Months then Six Monthly up to 2 Years Post First Infusion***

In addition to those requred in a) above,.

i) Lymphocyte subsets
ii) Viral Serology (HAV, HBV, HCV, EBV, CMV, HIV, parvovirus)

*These sampling schedules are summarised in Appendix II.*

## 6.4 Procedure on Suspected Hepatitis Transmission

### 6.4.1 If ALT (or AST) > 50% over local normal range

Immediately

1 Retest sample locally

2. Recall patient for further sample. If ALT (AST) within normal range no further action required.

If ALT (AST) above normal range

a. continue to sample weekly until diagnosis of hepatitis confirmed or refuted.

b. Full clinical history and examination.
(Check list eg Alcohol
Drugs
Contact with an individual suffering from hepatitis or carrier
Abroad
Contact with other blood products
Parenteral drug abuse
Tattoo)

c. Virology to be undertaken locally. If patient develops hepatitis, serum sample to be sent to a Virology Reference Laboratory.

d. Inform Co-ordinating Centre by telephone and send written confirmation by first class post.

### 6.4.2 Definition of Hepatitis

Hepatitis is diagnosed by finding an ALT level greater than 2 and a half times the upper limit of the normal range in two samples taken more than 14 days apart.

### 6.4.3 Investigation of Suspected Case of Hepatitis

All episodes of hepatitis will be reported to the Communicable Disease (Scotland) Unit who will investigate and report to the Co-ordinator and Chairman of the Independent Data Review Committee.

### 6.4.4 Data Review Committee

An Independent Data Review Committee is established. All episodes of Hepatitis will be reported to the Chairman of this group who will take what action is considered appropriate.

### 6.5 Detection of Inhibitors to Factor VIII(c)

Samples should be taken to test for the presence of inhibitors to Factor VIII(c) before the first infusion and three monthly thereafter. Factor VIII inhibitor activity will be measured in Bethesda units.

### 6.6 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. *Report of Infusion Form (Form B)* should be completed on each occasion when the patient receives HPVIII or any other blood product and sent to the Co-ordinating Centre immediately.

3. *Laboratory Report Form (Form C)* should be completed and sent to Co-ordinating Centre immediately the results of each blood sample are known.

4. *Virology Report Form (Form D)* should be completed retrospectively for each patient at time of entry and six monthly thereafter.

### 6.7 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.

### 6.8 Analysis of Data

The role of formal statistical inference in all studies of this kind should be very limited. With 60 patients randomly selected, if no side effects are seen, we can state with 95% confidence that the 'population' side effect rate does not exceed 5%. This type of statement will commonly be quoted in a protocol of this kind, but it is misleading. The patients are in no way a random sample, as they are seen over a short period of time, and in consequence will be receiving a limited number of batches of the product being tested. In a situation where batch variability may be important, conventional analysis will therefore give over-optimistic confidence intervals. With side effects expected to be rare, no useful statistical inference will be obtained on batch variability. Therefore, we believe that the best approach will be to report the data obtained descriptively.Page 11

In the presentation of results it will be important to stratify according to whether or not the patient has been previously untreated with blood products (Group 1) or previously treated with unfractionated products (Group 2) or previously treated with Z8 and prospectively monitored after such treatment (Group 3). In Group 2 early evidence of non-A non-B hepatitis may be a consequence of previous treatment and all relevant previous treatment would be included in the presentation.

Throughout the study, any incident of non-A non-B hepatitis, or other possible major side effect will lead to a review of the data.

## 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 volunteers. 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 amended by the 35th World Medical Assembly, Venice 1983, and the 40th World Medical Assembly, Hong Kong 1988. 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 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 invetigators 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. Volunteers 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 5 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 the ABPI Healthy Volunteer Study Guidelines. The Department requires to review each trial before it can proceed.

## 7.8 Pre-study 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 Miss Jane Pelly 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.

### 7.9 Monitoring Responsibility

Monitoring of the trial will be the responsibility of Miss Jane Pelly 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 Bruce Cuthbertson, PFC Quality Assurance Manager or his deputy (Tel No GRO-C GRO-C. 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 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.

## 8. REFERENCES

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

*APPENDIX I*

## CLINICAL MONTITORING SCHEDULE

| | Blood Pressure | Pulse Rat |
|---|---|---|
| Pre-infusion | X | X |
| 15 minutes | X | X |
| 30 minutes | X | X |
| 1 hour | X | X |

APPENDIX II

## SAMPLING SCHEDULE

| | Prior to Therap | Week 2 | Week 4 | Week 6 | Week 8 | Week 1 | Week 1 |
|---|---|---|---|---|---|---|---|
| LFT | X | X | X | X | X | X | X |
| Full Blood Count | X | X | X | X | X | X | X |
| Serum store (5ml) | X | X | X | X | X | X | X |
| Virology | X | | | | | | X |
| Lymphocyt subsets | X | | | | | | X |
| Factor VIII inhibitors | X | | | | | | X |

| | Week 1 | Week 1 | Week 1 | Week 2 | Week 2 | Week 2 | Week 2 |
|---|---|---|---|---|---|---|---|
| LFT | X | X | | | | | X |
| Full Blood Count | X | X | | | | | X |
| Serum store (5ml) | X | X | | | | | X |
| Virology | | | | | | | X |
| Lymphocyt subsets | | | | | | | X |
| Factor VIII inhibitors | | | | | | | X |

NB: Repeat week 26 every 6 months until 2 years after entry or 26 weeks after last infusion whichever is the lesser.



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APPENDIX III

## INFORMATION FOR PATIENTS

# Clinical Trial Of High Potency Factor VIII

**Trial Number: HP 012**

You are invited to take part in a clinical trial of a new preparation of Factor VIII. This product is prepared by the Protein Franctionation Centre of the SNBTS 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 Hepatitis B surface antigen. The factor VIII concentrate is of a higher potency than that previously 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 noticable 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 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 improvment 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 wellbeing.



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The Scottish Home and Health Department has agreed to indemnify the Haemophilia Directors and their staff for any claims for compensation for damage or loss which patients suffer as a consequence of the use of Scottish National Blood Transfusion Service Products during clinical trials. This indemnity is in line with that which is normally offered by pharmaceutical companies in the UK (so called ABPI Guidelines: see British Medical Journal, volume 287, page 675).

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 pubications, 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 if 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 your 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.

# APPENDIX 7

# ADDENDUM TO PROTOCOL FOR SNBTS CLINICAL TRIAL HP012

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 NON-HIV INFECTED PATIENTS WITH HAEMOPHILIA A (HP012)

**Participating Centres:**

Aberdeen
Belfast
Dundee
Edinburgh
Glasgow (GRI & Yorkhill)
Inverness
Dumfries & Galloway

## ADDENDUM TO PROTOCOL

**25 April, 1994**

**S. J. Pelly**
**SNBTS Product Services Manager**

**Tel:** GRO-C
**Fax:**

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

# SCOTLAND/NORTHERN IRELAND HAEMOPHILIA DIRECTORS CLINICAL TRIAL TO ASSESS THE TOLERABILITY OF HIGH POTENCY FACTOR VIII CONCENTRATE (HPVIII) MANUFACTURED BY SNBTS IN NON-HIV INFECTED PATIENTS WITH HAEMOPHILIA A (HP012)

**Protocol dated:** .....

**Clinical Investigator**

Name .....

Title .....

Address .....

.....

Signed ..... Date .....

**Monitor** Miss Jane Pelly
Scottish National Blood Transfusion Service
Product Services Department
Livingstone House
39 Cowgate
Edinburgh
EH1 1JR

Signed ..... Date .....

## 1. Introduction

This Addendum to trial HP012 is to cover the period following the main trial until a product licence is granted. Patients receiving HP8 will be maintained on an adjunct to the trial under the conditions contained in this Addendum. This will be agreed by the clinical investigators and the SNBTS and will be signed in confirmation of such agreement. The Addendum will be approved by the SOHHD, Medicines Control Agency and the Local Ethics Committees.

## 2. Follow Up Samples

Samples up to12 months post first infusion will be taken as specified in the main protocol.

Thereafter samples should be taken at 6 monthly intervals.

1. Liver function test (including ALT or AST)
2. Full blood count.
3. Lymphocyte subsets.
4. APTT screening test forFactor VIII inhibitors.
5. Virology (HBsAg, anti-HAV, anti-HBs, anti HCV, Anti-$B_{19}$) until 2 consecutive samples positive.
6. Serum sample stored at -40°C 5ml (for children <5 years 1ml).

A summary of this sampling schedule appears in Appendix 1.

## 3. Documentation

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 print out, signed and dated, is acceptable.

The Addendum Laboratory Report Form (Form $C_a$) shall be completed for each patient, on which the results of those tests required as stated in this Addendum shall be recorded.

The Addendum Virology Report Form (Form $D_a$) shall be completed for each patient, on which the results of those tests required as stated in this Addendum shall be recorded

## 4. Adverse Event Reporting

Any serious adverse event which occurs subsequent to the infusion of HP8 should be reported immediately to the Quality Assurance Manager, Protein Fractionation Centre, or his deputy (031-664-2317). A serious adverse event includes the death of any patient in the study from whatever causes even if apparently unrelated to the trial medication. This is necessary as the SNBTS must report such reaction to the Medicines Control Agency promptly. Minor adverse events would be reported at the next regular monitoring meeting.

# SAMPLING SCHEDULE

| | 18 MONT | 24 MONT | 30 MONT | 36 MONT |
|---|---|---|---|---|
| Liver Function Tests (including ALT or AST) | X | X | X | X |
| Full Blood Count | X | X | X | X |
| Lymphocyte Subsets | X | X | X | X |
| APTT Screening Test - Factor VIII Inhibitors | X | X | X | X |
| Virology | X | X | X | X |
| Serum sample stored 5ml | X | X | X | X |

# DRAFT INTERIM REPORT FOR SNBTS CLINICAL TRIAL HP013

CONFIDENTIAL

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

# HP013

# SCOTLAND/NORTHERN IRELAND HAEMOPHILIA DIRECTORS CLINICAL TRIAL TO ASSESS THE TOLERABILITY OF HIGH POTENCY FACTOR VIII/CONCENTRATE (LIBERATE) MANUFACTURED BY SNBTS IN PATIENTS WITH HAEMOPHILIA A WHO POSSESS ANTIBODIES TO HIV

## DRAFT INTERIM REPORT

**SNBTS Product Services Department**

**Tel: 0131 220 4590**
**Fax: 0131 220 3105**

**SNBTS Monitor :** Dr R R C Stewart, Product Services Manager (succeeded by Miss J Pelly, Product Services Manager 1/12/93)

**Principal Investigators:**

| | |
|---|---|
| Dr A Dawson | Aberdeen |
| Prof G D O Lowe | Glasgow |
| Dr C A Ludlam | Edinburgh |
| Dr E Mayne | Belfast |
| Dr A Stark | Dumfries |

**Report Author:** Miss E McIntosh, Clinical Research Associate

**Date** 26 January 1995

## SUMMARY

This study is designed to examine the tolerability of Liberate in patients who have Haemophlia A and are positive to HIV. The study will pay particular attention to the acute tolerance of Liberate and the long term effects on the patients immune function.

This is done by assessing immediate reactions, measurement of lymphocyte subset numbers and measurement of lymphocyte subset numbers and measurement of development of inhibitors to Factor VIII.

As many patients as possible will be included in the trial. Patients are recruited by the Haemophilia Directors of Scotland & Northern Ireland.

To preserve patient confidentiality patients are referred to by subject number. This number identifies the trial centre, trial number and patient number :-eg E-13-01 is the first patient from Edinburgh enrolled on HP013.

Initial studies in HIV infected patients were undertaken over a period of 6 months, in the early 1990's. These patients, previously treated with Z8 were infused with HPVIII produced in France using Scottish Plasma. Lymphocyte subset and inhibitor data from these patients is included on Appendix 1 for reference.



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## STUDY PERSONNEL

| | |
|---|---|
| **SNBTS Monitor:** | Dr R R C Stewart BSc PhD<br>Product Services manager until Nov 93<br>Miss Jane Pelly, GRSC<br>Product Services Manager from 1/12/93 |
| **Medical Advisor:** | Professor J D Cash, BSc, MBChB, PhD, FRCPath, FRCPE, FRCP(Glas), FRCS(Edin) |
| **Investigators** | |
| **Aberdeen:**<br>Royal Infirmary | Dr A Dawson, MBChB, FRCP (Edin)<br>Dr R Soutar, MD, FRCPath |
| **Belfast:** | Dr E Mayne, MBChB, BaO MD, FRCP(Glas), FRCPath<br>Dr O McNulty, MBChB, BaO |
| **Dumfries** | Dr A Stark |
| **Edinburgh:** | Dr C A Ludlam, BSc(Hons), MBChB, PhD, FRCP(Edin), FRCPath<br>SN S Trainer, RGN |
| **Glasgow:**<br>Royal Infirmary | Professor G D O Lowe, MBChB, JCHMT (General Medicine), MD<br>Dr I Walker, MD, FRCP, FRCPath |
| **Inverness** | Dr T Taylor |

# INDEX



APPENDICES

## 1. STUDY DESIGN

This is an open labelled surveillance study.

Patients will be hospital patients or outpatients recruited by the Haemophilia Directors of Scotland and Northern Ireland. As many patients as possible will be recruited.

## 2. INCLUSION CRITERIA

1. Patients whom the physician believes require Factor VIII.
2. Patients with antibodies to HIV
3. Patients with Haemophilia A or von Willebrand's Disease.
4. Patients of either sex.
5. Patients of any age.

## 3. EXCLUSION CRITERIA

Intolerance to Factor VIII Concentrate.

## 4. TRIAL SAMPLING

Pre-Infusion

All samples will be analysed locally on entry:

1. Lymphocyte subsets
2. Serum stored 5ml, at -40°C (for children < 5 year - 1ml)
3. Inhibitors to Factor VIII

Follow Up Samples

3 months, 6 months, 12 months post first infusion and thereafter at 3 monthly intervals until 36 months after the first infusion.

1. T cell subset numbers shall be determined
2. Serum sample stored
3. Inhibitors to Factor VIII

## 5. ETHICAL APPROVAL

The trial was approved by the Ethics Committee of each of the Haemophilia Centres which supplied the volunteers informed consent was obtained from all volunteers prior to the study commencement. The Trial was performed under the Clinical Trials Exemption (CTX) Scheme, and conformed to the recommendations of the Declaration of Helsinki as adopted at the 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.

## 6. RESULTS

### 6.1 *Enrolment*

52 patients were intially enrolled on the trial. 42 patients are currently participating in the trial (9 patients have died of AIDS related conditions since commencing on the trial and one patient has been transferred to alternative Factor VIII therapy). All of these patients have received one or more infusions of Liberate. Demographic data is included at Appendix 2.

### 6.2 *Lymphocyte Subsets*

Results are available for most patients up to 18 months. These data shows no significant trends in either CD4, CD8 or the CD4/CD8 ratio. These results are shown in Appendix 3.

### 6.3 *Full Blood Count*

Many of the full blood count results showed abnormalities. These were believed to be due to the patients underlying disease and determined to be not clinically significant for trial purposes.

### 6.4 *Factor VIII Inhibitors*

One patient appears to have developed inhibitors to Factor VIII, although confirmation of this is awaited.

G-13-07 - shows inhibitor after 12 months.

Two further patients developed transient inhibitors. Transient inhibitors are taken to be inhibitors which have subsequently been shown to disappear. (Appendix 4).

E-13-05 displays inhibitors at 6 months and not at 12 months.

G-13-18 displays inhibitors at 6 months and 12 months but not at 15 months.

### 6.5 *Adverse Events*

Excepting the patients who developed inhibitors (discussed at 6.4 above) there were no adverse events reported.

## 7. CONCLUSION

Liberate appears to be well tolerated in patients who are positive to HIV.

# APPENDIX 1

# LYMPHOCYTE SUBSET & INHIBITOR DATA FOR PATIENTS TREATED WITH FRENCH MADE HPVIII

CD4, CD8 lymphocyte numbers and CD4/CD8 ratio in patients with Haemophilia A treated with HP-VIII
Counts x $10^9$/L are shown before and 3 and 6 months after first infusion

| PATIENT | PRE-INFUSION | | | 3 MONTHS | | | 6 MONTHS | | |
|---|---|---|---|---|---|---|---|---|---|
| | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 |
| E1 | 0.19 | 0.55 | 0.35 | 0.37 | 0.70 | 0.53 | 0.43 | 0.95 | 0.45 |
| E2 | - | - | - | - | - | - | - | - | - |
| E3 | 0.22 | 0.80 | 0.28 | 0.64 | 1.97 | 0.32 | - | - | - |
| E4 | - | - | - | - | - | - | - | - | - |
| E5 | - | - | - | - | - | - | - | - | - |
| E6 | 0.05 | 0.63 | 0.08 | 0.06 | 0.41 | 0.15 | 0.16 | 0.90 | 0.18 |
| E7 | - | - | - | - | - | - | - | - | - |
| E8 | - | - | - | - | - | - | - | - | - |
| E9 | - | - | - | - | - | - | - | - | - |
| E10 | 0.17 | 0.83 | 0.20 | 0.15 | 0.52 | 0.29 | 0.1 | 0.42 | 0.24 |
| E11 | - | - | - | - | - | - | - | - | - |
| E12 | 0.2 | 0.42 | 0.48 | 0.23 | 0.67 | 0.34 | 0.22 | - | - |
| E13 | 0.11 | 0.38 | 0.29 | 0.23 | 0.60 | 0.38 | - | - | - |
| E14 | 0.21 | 1.56 | 0.13 | - | - | - | - | - | - |
| E15 | - | - | - | - | - | - | - | - | - |
| E16 | 0 | 0.22 | 0 | - | - | - | - | - | - |
| G1 | 0.11 | 1.00 | 0.11 | 0.83 | 0.87 | 0.95 | - | - | - |
| G2 | 0.46 | 1.01 | 0.45 | 0.31 | 0.77 | 0.40 | 0.37 | 0.90 | 0.40 |
| G3 | 0.16 | 0.45 | 0.36 | 0.22 | 0.67 | 0.33 | 0.41 | 1.12 | 0.36 |
| G4 | 0.39 | 1.18 | 0.33 | 0.28 | 0.61 | 0.45 | 0.24 | 0.74 | 0.32 |
| G5 | 0.05 | 0.98 | 0.05 | - | - | - | 0.02 | 0.41 | 0.04 |
| G6 | 0.35 | 0.77 | 0.45 | 0.28 | 0.46 | 0.61 | 0.24 | 0.61 | 0.38 |
| G7 | 0.18 | 0.53 | 0.33 | 0.15 | 0.59 | 0.25 | 0.16 | 0.71 | 0.22 |
| G8 | 0.30 | 0.12 | 2.60 | 0.29 | 0.94 | 0.30 | 0.33 | 1.33 | 0.25 |
| G9 | 0.33 | 0.53 | 0.63 | 0.37 | 0.67 | 0.56 | 0.37 | 0.63 | 0.59 |
| G10 | - | - | - | - | - | - | - | - | - |
| G11 | 0.35 | 0.78 | 0.45 | - | - | - | 0.30 | 0.87 | 0.35 |
| G12 | 0.02 | 0.12 | 0.18 | 0.01 | 0.13 | 0.09 | 0.01 | 0.17 | 0.08 |
| G13 | 0.45 | 1.21 | 0.37 | 0.49 | 1.63 | 0.30 | 0.55 | 1.61 | 0.34 |
| G14 | 0.01 | 0.28 | 0.04 | 0.02 | 0.34 | 0.06 | 0.01 | 0.37 | 0.03 |
| G15 | 0.41 | 1.27 | 0.32 | 0.29 | 1.22 | 0.23 | 0.31 | 1.12 | 0.28 |
| G16 | 0.01 | 0.32 | 0.04 | 0.01 | 0.17 | 0.05 | - | - | - |
| G17 | 0.47 | 0.66 | 0.72 | 0.29 | 0.54 | 0.54 | 0.30 | 0.59 | 0.50 |
| Mean | 0.22 | 0.69 | 0.39 | 0.28 | 0.72 | 0.36 | 0.25 | 0.78 | 0.30 |
| 95% Confidence Interval | 0.16 to 0.28 | 0.54 to 0.85 | 0.18 to 0.59 | 0.19 to 0.37 | 0.53 to 0.92 | 0.26 to 0.45 | 0.18 to 0.32 | 0.16 to 0.95 | 0.23 to 0.37 |



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The occurrence of factor VIII inhibitors in patients with Haemophilia A treated with HPFVIII. Values are shown are :
pos : inhibitory activity present
neg : inhibitory activity absent
for before the first infusion and three and six months thereafter

| PATIENT | PRE-INFUSION | 3 MONTH | 6 MONTH |
|---|---|---|---|
| E1 | Neg | Neg | Neg |
| E2 | | | |
| E3 | | Neg | |
| E4 | | | |
| E5 | | | |
| E6 | Neg | Neg | Neg |
| E7 | | | |
| E8 | | | |
| E9 | | | |
| E10 | Neg | Neg | Neg |
| E11 | | | |
| E12 | | Neg | |
| E13 | Neg | Neg | |
| E14 | | Neg | |
| E15 | | Neg | |
| E16 | Neg | | |
| G1 | Neg | | Neg |
| G2 | Neg | Neg | |
| G3 | Neg | | Neg |
| G4 | Neg | | |
| G5 | Neg | | Neg |
| G6 | Neg | | Neg |
| G7 | Pos | Pos | Pos |
| G8 | Neg | Neg | Neg |
| G9 | Neg | | Neg |
| G10 | | | |
| G11 | Neg | | |
| G12 | Neg | Neg | Neg |
| G13 | Neg | Neg | Neg |
| G14 | Neg | Neg | |
| G15 | Neg | | |
| G16 | Neg | | |
| G17 | | | |
| POSITIVE | 1 | 1 | 1 |
| TESTED | 20 | 14 | 12 |

# APPENDIX 1

# DEMOGRAPHIC DATA FOR SNBTS CLINICAL TRIAL HP013

| STUDY NUMBER | DATE OF BIRTH | INITIALS |
|---|---|---|
| G-13-01 | 70 | |
| G-13-02 | 74 | |
| G-13-03 | 48 | |
| G-13-04 | 56 | |
| G-13-05 | 62 | |
| G-13-06 | 69 | |
| G-13-07 | 52 | |
| G-13-08 | GRO-A 47 | |
| G-13-09 | 74 | |
| G-13-10 | 92 | |
| G-13-11 | 70 | |
| G-13-12 | 49 | |
| G-13-13 | 69 | |
| G-13-14 | 61 | |
| G-13-15 | 75 | GRO-A |
| G-13-16 | 75 | |
| G-13-17 | 75 | |
| G-13-18 | 75 | |
| G-13-19 | 66 | |
| G-13-20 | 68 | |
| G-13-21 | 67 | |
| G-13-22 | GRO-A 76 | |
| G-13-23 | 57 | |
| G-13-24 | 70 | |
| G-13-25 | 32 | |
| G-13-26 | 75 | |
| I-13-01 | 74 | |
| DM-13-01 | 75 | |

# APPENDIX 3.

# LYMPHOCYTE SUBSET RESULTS FOR SNBTS CLINICAL TRIAL HP013

White blood cell counts and lymphocyte subsets in patients with haemophilia A who possess anti-HIV, treated with H8 (counts x 10^9/l). Data presented are pre-infusion values and 3 and 6 months post infusion

| | PREINFUSION | | | | 3 MONTHS | | | | 6 MONTHS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PATIENT | WCC | CD4 | CD8 | CD4/CD8 | WCC | CD4 | CD8 | CD4/CD8 | WCC | CD4 | CD8 | CD4/CD8 |
| A-13-01 | 2 | 3.5% | 41% | | | | | | | | | |
| B-13-01 | 1.82 | 0.04 | 0.27 | 0.148 | 1.97 | 0.03 | 0.26 | 0.115 | 1.65 | 0.02 | 0.21 | 0.095 |
| B-13-02 | 3.97 | 0.35 | 0.45 | 0.778 | | | | | 4.2 | 0.35 | 0.6 | |
| B-13-03 | 3.4 | 0.09 | 0.52 | 0.173 | 3.4 | 0.04 | 0.38 | 0.105 | | | | |
| B-13-04 | 4.94 | 0.65 | 1.24 | 0.524 | 4.24 | 0.56 | 0.73 | 0.767 | 4.29 | 0.32 | 0.88 | 0.364 |
| B-13-05 | 4.29 | 0.16 | 2 | 0.080 | 3.27 | 0.16 | 0.64 | 0.250 | 3.71 | 0.1 | 0.74 | 0.135 |
| B-13-06 | 4.61 | 0.48 | 1.33 | 0.361 | 5.5 | 0.51 | 0.92 | 0.554 | 5.44 | 0.46 | 1 | 0.460 |
| B-13-07 | 4.34 | 0.12 | 0.78 | 0.154 | 3.39 | 0.1 | 0.46 | 0.217 | | | | |
| E-13-01 | 4.7 | 0.21 | 1.56 | 0.135 | 4.6 | 0.28 | 1.37 | 0.204 | 4.8 | 0.22 | 1.2 | 0.183 |
| E-13-02 | 1.8 | 0.12 | 0.29 | 0.414 | 2.1 | 0.23 | 0.6 | 0.383 | 2.6 | 0.21 | 0.76 | 0.276 |
| E-13-03 | 2.6 | 0.23 | 0.53 | 0.434 | 2.9 | 0.27 | 0.7 | 0.386 | 2.9 | 0.39 | 1.2 | 0.325 |
| E-13-04 | 2.4 | 0.02 | 0.23 | 0.087 | 2.3 | 0.02 | 0.24 | 0.083 | 2.6 | 0.02 | 0.32 | 0.063 |
| E-13-05 | 3.3 | 0.15 | 0.52 | 0.288 | 3 | 0.1 | 0.42 | 0.238 | 3 | 0.18 | 0.63 | 0.286 |
| E-13-06 | 4 | 0.26 | 0.52 | 0.500 | 8.4 | 0.3 | 0.85 | 0.353 | 3.7 | 0.24 | 0.6 | 0.400 |
| [illegible]13-07 | 3.2 | 0.01 | 0.08 | 0.125 | 1.8 | 0.01 | 0.08 | 0.125 | | | | |
| 13-08 | 3.2 | 0.15 | 0.31 | 0.484 | 3.2 | 0.05 | 0.44 | 0.114 | 1.6 | 0.01 | 0.14 | 0.071 |
| E-13-09 | 3.7 | 0.06 | 0.4 | 0.150 | 4.3 | 0.16 | 0.9 | 0.178 | 5.1 | 0.26 | 1.52 | 0.171 |
| E-13-10 | 5.2 | 0.09 | 0.26 | 0.346 | 4.8 | 0.15 | 0.45 | 0.333 | 2.6 | 0.11 | 0.25 | 0.440 |
| E-13-11 | 7.6 | 0 | 0.32 | 0.000 | 3.5 | 0 | 0.23 | 0.000 | 2.4 | 0 | 0.2 | 0.000 |
| E-13-12 | | 0.27 | 1.19 | 0.227 | 4 | 0.46 | 1.42 | 0.324 | 4.8 | 0.35 | 1.18 | 0.297 |
| E-13-13 | 2.6 | 0 | 0.73 | 0.000 | | 0 | 0.21 | 0.000 | 2.8 | 0.01 | 0.43 | 0.023 |
| E-13-14 | 4.5 | 0.01 | 0.6 | 0.017 | 4.6 | 0 | 1.48 | 0.000 | 4.6 | 0 | 0.64 | 0.000 |
| E-13-15 | 2.2 | 0 | 0.22 | 0.000 | 3.9 | 0 | 0.31 | 0.000 | 1.8 | 0.01 | 0.57 | 0.018 |
| E-13-16 | 3.5 | 0.11 | 0.8 | 0.138 | 4.9 | 0.15 | 1.44 | 0.104 | 3 | 0.14 | 1.17 | 0.120 |
| G-13-01 | 4.3 | 0.093 | 0.904 | 0.103 | 3.5 | 0.096 | 0.725 | 0.132 | 3.5 | | | |
| G-13-02 | | 0.307 | 0.769 | 0.399 | 3.7 | 0.365 | 0.904 | 0.404 | 3.1 | 0.255 | 0.551 | 0.463 |
| G-13-03 | 2.6 | 0.219 | 0.672 | 0.326 | 2.2 | 0.408 | 1.124 | 0.363 | 4 | 0.161 | 0.766 | 0.210 |
| G-13-04 | 1.8 | 0.276 | 0.611 | 0.452 | 2.3 | 0.24 | 0.741 | 0.324 | 3.3 | 0.214 | 0.654 | 0.327 |
| G-13-05 | 3.3 | 1.154 | 0.982 | 1.175 | 2.3 | 0.18 | 0.407 | 0.442 | | | | |
| G-13-06 | 6.3 | 0.348 | 0.768 | 0.453 | 5.9 | 0.236 | 0.613 | 0.385 | 5.6 | 0.166 | 0.516 | 0.322 |
| G-13-07 | 6.2 | 0.148 | 0.585 | 0.253 | 4.6 | 0.157 | 0.714 | 0.220 | 4.3 | 0.124 | 0.712 | 0.174 |
| G-13-08 | 6.9 | 0.285 | 0.936 | 0.304 | 6.55 | 0.304 | 1.177 | 0.258 | 4.55 | 0.245 | 1.064 | 0.230 |
| G-13-09 | 4.2 | 0.374 | 0.665 | 0.562 | 3.8 | 0.369 | 0.629 | 0.587 | | 0.35 | | |
| -13-10 | | | | | | | | | | | | |
| G-13-11 | 4.2 | 0.352 | 0.784 | 0.449 | 6.6 | 0.302 | 0.873 | 0.346 | 7 | | | |
| G-13-12 | 6.4 | 0.063 | 0.506 | 0.125 | 6.7 | 0.145 | 0.02 | 7.250 | | | | |
| G-13-13 | 5 | 0.546 | 1.613 | 0.338 | 4.7 | 0.412 | 1.454 | 0.283 | 5.2 | 0.353 | 1.078 | 0.327 |
| G-13-14 | 2.4 | 0.022 | 0.343 | 0.064 | 2.2 | 0.011 | 0.369 | 0.030 | 1.7 | 0.012 | | |
| G-13-15 | 3.7 | 0.285 | 1.219 | 0.234 | 3.4 | 0.313 | 1.122 | 0.279 | 4 | 0.292 | 1.115 | 0.262 |
| G-13-16 | 2.5 | 0.008 | 0.1655 | 0.048 | | | | | | | | |
| G-13-17 | 4.1 | 0.472 | 0.656 | 0.720 | 3.3 | 0.297 | 0.594 | 0.500 | 5.7 | 0.369 | 0.908 | 0.406 |
| G-13-18 | 2.3 | 0.091 | 0.289 | 0.315 | 4 | 0.07 | 0.331 | 0.211 | 3.95 | 0.056 | 0.205 | 0.273 |
| G-13-19 | 4.1 | 0.255 | 0.423 | 0.603 | 3.85 | 0.262 | 0.501 | 0.523 | 4.15 | 0.126 | 0.343 | 0.367 |
| G-13-20 | 3.3 | 0.108 | 0.762 | 0.142 | 3.9 | 0.158 | 1.067 | 0.148 | 4.1 | 0.177 | 0.988 | 0.179 |
| G-13-21 | 3.4 | 0.152 | 0.587 | 0.259 | 3.5 | 0.167 | 0.529 | 0.316 | 2.9 | 0.124 | 0.526 | 0.236 |
| G-13-22 | | | | | 6.35 | 0.977 | 0.869 | 1.124 | 4.8 | 0.846 | 0.846 | 1.000 |
| G-13-23 | 3.85 | 0.228 | 0.848 | 0.269 | 3.6 | 0.226 | 0.718 | 0.315 | 8.4 | 0.181 | 0.876 | 0.207 |
| G-13-24 | 5.7 | 0.311 | 0.55 | 0.565 | 4.2 | 0.192 | 0.349 | 0.550 | 5.1 | 0.252 | 0.538 | 0.468 |
| G-13-25 | 3.5 | 0.007 | 0.343 | 0.020 | 7.337 | 0.004 | 0.233 | 0.017 | 3.5 | 0.021 | 0.207 | 0.101 |
| G-13-26 | 4.8 | 0.059 | 0.791 | 0.075 | 4.6 | 0.023 | 0.68 | 0.034 | 4.1 | 0.092 | 0.929 | 0.099 |
| G-13-34 | | | | | | | | | | | | |
| I-13-01 | 5 | 0.45 | 0.9 | 0.500 | 4.2 | 28% | | | 5.7 | 28% | | |
| DM-13-01 | 1.3 | 0.012 | 0.195 | 0.062 | | | | | 0.74 | 0.004 | 0.12 | 0.033 |
| MEAN | 3.85 | 0.21 | 0.67 | 0.29 | 4.07 | 0.21 | 0.68 | 0.43 | 3.88 | 0.19 | 0.70 | 0.25 |
| 95% CI | 4.26 | 0.27 | 0.79 | 0.36 | 4.50 | 0.26 | 0.79 | 0.73 | 4.33 | 0.24 | 0.81 | 0.31 |
| | 3.45 | 0.15 | 0.56 | 0.22 | 3.64 | 0.15 | 0.57 | 0.13 | 3.44 | 0.14 | 0.59 | 0.19 |

White blood cell counts and lymphocyte subsets in patients with haemophilia A who possess anti-FIX, treated with H8 (counts x 10^9/l). Data presented are 12, 15 and 18 months post infusion

| | 12 MONTHS | | | | 15 MONTHS | | | | 18 MONTHS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PATIENT | WCC | CD4 | CD8 | CD4/CD8 | WCC | CD4 | CD8 | CD4/CD8 | WCC | CD4 | CD8 | CD4/CD8 |
| A-13-01 | | | | | | | | | | | | |
| B-13-01 | 1.15 | 0.003 | 0.11 | 0.027 | 1.56 | 0.002 | 0.13 | 0.015 | 2.88 | 0.04 | 0.27 | 0.148 |
| B-13-02 | | | | | 4.6 | 0.26 | 0.43 | | 4.43 | 0.36 | 0.6 | |
| B-13-03 | 1.72 | 0.004 | 0.19 | 0.021 | 3.4 | | | | 1.88 | 0.005 | 0.29 | 0.017 |
| B-13-04 | 4.27 | 0.48 | 0.8 | 0.600 | 4.7 | 0.56 | 1.36 | 0.412 | 5.31 | 0.68 | 1.29 | 0.527 |
| B-13-05 | 4.02 | 0.06 | 0.64 | 0.094 | | | | | 4.12 | 0.11 | 1.51 | 0.073 |
| B-13-06 | | | | | 5.6 | 0.5 | 1.15 | 0.435 | | | | |
| B-13-07 | 3.5 | 0.06 | 0.72 | 0.083 | 3.54 | 0.08 | 0.51 | 0.157 | 3.4 | 0.1 | 0.6 | 0.167 |
| E-13-01 | | | | | | | | | | | | |
| E-13-02 | 2.3 | 0.15 | 0.61 | 0.246 | | | | | 4.6 | 0.1 | 0.96 | 0.104 |
| E-13-03 | 2.2 | 0.14 | 0.38 | 0.368 | | | | | | | | |
| E-13-04 | | | | | 1.1 | | | | 0.9 | 0.01 | 0.19 | 0.053 |
| E-13-05 | 3 | 0.18 | 0.68 | 0.265 | | | | | 2.5 | 0.13 | 0.7 | 0.186 |
| E-13-06 | 3.5 | 0.25 | 0.66 | 0.379 | | | | | | | | |
| F-13-07 | | | | | | | | | | | | |
| -13-08 | | | | | 1.4 | 0 | 0.014 | 0.000 | 2.3 | 0 | 0.027 | 0.000 |
| E-13-09 | 5.1 | 0.25 | 0.62 | 0.403 | | | | | 4.8 | 0.38 | 0.99 | 0.384 |
| E-13-10 | 3.3 | 0.12 | 0.42 | 0.286 | | | | | 2.9 | 0.09 | 0.31 | 0.290 |
| E-13-11 | | | | | 4.8 | 0 | 0.07 | 0.000 | 4.3 | 0 | 0.19 | 0.000 |
| E-13-12 | 3.5 | 0.27 | 1.19 | 0.227 | | 0.27 | | | 4.5 | 0.6 | 1.88 | 0.319 |
| E-13-13 | 3.8 | 0.01 | 0.45 | 0.022 | | | | | 1.7 | 0 | 0.2 | 0.000 |
| E-13-14 | 3.7 | 0.01 | 0.45 | 0.022 | | | | | | | | |
| E-13-15 | | 0.01 | 0.57 | 0.018 | | | | | | | | |
| E-13-16 | 3.8 | 0.16 | 1.14 | 0.140 | | | | | | | | |
| G-13-01 | 2.8 | 0.29 | 0.44 | 0.659 | 4.3 | 0.022 | 0.375 | 0.059 | | | | |
| G-13-02 | 3.6 | 0.327 | 0.891 | 0.367 | | | | | 3.3 | 0.369 | 0.739 | 0.499 |
| G-13-03 | 2.5 | 0.072 | 0.588 | 0.122 | 4 | 0.072 | 0.588 | 0.122 | 2.8 | 0.051 | 0.422 | 0.121 |
| G-13-04 | 3.1 | 0.182 | 0.564 | 0.323 | 2.3 | 0.206 | 0.434 | 0.475 | 3 | 0.212 | 0.61 | 0.348 |
| G-13-05 | | | | | | | | | | | | |
| G-13-06 | 5.3 | 0.18 | 0.541 | 0.333 | 3.7 | 0.238 | 0.678 | 0.351 | 5 | 0.192 | 0.862 | 0.223 |
| G-13-07 | 3 | 0.096 | 0.56 | 0.171 | | | | | | | | |
| G-13-08 | 4.6 | 0.111 | 0.587 | 0.189 | 5.1 | 0.215 | 1.026 | 0.210 | 5.4 | 0.199 | 0.96 | 0.207 |
| G-13-09 | 2.6 | 0.97 | | | | | | | 4.5 | 0.335 | 0.546 | 0.614 |
| -13-10 | 3.9 | 0.013 | 0.28 | 0.046 | 4.1 | 0.024 | 0.262 | 0.092 | | | | |
| -13-11 | 4.4 | 0.232 | 0.64 | 0.363 | | | | | 7.9 | 0.287 | 0.587 | 0.489 |
| G-13-12 | | | | | | | | | | | | |
| G-13-13 | 5.6 | 0.686 | 1.424 | 0.482 | 6.3 | 0.479 | 1.297 | 0.369 | 5.8 | | | |
| G-13-14 | 2.6 | 0.015 | 0.265 | 0.057 | 2.7 | 0.005 | 0.217 | 0.023 | 0.8 | 0.002 | 0.069 | 0.029 |
| G-13-15 | 6 | 0.321 | 1.848 | 0.174 | 6 | 0.321 | 1.848 | 0.174 | 6 | 0.261 | 1.391 | 0.188 |
| G-13-16 | | | | | | | | | | | | |
| G-13-17 | 4.1 | 0.256 | 0.514 | 0.498 | | | | | 4.8 | | | |
| G-13-18 | 1.4 | 0 | 0.148 | 0.000 | 2 | 0.002 | 0.09 | 0.022 | 2 | 0.003 | 0.112 | 0.027 |
| G-13-19 | 3.7 | 0.248 | 0.538 | 0.461 | | | | | 3.7 | 0.058 | 0.355 | 0.163 |
| G-13-20 | 5.4 | 0.162 | 1.035 | 0.157 | 3.8 | | | | | | | |
| G-13-21 | 2.3 | 0.113 | 0.463 | 0.244 | 2.6 | 0.114 | 0.463 | 0.246 | 2.7 | | | |
| G-13-22 | 6 | 0.874 | 1.026 | 0.852 | 6.4 | 0.932 | 0.777 | 1.199 | 5.1 | 0.666 | 0.577 | 1.154 |
| G-13-23 | 4.9 | 0.357 | 1.784 | 0.200 | | | | | | | | |
| G-13-24 | | | | | | 0.36 | 0.719 | | 3.3 | 0.226 | 0.392 | 0.577 |
| G-13-25 | | 0.002 | 0.077 | 0.026 | 2.3 | 0.006 | 0.093 | 0.065 | | | | |
| G-13-26 | 4.8 | 0.035 | 0.535 | 0.065 | 4.4 | 0.016 | 0.378 | 0.042 | 4.6 | 0.023 | 0.542 | 0.042 |
| G-13-34 | 3.1 | 0.182 | 0.564 | 0.323 | | | | | | | | |
| I-13-01 | | | | | | | | | | | | |
| DM-13-01 | | 0.012 | 0.195 | 0.062 | | | | | | | | |
| MEAN | 3.64 | 0.20 | 0.64 | 0.24 | 3.78 | 0.20 | 0.59 | 0.22 | 3.79 | 0.19 | 0.63 | 0.25 |
| 95% CI | 4.03 | 0.27 | 0.77 | 0.30 | 4.40 | 0.30 | 0.79 | 0.35 | 4.33 | 0.26 | 0.80 | 0.34 |
| | 3.24 | 0.13 | 0.52 | 0.18 | 3.16 | 0.11 | 0.38 | 0.10 | 3.25 | 0.12 | 0.46 | 0.15 |

# APPENDIX 4.

# FACTOR VIII INHIBITOR LEVELS FOR SNBTS CLINICAL TRIAL HP013

| STUDY NUMBER | PREINFUSION | 3 M | 6 M | 12 M | 18 M |
|---|---|---|---|---|---|
| A-13-01 | NT | NT | NT | NT | NT |
| B-13-01 | N | NT | NT | NT | N |
| B-13-02 | N | NT | N | N | NT |
| B-13-03 | N | N | NT | N | NT |
| B-13-04 | N | NT | NT | N | N |
| B-13-05 | N | NT | NT | NT | N |
| B-13-06 | N | N | N | N | NT |
| B-13-07 | N | NT | NT | NT | NT |
| E-13-01 | N | N | N | N | NT |
| E-13-02 | N | N | NT | NT | NT |
| E-13-03 | N | N | N | N | NT |
| E-13-04 | NT | NT | NT | NT | N |
| E-13-05 | N | N | N | N | N |
| E-13-06 | N | NT | N | N | NT |
| E-13-07 | NT | NT | NT | NT | NT |
| E-13-08 | N | N | N | N | NT |
| E-13-09 | N | N | NT | N | NT |
| E-13-10 | N | N | N | N | NT |
| E-13-11 | N | NT | N | NT | NT |
| E-13-12 | N | N | N | N | NT |
| E-13-13 | NT | NT | N | N | NT |
| E-13-14 | N | N | N | N | NT |
| E-13-15 | N | N | N | N | NT |
| E-13-16 | NT | N | N | N | NT |
| G-13-01 | N | NT | N | NT | NT |
| G-13-02 | N | NT | N | N | NT |
| G-13-03 | N | N | N | N | NT |
| G-13-04 | N | N | N | N | NT |
| G-13-05 | N | N | NT | NT | NT |
| G-13-06 | N | N | N | N | NT |
| G-13-07 | N | NT | NT | Y(1.0) | NT |
| G-13-08 | N | N | N | N | NT |
| G-13-09 | N | NT | N | N | NT |
| G-13-10 | NT | NT | NT | N | NT |
| G-13-11 | N | NT | NT | N | NT |
| G-13-12 | N | NT | NT | NT | NT |
| G-13-13 | N | NT | N | N | NT |
| G-13-14 | N | NT | NT | N | NT |
| G-13-15 | N | NT | N | NT | NT |
| G-13-16 | NT | NT | NT | NT | NT |
| G-13-17 | NT | NT | NT | N | NT |
| G-13-18 | N | NT | Y(1.3) | Y(1.3) | NT |
| G-13-19 | N | NT | N | N | NT |
| G-13-20 | N | N | N | N | NT |
| G-13-21 | N | N | N | N | NT |
| G-13-22 | NT | N | N | N | NT |
| G-13-23 | N | N | N | N | NT |
| G-13-24 | N | N | N | N | NT |
| G-13-25 | N | N | N | N | NT |
| G-13-26 | N | N | N | N | NT |
| G-13-34 | NT | NT | NT | NT | NT |
| DM-13-01 | N | NT | N | N | N |



SBTS0003795_062_0115

Co-Directors:
Dr. G. D. O. Lowe
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Ext. GRO-C
Direct Line: GRO-C



GRO-C

August 30, 1993

Dr. Robert Stewart
SNBTS
Livingstone House
39 Cowgate
EDINBURGH EH1 1JR

re: Development of Factor VIII inhibitor in patient in Trial HP013 (patient GRO-C)

Dear Bob:

Thank you for your letter of August 13. The patient who developed an inhibitor was found on routine inhibitor screening at his last three monthly visit to have only a borderline query inhibitor with a titre of just over 1 Bethesda units per ml. We have been seeking to obtain a second sample to see whether this is a definite inhibitor or not, however, the patient has been recurrently hospitalized at another hospital for problems with infection, and thus far we have been unable to repeat his inhibitor screen, but we hope to do this in the next week or so. I will let you know the result as soon as possible.

In the meantime, he has not had any bleeding problems to suggest a clinically significant Factor VIII inhibitor.

Kind regards.

Yours sincerely,

GRO-C

Professor Gordon Lowe
CONSULTANT PHYSICIAN

GDOL:ldb

# APPENDIX 5

# PROTOCOL
# FOR SNBTS CLINICAL TRIAL HP013

**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 WHO POSSESS ANTIBODIES TO HIV (HP 013)

**Participating Centres**

**Aberdeen**
**Belfast**
**Dundee**
**Edinburgh**
**Glasgow (GRI & Yorkhill)**
**Inverness**

**PROTOCOL**
**25 NOVEMBER 1991**
**(AMENDED 5 APRIL 1993)**

**R R C STEWART**

GRO-C

SCOTLAND/NORTHERN IRELAND BLOOD TRANSFUSION SERVICE

# CLINICAL TRIAL TO ASSESS THE TOLERABILITY OF HIGH POTENCY FACTOR VIII/CONCENTRATE (HPVIII) MANUFACTURED BY SNBTS IN PATIENTS WITH HAEMOPHILIA A WHO POSSESS ANTIBODIES TO HIV

**Protocol dated** .....

**Clinical Investigator**

Name .....

Title .....

Address .....

.....

Signed ..... Date .....

Monitor Miss Jane Pelly
Scottish National Blood Transfusion Service
Product Services Department
Livingstone House
39 Cowgate
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EH1 1JR

Signed ..... Date .....

# CONTENTS

## 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 who possess antibodies to HIV, particularly in respect to acute tolerance and the long term effects of treatment on immune function.

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.

## 2. METHODS

### 2.1 Patients

The patients will be hospital 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 and who are positive for antibodies to HIV. Patients with Haemophilia A or von Willebrand's Disease may be recruited.

### 2.3 Exclusion Criterion

The only exclusion criterion is intolerance to Factor VIII concentrates.

### 2.4 Number of Patients

As many patients who fulfil the entry criteria and who require treatment with HPVIII will be enrolled.

## 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°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 allows 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 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. Full blood count
3. Serum stored (5ml, for children < 5 year - 1ml) at -40°C

#### 6.2.2 *Follow Up Samples*

THREE MONTHS, SIX MONTHS AND TWELVE MONTHS POST FIRST INFUSION

1. T cell subset numbers should be determined
2. Full blood count
3. Serum sample stored

These sampling schedules are summarised in Appendix I.

### 6.3 Detection of Inhibitors to Factor VIII(c)

Samples should be taken to test for the presence of inhibitors to Factor VIII(c) before the first infusion and at 3 months, 6 months and 12 months thereafter.

### 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.

### 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 the sample of patients inevitably will be small, it will not be possible to perform a rigorous statistical analysis. The data therefore will be presented descriptively.

## 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 volunteers. 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 29th World Medical Assembly, Hong Kong 1989, Japan 1975. 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 Miss Jane Pelly. In addition each major investigator will be required to sign an Investigator's Agreement.

## 7.8 Pre-Study 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 Miss Jane Pelly 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 Miss Jane Pelly 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 Bruce Cuthbertson, PFC Quality Assurance Manager or his deputy (Tel No GRO-C GRO-C). 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 | 3 Months | 6 Months | 12 Month |
|---|---|---|---|---|
| Full Blood Count | X | X | X | X |
| Serum Stored (5ml) | X | X | X | X |
| Lymphocyte Subsets | X | X | X | X |
| Factor VIII Inhibitors | X | X | X | X |

X

APPENDIX II

## INFORMATION FOR PATIENTS

# CLINICAL TRIAL OF HIGH POTENCY FACTOR VIII

**Trial Number: HP 013**

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 milligram 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 reimbursed. 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.



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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.

# APPENDIX 6

# ADDENDUM TO PROTOCOL FOR SNBTS CLINICAL TRIAL HP013

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

CONFIDENTIAL

# SCOTLAND/NORTHERN IRELAND HAEMOPHILIA DIRECTORS CLINICAL TRIAL TO ASSESS THE TOLERABILITY OF HIGH POTENCY FACTOR VIII CONCENTRATE (H8) MANUFACTURED BY SNBTS IN PATIENTS WITH HAEMOPHILIA A WHO POSSESS ANTIBODIES TO HIV (HP013)

**Participating Centres:**

Aberdeen
Belfast
Dundee
Edinburgh
Glasgow (GRI & Yorkhill)
Inverness
Dumfries & Galloway

## ADDENDUM TO PROTOCOL

**5 April 1994**

**S. J. Pelly**
**SNBTS Product Services Manager**

**Tel:** GRO-C
**Fax:**

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

**SCOTLAND/NORTHERN IRELAND HAEMOPHILIA DIRECTORS CLINICAL TRIAL TO ASSESS THE TOLERABILITY OF HIGH POTENCY FACTOR VIII CONCENTRATE (H8) MANUFACTURED BY SNBTS IN PATIENTS WITH HAEMOPHILIA A WHO POSSESS ANTIBODIES TO HIV (HP013)**

**Addendum to Protocol dated** .....

**Clinical Investigator**

**Name** .....

**Title** .....

**Address** .....

.....

**Signed** ..... **Date** .....

**Monitor** Miss Jane Pelly
Scottish National Blood Transfusion Service
Product Services Department
Livingstone House
39 Cowgate
Edinburgh
EH1 1JR

**Signed** ..... **Date** .....

6.2 Sample Collection Arrangements

6.2.1 Prior to Therapy

See Appendix 1

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. Full blood count
3. Serum stored (5ml, for children < 5 year - 1ml) at -40°C

6.2.2 Follow Samples

Samples should be taken at 3, 6 and 12 months post-infusion and thereafter at 3 monthly intervals until 36 months after the first infusion.

1. Lymphocyte subset numbers should be determined.

2. A full blood count should be carried out.

3. A serum sample should be stored.

These sampling schedules are summarised in Appendix I.

6.3 Detection of Inhibitors to Factor VIII (c)

Samples should be taken and tested for the presence of inhibitors to Factor VIII(c) before the first infusion, at 3, 6 and 12 months post infusion and thereafter at 3 monthly intervals until 36 months after the first infusion."

# DRAFT INTERIM REPORT

# FOR SNBTS CLINICAL TRIAL HP016

**CONFIDENTIAL**

**SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE**

# HP016

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

## DRAFT INTERIM REPORT

**SNBTS Product Services Department**

**Tel: 0131 220 4590**
**Fax: 0131 220 3105**

**SNBTS Monitor :** Dr R R C Stewart, Product Services Manager (succeeded by Miss J Pelly, Product Services Manager 1/12/93)

**Principal Investigators:**

| | |
|---|---|
| Aberdeen | Dr A Dawson |
| Aberdeen (Paed) | Dr D King |
| Belfast | Dr E Mayne |
| Dundee | Dr P Cachia |
| Dundee (Paed) | Dr R Wilkie |
| Dumfries | Dr S Stark |
| Edinburgh | Dr C A Ludlam |
| Glasgow | Prof G D O Lowe |
| Glasgow (Paed) | Dr B E S Gibson |
| Inverness | Dr T Taylor |

**Report Author:** Miss E McIntosh, Clinical Research Associate

**Date:** 26 January 1995

## SUMMARY

Liberate is a more refined product developed by SNBTS in response to worries about viral transmission and an apparent immune disturbance in non-HIV infected patients.

This surveillance study aims to assess the tolerability of HP016.

The study assesses immediate reaction, virology safety, effects of Liberate on immune system and the development of inhibitors to Liberate.

All the Haemophilia Directors for Scotland and Northern Ireland have recruited patients with Haemophilia A to take part in the study, thus providing a broad group of patients.

To preserve patient confidentiality patients are referred to by subject number. This number identifies the trial centre, trial number, and the patient number:- eg E-16-01 is the first patient from Edinburgh on HP016

## STUDY PERSONNEL

| | |
|---|---|
| **SNBTS Monitor:** | Dr R R C Stewart BSc PhD<br>Product Services Manager until Nov 93<br>Miss Jane Pelly, GRSC<br>Product Services Manager from 1/12/93 |
| **Medical Advisor:** | Professor J D Cash, BSc, MBChB, PhD, FRCPath, FRCPE, FRCP(Glas), FRCS(Edin) |

**Investigators**

| | |
|---|---|
| **Aberdeen:** | |
| Royal Infirmary | Dr A Dawson, MBChB, FRCP (Edin)<br>Dr R Soutar, MD, FRCPath |
| Royal Children's Hospital | Dr D King, BMedBid, MBChB, MRCPath(Haem), FRCP (Edin) |
| **Belfast:** | Dr E Mayne, MBChB, BaO MD, FRCP(Glas), FRCPath<br>Dr O McNulty, MBChB, BaO |
| **Dundee:** | |
| Adults | Dr P Cachia, BSc(MedSci) MBChB MRCP, MD, MRCPath |
| Children | Dr R Wilkie |
| **Dumfries** | Dr A Stark |
| **Edinburgh:** | Dr C A Ludlam, BSc(Hons), MBChB, PhD, FRCP(Edin), FRCPath<br>SN S Trainer, RGN |
| **Glasgow:** | |
| Glasgow Royal Infirmary | Professor G D O Lowe, MBChB, JCHMT (General Medicine), MD<br>Dr B Shaw, MBChB, FRCP (Edin & Glas), FRCP(Lond), DRCOG<br>Dr I Walker, MD, FRCP, FRCPath |
| Royal Hospital for Sick Children | Dr B E S Gibson, MBChB, MRCPath, FRCP(Glas), Dip in Forensic Medicine<br>Dr R Ahmed, MBChB, MRCP |
| **Inverness** | Dr T Taylor |

# CONTENTS

## 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 impurities in 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 in Edinburgh, in collaboration with French colleagues, have developed such a product.

This surveillance study is designed to assess the safety of Liberate with respect to transmission of potentially infectious viruses. The protocol is based on the International Committee of Thrombosis and Haemostasis recommendations but entry criteria have been broadened and follow up more prolonged in certain circumstances.

## 2. OBJECTIVES

The aim of this study is to assess the tolerability of Liberate. This will be done by measuring the following:

i. Immediate (allergic-type) reactions.

ii. Virological safety - to assess HIV, hepatitis C and parvovirus transmission by Liberate.

iii. To assess effect of Liberate on immune function, by measurement of lymphocyte subset numbers.

iv. To assess the development of inhibitors to Factor VIII in patients on Liberate.

## 3. METHODOLOGY

This is an open labelled study involving up to 250 patients. Both in-patients and out-patients will be recruited by the Haemophilia Directors of Scotland and Northern Ireland.

## 4. INCLUSION CRITERIA

1. Patients of either sex
2. Patients of any age
3. Patients with Haemophilia A
4. Patients whom the physician believes require Factor VIII.



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## 5. EXCLUSION CRITERIA

Intolerance to Factor VIII Concentrate.

## 6. CLINICAL MONITORING

Blood Samples

Pre-infusion

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, at -40°C (for children < 5 year - 1ml)
5. Inhibitors to Factor VIII

Follow Up Samples

3 Months, 6 Months, !2 Months post first infusion

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-HBc, anti-HCV, anti-parvovirus B19
4. Serum sample stored
5. Inhibitors to Factor VIII

Thereafter samples should be taken at 6 monthly intervals.

1. Lymphocyte subsets
2. Liver function test (including ALT or AST)
3. APTT screening test for Factor VIII inhibitors
4. Virology (HBsAg, anti-HAV, anti-HBs, anti-HCV, anti-$B_{19}$) until 2 consecutive samples positive.
5. Serum sample stored at -40°C -5ml (for children < 5 years 1ml).

## 7. ETHICAL APPROVAL

The trial was approved by the Ethics Committee of each of the Haemophilia Centres which supplied the volunteers informed consent was obtained from all volunteers prior to the study commencement. The Trial was performed under the Clinical Trials Exemption (CTX) Scheme, and conformed to the recommendations of the Declaration of Helsinki as adopted at the 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.

# 8. RESULTS

195 patients have been enrolled so far. 19 patients have not yet had their first infusion of Liberate.

## 8.1 *Liver Function Tests*

All results are within the normal limits (Appendix 2).

## 8.2 *Virology*

### 8.2.1 Anti-HAV, HBsAg, Anti-HBc, Anti-HCV

Although all results are not available for these tests, no patient has seroconverted to any of the above viruses (Appendix 3).

### 8.2.2 Parvovirus ($B_{19}$)

12 patients appear to have become positive to the virus $B_{19}$.

| *Patient* | *Seroconverted At:* |
|---|---|
| A-16-13 | 3 months |
| A-16-17 | 12 months |
| B-16-33 | 3 months |
| B-16-34 | 3 months |
| B-16-36 | 6 months |
| D-16-22 | 3 months |
| E-16-13 | 12 months |
| E-16-15 | 18 months |
| E-16-16 | 6 months |
| E-16-17 | 6 months |
| E-16-22 | 12 months |
| Y-22-18 | 3 months |

* It is impossible to conclude whether these seroconversions are due to Liberate because of the high seroprevalence of parvovirus in the population.

### 8.2.3 Lymphocyte Subsets

Some results are unavailable for this study, however, many results are available up to and including those at 12 months.

No significant trends can be seen in CD4 or CD8 levels or indeed in the CD4/CD8 ratio (Appendix 4).

8.2.4 Inhibitors to Factor VIII

Four patients appear to have developed inhibitors to Factor VIII for which we are awaiting confirmation:

| *Patient* | *Showed Inhibitors At:* |
|---|---|
| B-16-43 | 6 & 12 Months |
| E-16-03 | 18 Months |
| E-16-10 | 12 Months |
| G-16-38 | 6 & 12 Months |

Patient E-16-03 (MM) has not previously been infused with any blood products and would therefore have been eligible for the PUP study (HP012). However, due to parental concern about the amount of blood to be taken he was enrolled in HP016.

This patient shows inhibitor development after 18 months of treatment with Liberate.

Three patients on this trial developed transient inhibitors to Factor VIII. Transient inhibitors are taken to be inhibitors which have subsequently been shown to disappear.

A-16-02 showed inhibitors at 3 months but not at 6 months

B-16-21 showed inhibitors at 6 months but not at 12 months

B-16-22 showed inhibitors at 6 months but not at 12 months

Six patients showed pre-existing inhibitors (A-16-07, A-16-12, D-16-10, E-16-05, E-16-23, Y-16-09), and one patient had inhibitors pre-infusion which were absent at 6 months and then recurred at 12 months (A-16-05). All data can be found in Appendix 5.

## 9. ADVERSE EVENTS

Excepting the patients who seroconverted to Parvovirus (B19) and those who developed inhibitors to Factor VIII (further information on E-16-03 (mm) and E-16-10 (PRGS) is included at Appendix 6) there were no other adverse events noted.

## 10. CONCLUSION

Liberate has been well tolerated by the study group and is demonstrated to be a safe Factor VIII complex concentrate in terms of virological transmission, inhibitor development and effect on the immune system.

# APPENDIX 1

# DEMOGRAPHIC DATA FOR SNBTS CLINICAL TRIAL HP016

# DEMOGRAPHIC DATA FOR SNBTS CLINICAL TRIAL HP016

(Key: * Not yet infused)

| STUDY NUMBER | PATIENT INITIALS | DATE OF BIRTH |
|---|---|---|
| A-16-01 | GRO-A | 81 |
| A-16-02 | | 88 |
| A-16-03 | | 85 |
| A-16-04 | | 86 |
| A-16-05 | | 80 |
| A-16-06 | | 80 |
| A-16-07 | | 80 |
| A-16-08* | | 83 |
| A-16-09* | | 64 |
| A-16-10 | | 77 |
| A-16-11* | | 67 |
| A-16-12 | | 44 |
| A-16-13 | | 40 |
| A-16-14 | | 26 |
| A-16-15 | | 71 |
| A-16-16 | | 70 |
| A-16-17 | | 60 |
| A-16-18 | | 47 |
| A-16-20 | | 92 |
| A-16-21 | | 93 |



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| STUDY NUMBER | PATIENT INITIALS | DATE OF BIRTH |
|---|---|---|
| B-16-01 | GRO-A | 63 |
| B-16-02 | | 58 |
| B-16-03 | | 73 |
| B-16-04 | | 65 |
| B-16-05 | | 63 |
| B-16-06 | | 68 |
| B-16-07 | | 67 |
| B-16-08 | | 40 |
| B-16-09 | | 64 |
| B-16-10 | | 73 |
| B-16-11 | | 58 |
| B-16-12 | | 47 |
| B-16-13* | | GRO-A 29 |
| B-16-14 | | 27 |
| B-16-15 | | 86 |
| B-16-16 | | 55 |
| B-16-17 | | 42 |
| B-16-18 | | 26 |
| B-16-19 | | 59 |
| B-16-20 | | 75 |
| B-16-21 | | 41 |
| B-16-22 | | 34 |
| B-16-23 | | 38 |
| B-16-24 | | 43 |
| B-16-25 | | 29 |

| | | | | | |
|---|---|---|---|---|---|
| B-16-26 | | GRO-A | | GRO-A | .36 |
| B-16-27 | | | | | .80 |
| B-16-28 | | | | | .80 |
| B-16-29 | | | | | .82 |
| B-16-30 | | | | | .82 |
| B-16-31 | | | | | .84 |
| B-16-32 | | | | | .78 |
| B-16-33 | | | | | .90 |
| B-16-34 | | | | | .85 |
| B-16-35 | | | | | .78 |
| B-16-36 | | | | | .89 |
| B-16-37 | | | | | .80 |
| B-16-38* | | | | | .92 |
| B-16-39 | | | | | |
| B-16-40 | | | | | .76 |
| B-16-41 | | | | | .89 |
| B-16-42 | | | | | .91 |
| B-16-43 | | | | | .92 |
| B-16-44 | | | | | .87 |

| STUDY NUMBER | PATIENT INITIALS | DATE OF BIRTH |
|---|---|---|
| D-16-01 | GRO-A | .31 |
| D-16-02 | | .47 |
| D-16-03 | | .67 |
| D-16-04 | | .47 |
| D-16-05 | | .68 |
| D-16-06 | | .64 |
| D-16-07 | | .71 |
| D-16-08 | | .62 |
| D-16-09 | | GRO-A .67 |
| D-16-10 | | .34 |
| D-16-21 | | .82 |
| D-16-22 | | .92 |
| D-16-23 | | .92 |
| D-16-24 | | .80 |
| D-16-25 | | .88 |
| DM-16-02 | | .66 |
| DM-16-03 | | .66 |

| STUDY NUMBER | PATIENT INITIALS | DATE OF BIRTH |
|---|---|---|
| E-16-01 | GRO-A | GRO-A 89 |
| E-16-02 | | 68 |
| E-16-03 | | 91 |
| E-16-04 | | 80 |
| E-16-05 | | 61 |
| E-16-06 | | 91 |
| E-16-07 | | 87 |
| E-16-08 | | 67 |
| E-16-09 | | 55 |
| E-16-10 | | 40 |
| E-16-11 | | 28 |
| E-16-12 | | 88 |
| E-16-13 | | 91 |
| E-16-14 | | 91 |
| E-16-15 | | 90 |
| E-16-16 | | 87 |
| E-16-17 | | 90 |
| E-16-18 | | 19 |
| E-16-19 | | 67 |
| E-16-20 | | 58 |
| E-16-21 | | 47 |
| E-16-22 | | 92 |
| E-16-23 | | 81 |
| E-16-24 | | 60 |
| E-16-25 | | 55 |



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| STUDY NUMBER | PATIENT INITIALS | DATE OF BIRTH |
|---|---|---|
| G-16-01 | GRO-A | 43 |
| G-16-02 | | 74 |
| G-16-03 | | 57 |
| G-16-04 | | 69 |
| G-16-05 | | 22 |
| G-16-06 | | 20 |
| G-16-07* | | 57 |
| G-16-08 | | 59 |
| G-16-09* | | 22 |
| G-16-11 | | 46 |
| G-16-12 | | 43 |
| G-16-13 | | GRO-A 55 |
| G-16-14 | | 59 |
| G-16-15 | | 57 |
| G-16-16 | | 43 |
| G-16-17 | | 47 |
| G-16-18 | | 59 |
| G-16-19 | | 68 |
| G-16-20* | | 61 |
| G-16-21 | | 65 |
| G-16-22 | | 58 |
| G-16-23 | | 63 |
| G-16-24 | | 46 |
| G-16-25* | | - |



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| | | | | | |
|---|---|---|---|---|---|
| G-16-26 | | GRO-A | | GRO-A | 61 |
| G-16-27* | | | | | 67 |
| G-16-28 | | | | | 48 |
| G-16-29 | | | | | 50 |
| G-16-30* | | | | | 40 |
| G-16-31 | | | | | 37 |
| G-16-32 | | | | | 55 |
| G-16-33 | | | | | 57 |
| G-16-34 | | | | | 62 |
| G-16-35* | | | | | 34 |
| G-16-36 | | | | | 71 |
| G-16-37 | | | | | 23 |
| G-16-38 | | | | | 62 |
| G-16-39 | | | | | 56 |
| G-16-40* | | | | | 56 |
| G-16-41 | | | | | 35 |
| G-16-42 | | | | | 68 |
| G-16-43* | | | | | 61 |
| G-16-44* | | | | | 36 |
| G-16-45* | | | | | 54 |
| G-16-46* | | | | | 70 |

| STUDY NUMBER | PATIENT INITIALS | DATE OF BIRTH |
|---|---|---|
| I-16-01 | GRO-A | 90 |
| I-16-02 | | 76 |
| I-16-03 | | 36 |
| I-16-04 | | 61 |
| I-16-05 | | 87 |
| I-16-06 | | 86 |
| I-16-07 | | |
| I-16-08 | | 64 |
| I-16-09 | | 68 |

| STUDY NUMBER | PATIENT INITIALS | DATE OF BIRTH |
|---|---|---|
| Y-16-02 | GRO-A | GRO-A 81 |
| Y-16-03 | | 79 |
| Y-16-04 | | 81 |
| Y-16-05 | | 85 |
| Y-16-07 | | 83 |
| Y-16-08 | | 82 |
| Y-16-09 | | 86 |
| Y-16-10 | | 84 |
| Y-16-11 | | 82 |
| Y-16-12 | | 81 |
| Y-16-13 | | 90 |
| Y-16-14 | | 80 |
| Y-16-15 | | 85 |
| Y-16-16 | | 85 |
| Y-16-17 | | 82 |
| Y-16-18 | | 87 |
| Y-16-19* | | 84 |
| Y-16-20 | | 86 |
| Y-16-22 | | 90 |
| Y-16-23* | | 85 |
| Y-16-24 | | 79 |
| Y-16-25 | | 80 |
| Y-16-26 | | 80 |



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# APPENDIX 2

# LIVER FUNCTION TEST RESULTS FOR SNBTS CLINICAL TRIAL HP016

# TABLE 1: SERUM ALT LEVELS IN PATIENTS ON SNBTS HP016 CLINICAL TRIAL

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTH |
|---|---|---|---|---|---|
| A-16-01 | NT | NT | NT | NT | NT |
| A-16-02 | NT | NT | NT | NT | NT |
| A-16-03 | NT | NT | NT | NT | NT |
| A-16-04 | NT | NT | NT | NT | NT |
| A-16-05 | NT | NT | NT | NT | NT |
| A-16-06 | NT | NT | NT | NT | NT |
| A-16-07 | NT | NT | NT | NT | NT |
| A-16-10 | NT | NT | NT | NT | NT |
| A-16-11 | NT | NT | NT | NT | NT |
| A-16-12 | NT | NT | NT | NT | NT |
| A-16-13 | NT | NT | NT | NT | NT |
| A-16-14 | NT | NT | NT | NT | NT |
| A-16-15 | NT | NT | NT | NT | NT |
| A-16-16 | NT | NT | NT | NT | NT |
| A-16-17 | NT | NT | NT | NT | NT |
| A-16-18 | NT | NT | NT | NT | NT |
| A-16-20 | NT | NT | NT | NT | NT |
| B-16-01 | NT | 72 | NT | 111 | NT |
| B-16-02 | NT | 132 | 84 | 257 | 120 |
| B-16-03 | NT | NT | 139 | 310 | 181 |
| B-16-04 | NT | 200 | NT | 152 | NT |
| B-16-05 | 49 | NT | 46 | 44 | 36 |
| B-16-06 | NT | 60 | NT | NT | NT |
| B-16-07 | NT | 223 | NT | NT | 173 |
| B-16-08 | 34 | 66 | 54 | 46 | NT |
| B-16-09 | 24 | 25 | 25 | 21 | 14 |
| B-16-10 | 29 | 28 | 21 | 24 | 45 |
| B-16-11 | NT | 81 | NT | 55 | NT |
| B-16-12 | 41 | NT | NT | 45 | NT |
| B-16-14 | NT | 21 | 26 | NT | NT |
| B-16-15 | 11 | 18 | 26 | NT | 42 |
| B-16-16 | 65 | 79 | 25 | 28 | 25 |
| B-16-17 | NT | 49 | 532 | 577 | 61 |
| B-16-18 | NT | NT | 150 | NT | 105 |
| B-16-19 | 61 | 71 | 79 | 93 | 75 |
| B-16-20 | 57 | 84 | 87 | 175 | 195 |
| B-16-21 | NT | 123 | 47 | 219 | 59 |
| B-16-22 | NT | NT | 59 | 48 | 83 |
| B-16-23 | 42 | NT | NT | 80 | 94 |
| B-16-24 | 81 | 109 | 128 | 93 | 102 |
| B-16-25 | 39 | 33 | 82 | 22 | NT |
| B-16-26 | NT | 631 | 38 | 76 | NT |
| B-16-27 | NT | NT | 46 | 49 | 79 |
| B-16-28 | NT | NT | 17 | 19 | 16 |
| B-16-29 | 29 | NT | NT | 25 | 20 |
| B-16-30 | 31 | 30 | 44 | 19 | NT |
| B-16-31 | 16 | 23 | NT | 23 | 20 |
| B-16-32 | 91 | NT | 103 | 126 | NT |
| B-16-33 | 16 | 15 | 18 | 12 | 13 |
| B-16-34 | 27 | 29 | 21 | NT | NT |
| B-16-35 | 79 | 63 | 85 | 83 | 86 |
| B-16-36 | 31 | 26 | NT | 16 | NT |
| B-16-37 | 87 | 81 | 33 | NT | 100 |
| B-16-38 | NT | NT | 28 | 14 | NT |
| B-16-39 | 56 | 71 | 37 | NT | NT |
| B-16-40 | 141 | 75 | 98 | 52 | 96 |
| B-16-41 | 26 | NT | 20 | 21 | 24 |
| B-16-42 | 18 | 22 | NT | NT | NT |
| B-16-43 | NT | 33 | NT | 24 | NT |
| B-16-44 | 20 | NT | 24 | 23 | 45 |
| D-16-01 | 45 | 35 | 45 | 55 | 45 |
| D-16-02 | 83 | 74 | 81 | 76 | 77 |
| D-16-03 | 90 | 49 | 48 | NT | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| D-16-04 | 38 | NT | 44 | 57 | NT |
| D-16-05 | 107 | NT | 76 | NT | NT |
| D-16-06 | 30 | NT | 65 | 45 | NT |
| D-16-07 | NT | NT | 66 | 70 | NT |
| D-16-08 | 98 | NT | 62 | 48 | NT |
| D-16-09 | 10 | NT | 51 | NT | NT |
| D-16-10 | 52 | 17 | 46 | NT | NT |
| D-16-21 | 70 | NT | NT | NT | NT |
| D-16-22 | 15 | NT | NT | NT | NT |
| D-16-23 | 25 | 3 | 18 | NT | NT |
| D-16-24 | 72 | 62 | NT | 46 | NT |
| D-16-25 | NT | 11 | NT | NT | NT |
| E-16-01 | 9 | 6 | 9 | 26 | 19 |
| E-16-02 | 118 | 81 | 151 | 80 | 75 |
| E-16-03 | 118 | 18 | 26 | 32 | NT |
| E-16-04 | 20 | 14 | 18 | 31 | 29 |
| E-16-05 | 42 | 60 | 60 | 42 | 61 |
| E-16-06 | 9 | NT | 8 | 19 | 8 |
| E-16-07 | 15 | 12 | NT | 12 | NT |
| E-16-08 | 92 | 103 | 92 | 118 | 79 |
| E-16-09 | 83 | NT | 15 | 24 | 19 |
| E-16-10 | 116 | 71 | 48 | 53 | NT |
| E-16-11 | 52 | 49 | 29 | 49 | NT |
| E-16-12 | 16 | 11 | 6 | 27 | 14 |
| E-16-13 | 14 | 12 | NT | 8 | NT |
| E-16-14 | 5 | 21 | 21 | 26 | NT |
| E-16-15 | 8 | NT | 10 | NT | 17 |
| E-16-16 | 15 | NT | 25 | 18 | NT |
| E-16-17 | 4 | 14 | 24 | 27 | 24 |
| E-16-18 | 427 | 103 | 72 | 89 | NT |
| E-16-19 | 113 | NT | 93 | 119 | NT |
| E-16-20 | 104 | 139 | 101 | 217 | NT |
| E-16-21 | 34 | 24 | 42 | 14 | NT |
| E-16-22 | 25 | 3 | 18 | NT | 11 |
| E-16-23 | 27 | NT | 28 | NT | NT |
| E-16-24 | 29 | NT | NT | 15 | NT |
| E-16-25 | 50 | 34 | 42 | NT | NT |
| E-16-26 | 122 | 52 | NT | NT | NT |
| E-16-27 | 15 | NT | NT | NT | NT |
| E-16-28 | 60 | 52 | NT | NT | NT |
| E-16-29 | 53 | 55 | NT | NT | NT |
| E-16-30 | 51 | 293 | 50 | 51 | NT |
| E-16-31 | 78 | NT | NT | NT | NT |
| E-16-32 | 137 | 105 | 22 | NT | NT |
| E-16-33 | 91 | 49 | 39 | 45 | 71 |
| E-16-34 | 141 | 118 | NT | NT | |
| G-16-01 | 32 | 31 | 27 | 25 | NT |
| G-16-02 | 63 | NT | NT | 65 | NT |
| G-16-03 | 35 | 54 | 54 | 79 | NT |
| G-16-04 | 122 | NT | 94 | NT | NT |
| G-16-05 | 27 | NT | 24 | 29 | NT |
| G-16-06 | 54 | 61 | 58 | 58 | NT |
| G-16-08 | 48 | 59 | 47 | 47 | NT |
| G-16-11 | 27 | NT | 26 | 27 | NT |
| G-16-12 | 26 | 31 | 36 | 27 | NT |
| G-16-13 | 117 | NT | 65 | 221 | NT |
| G-16-14 | NT | 43 | 5 | 20 | NT |
| G-16-15 | 56 | 76 | NT | 76 | NT |
| G-16-16 | 73 | 73 | 58 | 19 | NT |
| G-16-17 | NT | 37 | NT | 21 | NT |
| G-16-18 | NT | 37 | NT | 21 | NT |
| G-16-19 | 135 | 42 | 75 | 54 | NT |
| G-16-21 | NT | NT | 55 | NT | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| G-16-22 | NT | 51 | 54 | 36 | NT |
| G-16-23 | 42 | 78 | NT | 54 | NT |
| G-16-24 | NT | 35 | NT | NT | NT |
| G-16-26 | 57 | NT | 78 | 62 | NT |
| G-16-28 | 11 | 27 | 23 | 26 | NT |
| G-16-29 | 33 | 35 | NT | 48 | NT |
| G-16-31 | 68 | NT | 62 | 57 | NT |
| G-16-32 | 37 | NT | 104 | 147 | NT |
| G-16-33 | NT | NT | NT | NT | NT |
| G-16-34 | 56 | NT | 64 | 58 | NT |
| G-16-35 | 24 | NT | NT | NT | NT |
| G-16-36 | NT | 31 | 35 | 59 | NT |
| G-16-37 | 20 | NT | NT | NT | NT |
| G-16-38 | 27 | NT | 31 | 23 | NT |
| G-16-39 | NT | NT | 52 | 226 | NT |
| G-16-41 | 48 | NT | NT | NT | NT |
| G-16-42 | 125 | NT | NT | NT | NT |
| I-16-01 | NT | NT | NT | 19 | NT |
| I-16-02 | 76 | 64 | 77 | 72 | NT |
| I-16-03 | 66 | 51 | 47 | NT | NT |
| I-16-04 | 26 | 101 | 23 | 22 | NT |
| I-16-05 | 13 | NT | 7 | 16 | NT |
| I-16-07 | 52 | 45 | NT | NT | NT |
| I-16-08 | 97 | NT | 64 | 55 | NT |
| I-16-09 | 50 | 93 | 45 | 40 | NT |
| Y-16-02 | 54 | 41 | 32 | 30 | 26 |
| Y-16-03 | 35 | 18 | 44 | 31 | 41 |
| Y-16-04 | 101 | 69 | 43 | 70 | 58 |
| Y-16-05 | 25 | 17 | 22 | 16 | 14 |
| Y-16-07 | 61 | 50 | 67 | 83 | 62 |
| Y-16-08 | 27 | 19 | 24 | 17 | 18 |
| Y-16-09 | 22 | 8 | 23 | 20 | 41 |
| Y-16-10 | 48 | 50 | 45 | 53 | 52 |
| Y-16-11 | 18 | 15 | 17 | 13 | NT |
| Y-16-12 | 47 | 46 | 42 | 28 | 28 |
| Y-16-13 | 14 | 11 | 21 | NT | 10 |
| Y-16-14 | 28 | 29 | 16 | 16 | 27 |
| Y-16-15 | 27 | 41 | 33 | 30 | 43 |
| Y-16-16 | 34 | 15 | 19 | 19 | 12 |
| Y-16-17 | 97 | 91 | 120 | 70 | 48 |
| Y-16-18 | 25 | 22 | 25 | 23 | 22 |
| Y-16-20 | 131 | 100 | 70 | 168 | 26 |
| Y-16-22 | 22 | 18 | 18 | 14 | NT |
| Y-16-24 | 14 | NT | 22 | NT | 12 |
| Y-16-25 | 19 | NT | NT | 24 | NT |
| Y-16-26 | 9 | NT | NT | NT | 9 |
| DM-16-02 | 16 | 11 | 12 | 12 | 20 |
| DM-16-03 | 22 | 113 | 26 | 32 | 17 |

# TABLE 2: SERUM AST LEVELS IN PATIENTS ON SNBTS HP016 CLINICAL TRIAL

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| B-16- | | | | | |
| A-16-01 | 19 | 24 | 23 | 16 | NT |
| A-16-02 | 26 | 39 | 18 | NT | NT |
| A-16-03 | 24 | 24 | 28 | 23 | NT |
| A-16-04 | 27 | 27 | NT | NT | NT |
| A-16-05 | 46 | 45 | 32 | 30 | NT |
| A-16-06 | NT | 72 | 73 | 17 | NT |
| A-16-07 | 28 | 29 | 31 | 21 | NT |
| A-16-10 | 17 | NT | 26 | 24 | NT |
| A-16-12 | 28 | 34 | 34 | NT | NT |
| A-16-13 | 30 | 25 | NT | 50 | NT |
| A-16-14 | 19 | 39 | 27 | 48 | NT |
| A-16-15 | NT | 22 | NT | NT | NT |
| A-16-16 | 100 | 129 | 162 | 187 | NT |
| A-16-17 | 19 | 17 | 17 | NT | NT |
| A-16-18 | 23 | 22 | 16 | NT | NT |
| A-16-20 | 45 | 30 | 33 | NT | NT |
| B-16-01 | 73 | 52 | NT | 80 | NT |
| B-16-02 | NT | 63 | 51 | 161 | NT |
| B-16-03 | NT | NT | 84 | NT | NT |
| B-16-04 | 97 | 84 | NT | 68 | NT |
| B-16-05 | 45 | NT | 35 | 37 | 33 |
| B-16-06 | 47 | 52 | NT | NT | NT |
| B-16-07 | 54 | 129 | NT | NT | 108 |
| B-16-08 | 36 | 54 | 50 | 47 | NT |
| B-16-09 | 26 | 36 | 38 | 31 | 21 |
| B-16-10 | 58 | 43 | 27 | 27 | 44 |
| B-16-11 | 61 | 53 | NT | 38 | NT |
| B-16-12 | 31 | NT | NT | 34 | NT |
| B-16-14 | 23 | 27 | 24 | NT | NT |
| B-16-15 | 36 | 41 | 47 | 44 | 54 |
| B-16-16 | 47 | 29 | 51 | 35 | 27 |
| B-16-17 | 165 | 38 | 197 | 315 | 65 |
| B-16-18 | 98 | NT | 132 | NT | 94 |
| B-16-19 | 41 | 48 | 53 | 64 | 45 |
| B-16-20 | 40 | 53 | 57 | 87 | 106 |
| B-16-21 | 87 | 81 | 51 | 134 | 65 |
| B-16-22 | 205 | NT | 44 | 43 | 62 |
| B-16-23 | 28 | NT | NT | 51 | 51 |
| B-16-24 | 39 | 59 | 56 | 53 | 49 |
| B-16-25 | 43 | 32 | 61 | 30 | NT |
| B-16-26 | 433 | 610 | 46 | 67 | NT |
| B-16-27 | 43 | NT | 41 | 41 | 50 |
| B-16-28 | 28 | NT | 24 | 30 | 29 |
| B-16-29 | 25 | NT | NT | 31 | 34 |
| B-16-30 | 43 | 40 | 47 | 34 | NT |
| B-16-31 | 29 | 34 | NT | 40 | 37 |
| B-16-32 | 57 | NT | 71 | 81 | NT |
| B-16-33 | 29 | 30 | 33 | 38 | 36 |
| B-16-34 | 31 | 48 | 35 | NT | NT |
| B-16-35 | 50 | 49 | 57 | 59 | 55 |
| B-16-36 | 33 | 37 | NT | 28 | NT |
| B-16-37 | 65 | 67 | 45 | NT | 67 |
| B-16-38 | NT | NT | 41 | 32 | NT |
| B-16-39 | 40 | 45 | 30 | NT | NT |
| B-16-40 | 55 | 51 | 49 | 42 | 53 |
| B-16-41 | 40 | NT | 38 | 42 | 45 |
| B-16-42 | 44 | 41 | NT | NT | NT |
| B-16-43 | NT | 55 | NT | 49 | NT |
| B-16-44 | 31 | NT | 38 | 35 | 30 |
| D-16-01 | NT | NT | NT | NT | NT |
| D-16-02 | NT | NT | NT | NT | NT |
| D-16-03 | NT | NT | NT | NT | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| D-16-04 | NT | NT | NT | NT | NT |
| D-16-05 | NT | NT | NT | NT | NT |
| D-16-06 | NT | NT | NT | NT | NT |
| D-16-07 | NT | NT | NT | NT | NT |
| D-16-08 | NT | NT | NT | NT | NT |
| D-16-09 | NT | NT | NT | NT | NT |
| D-16-10 | 37 | NT | NT | NT | NT |
| D-16-21 | NT | NT | NT | NT | NT |
| D-16-22 | NT | NT | NT | NT | NT |
| D-16-23 | NT | NT | NT | NT | NT |
| D-16-24 | NT | NT | NT | NT | NT |
| D-16-25 | NT | NT | NT | NT | NT |
| E-16-01 | NT | NT | NT | NT | NT |
| E-16-02 | NT | NT | NT | NT | NT |
| E-16-03 | NT | NT | NT | NT | NT |
| E-16-04 | NT | NT | NT | NT | 73 |
| E-16-05 | NT | NT | NT | NT | NT |
| E-16-06 | NT | NT | NT | NT | NT |
| E-16-07 | NT | NT | NT | NT | NT |
| E-16-08 | NT | NT | NT | NT | NT |
| E-16-09 | NT | NT | NT | NT | NT |
| E-16-10 | NT | NT | NT | NT | NT |
| E-16-11 | NT | NT | NT | NT | NT |
| E-16-12 | NT | NT | NT | NT | NT |
| E-16-13 | NT | NT | NT | NT | NT |
| E-16-14 | NT | NT | NT | NT | NT |
| E-16-15 | NT | NT | NT | NT | NT |
| E-16-16 | NT | NT | NT | NT | NT |
| E-16-17 | NT | NT | NT | NT | NT |
| E-16-18 | NT | NT | NT | NT | NT |
| E-16-19 | NT | NT | NT | NT | NT |
| E-16-20 | NT | NT | NT | NT | NT |
| E-16-21 | NT | NT | NT | NT | NT |
| E-16-22 | NT | NT | NT | NT | NT |
| E-16-23 | NT | NT | NT | NT | NT |
| E-16-24 | NT | NT | NT | NT | NT |
| E-16-25 | NT | NT | NT | NT | NT |
| E-16-26 | NT | NT | NT | NT | NT |
| E-16-27 | NT | NT | NT | NT | NT |
| E-16-28 | NT | NT | NT | NT | NT |
| E-16-29 | NT | NT | NT | NT | NT |
| E-16-30 | NT | NT | NT | NT | NT |
| E-16-31 | NT | NT | NT | NT | NT |
| E-16-32 | NT | NT | NT | NT | NT |
| E-16-33 | NT | NT | NT | NT | NT |
| E-16-34 | NT | NT | NT | NT | NT |
| G-16-01 | 68 | 68 | 113 | 99 | NT |
| G-16-02 | 30 | NT | NT | NT | 28 |
| G-16-03 | 29 | 31 | 31 | 73 | NT |
| G-16-04 | 54 | NT | 42 | NT | NT |
| G-16-05 | 25 | NT | 22 | 22 | NT |
| G-16-06 | 47 | 77 | 66 | 60 | NT |
| G-16-08 | 32 | 27 | 26 | 27 | NT |
| G-16-11 | 23 | NT | 23 | 23 | NT |
| G-16-12 | 19 | 19 | 27 | 20 | NT |
| G-16-13 | 64 | NT | 63 | 117 | NT |
| G-16-14 | NT | 27 | 13 | 19 | NT |
| G-16-15 | 29 | 43 | NT | 42 | NT |
| G-16-16 | 57 | 57 | 34 | 15 | NT |
| G-16-17 | NT | 38 | NT | 23 | NT |
| G-16-18 | NT | NT | 26 | 25 | NT |
| G-16-19 | 58 | 32 | 31 | 32 | 41 |
| G-16-21 | NT | NT | 41 | NT | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| G-16-22 | NT | 88 | 84 | 75 | NT |
| G-16-23 | 29 | 47 | NT | 32 | NT |
| G-16-24 | NT | 20 | NT | NT | NT |
| G-16-26 | 42 | NT | 50 | 41 | NT |
| G-16-28 | 185 | 27 | 23 | 29 | NT |
| G-16-29 | 23 | 20 | NT | 30 | NT |
| G-16-31 | 88 | NT | 86 | 94 | NT |
| G-16-32 | 37 | NT | 69 | 108 | NT |
| G-16-33 | NT | NT | NT | NT | NT |
| G-16-34 | 33 | NT | 41 | 35 | NT |
| G-16-35 | 23 | NT | NT | NT | NT |
| G-16-36 | NT | 26 | NT | 21 | NT |
| G-16-37 | 17 | NT | NT | NT | NT |
| G-16-38 | 21 | NT | 23 | 23 | NT |
| G-16-39 | NT | NT | 33 | 100 | NT |
| G-16-41 | 30 | NT | NT | NT | NT |
| G-16-42 | 78 | NT | NT | NT | NT |
| I-16-01 | NT | NT | NT | NT | NT |
| I-16-02 | NT | NT | NT | NT | NT |
| I-16-03 | NT | NT | NT | NT | NT |
| I-16-04 | NT | NT | NT | NT | NT |
| I-16-05 | NT | NT | NT | NT | NT |
| I-16-06 | NT | NT | NT | NT | NT |
| I-16-07 | NT | NT | NT | NT | NT |
| I-16-08 | NT | NT | NT | NT | NT |
| I-16-09 | NT | NT | NT | NT | NT |
| Y-16-02 | 60 | 52 | 32 | 44 | 38 |
| Y-16-03 | 34 | 42 | 46 | 39 | 93 |
| Y-16-04 | 24 | 57 | 40 | 61 | 57 |
| Y-16-05 | 44 | 42 | 32 | 35 | 40 |
| Y-16-07 | 46 | 51 | 47 | 61 | 54 |
| Y-16-08 | 30 | 39 | 44 | 33 | 52 |
| Y-16-09 | 38 | 57 | 42 | 40 | 11 |
| Y-16-10 | 48 | 42 | 41 | 56 | 54 |
| Y-16-11 | 33 | 36 | 31 | 40 | NT |
| Y-16-12 | 54 | 56 | 34 | 48 | 111 |
| Y-16-13 | 24 | 29 | 42 | NT | 45 |
| Y-16-14 | 32 | 33 | 28 | 28 | 47 |
| Y-16-15 | 33 | 36 | 41 | 48 | 68 |
| Y-16-16 | 43 | 45 | 34 | 34 | 43 |
| Y-16-17 | 65 | 76 | 45 | 71 | 57 |
| Y-16-18 | 29 | 33 | 31 | 52 | 40 |
| Y-16-20 | 96 | 71 | 90 | 121 | 51 |
| Y-16-22 | 41 | 30 | 44 | 53 | NT |
| Y-16-24 | 34 | NT | 31 | 33 | 33 |
| Y-16-25 | 49 | NT | NT | 30 | NT |
| Y-16-26 | 28 | NT | NT | NT | 18 |
| DM-16-02 | 14 | 18 | 18 | 18 | 14 |
| DM-16-03 | 21 | 68 | 38 | 36 | 17 |

# TABLE 3: SERUM GGT LEVELS IN PATIENTS ON SNBTS HP016 CLINICAL TRIAL

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| A-16-01 | 12 | 15 | 16 | 12 | NT |
| A-16-02 | 16 | 11 | 5 | NT | NT |
| A-16-03 | 7 | 7 | 3 | 6 | NT |
| A-16-04 | 14 | 14 | NT | NT | NT |
| A-16-05 | 125 | 116 | 101 | 103 | NT |
| A-16-06 | NT | 40 | 47 | 9 | NT |
| A-16-07 | 15 | 8 | 14 | 11 | NT |
| A-16-10 | 23 | NT | 19 | 20 | NT |
| A-16-12 | 16 | 20 | NT | NT | NT |
| A-16-13 | 20 | 15 | 16 | 53 | NT |
| A-16-14 | 59 | 90 | 64 | 80 | NT |
| A-16-15 | NT | 17 | NT | NT | NT |
| A-16-16 | 73 | 48 | 31 | 80 | NT |
| A-16-17 | 9 | 13 | 13 | NT | NT |
| A-16-18 | 6 | 9 | 11 | NT | NT |
| A-16-20 | 10 | 9 | 7 | NT | NT |
| B-16-01 | NT | 336 | 527 | NT | NT |
| B-16-02 | NT | 292 | 110 | 660 • | 297 |
| B-16-03 | NT | NT | 181 | 272 | 228 |
| B-16-04 | NT | 48 | NT | 39 | NT |
| B-16-05 | 30 | NT | 38 | 33 | 34 |
| B-16-06 | NT | 96 | NT | NT | NT |
| B-16-07 | NT | 66 | NT | NT | 90 |
| B-16-08 | 129 | 207 | 200 | 215 | NT |
| B-16-09 | NT | 19 | 21 | 20 | 21 |
| B-16-10 | 24 | 19 | 23 | 19 | 41 |
| B-16-11 | NT | 39 | NT | 37 | NT |
| B-16-12 | NT | NT | NT | 40 | NT |
| B-16-14 | NT | 25 | 28 | NT | NT |
| B-16-15 | 14 | 20 | 18 | 16 | 18 |
| B-16-16 | 23 | 25 | 22 | 20 | 20 |
| B-16-17 | NT | 61 | 192 | 240 | 58 |
| B-16-18 | NT | NT | 43 | NT | 32 |
| B-16-19 | 114 | NT | 135 | 144 | 163 |
| B-16-20 | NT | 36 | 37 | 63 | 48 |
| B-16-21 | NT | 599 | 307 | 985 | 397 |
| B-16-22 | NT | NT | 54 | 37 | 69 |
| B-16-23 | 14 | NT | NT | 19 | 25 |
| B-16-24 | NT | 78 | 66 | 62 | 64 |
| B-16-25 | 66 | 59 | 71 | 77 | NT |
| B-16-26 | NT | 201 | 47 | 43 | NT |
| B-16-27 | NT | NT | 27 | 52 | 32 |
| B-16-28 | NT | NT | 20 | 15 | 17 |
| B-16-29 | 22 | NT | NT | 17 | 20 |
| B-16-30 | 22 | 20 | 32 | 20 - | NT |
| B-16-31 | 16 | 15 | NT | 11 | 21 |
| B-16-32 | 22 | NT | 22 | 18 | NT |
| B-16-33 | 15 | 15 | 15 | 17 | 14 |
| B-16-34 | 15 | 13 | 19 | NT | NT |
| B-16-35 | 28 | 25 | 33 | 29 | 31 |
| B-16-36 | 17 | 17 | NT | 29 | 31 |
| B-16-37 | 20 | 19 | 18 | NT | 21 |
| B-16-38 | NT | NT | 17 | 12 | NT |
| B-16-39 | 51 | 47 | 52 | NT | NT |
| B-16-40 | 25 | 32 | 33 | 22 | NT |
| B-16-41 | 19 | NT | 23 | 18 | 21 |
| B-16-42 | 11 | 11 | NT | 17 | NT |
| B-16-43 | NT | 16 | NT | 17 | NT |
| B-16-44 | 17 | NT | 14 | 13 | 13 |
| D-16-01 | 192 | NT | 121 | 138 | 129 |
| D-16-02 | 260 | 332 | 217 | 332 | 394 |
| D-16-03 | 34 | 75 | 33 | NT | NT |
| D-16-04 | 25 | NT | 23 | 36 | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| D-16-05 | 66 | NT | 83 | NT | NT |
| D-16-06 | 22 | NT | 23 | NT | NT |
| D-16-07 | NT | NT | 7 | NT | NT |
| D-16-08 | 19 | NT | 22 | NT | NT |
| D-16-09 | NT | NT | 15 | NT | NT |
| D-16-10 | 130 | NT | 134 | NT | NT |
| D-16-21 | 10 | NT | NT | NT | NT |
| D-16-22 | NT | NT | NT | NT | NT |
| D-16-23 | 8 | NT | 7 | NT | NT |
| D-16-24 | 20 | 19 | NT | 20 | NT |
| D-16-25 | NT | 5 | NT | NT | NT |
| E-16-01 | NT | NT | NT | 14 | 11 |
| E-16-02 | 14 | 10 | 19 | 17 | 15 |
| E-16-03 | 15 | NT | NT | NT | NT |
| E-16-04 | 10 | 7 | 12 | 12 | 10 |
| E-16-05 | 66 | 72 | 68 | 54 | 66 |
| E-16-06 | 13 | NT | 10 | 11 | NT |
| E-16-07 | NT | 8 | NT | 13 | NT |
| E-16-08 | 27 | 22 | 27 | 23 | 16 |
| E-16-09 | 12 | NT | 21 | 15 | 13 |
| E-16-10 | 46 | 42 | 51 | 31 | NT |
| E-16-11 | 28 | 29 | 44 | 33 | NT |
| E-16-12 | 5 | 16 | 14 | 15 | 14 |
| E-16-13 | NT | 13 | NT | 11 | NT |
| E-16-14 | 11 | 9 | 9 | 8 | NT |
| E-16-15 | 7 | NT | 12 | NT | 10 |
| E-16-16 | 11 | NT | 29 | 10 | NT |
| E-16-17 | NT | 12 | 12 | NT | 12 |
| E-16-18 | 158 | 89 | 82 | 76 | NT |
| E-16-19 | 10 | NT | 13 | 11 | NT |
| E-16-20 | 105 | 107 | 80 | 196 | NT |
| E-16-21 | 49 | 38 | 52 | 42 | NT |
| E-16-22 | 8 | NT | 7 | NT | 8 |
| E-16-23 | NT | NT | NT | NT | NT |
| E-16-24 | 17 | NT | NT | 24 | NT |
| E-16-25 | 297 | 340 | 332 | NT | NT |
| E-16-26 | 113 | 52 | NT | NT | NT |
| E-16-27 | 12 | NT | NT | NT | NT |
| E-16-28 | 44 | 42 | 27 | NT | NT |
| E-16-29 | 20 | 21 | NT | NT | NT |
| E-16-30 | 86 | 374 | 64 | 74 | NT |
| E-16-31 | 20 | NT | NT | NT | NT |
| E-16-32 | 45 | 53 | 31 | NT | NT |
| E-16-33 | 47 | 38 | 61 | 254 | 222 |
| E-16-34 | 26 | 25 | NT | NT | NT |
| G-16-01 | 146 | 170 | 105 | NT | NT |
| G-16-02 | 26 | NT | NT | 21 | NT |
| G-16-03 | 20 | 28 | 28 | 44 | NT |
| G-16-04 | 64 | NT | 47 | NT | NT |
| G-16-05 | 27 | NT | 30 | 22 | NT |
| G-16-06 | 510 | 38 | 520 | 355 | NT |
| G-16-08 | NT | 27 | 28 | 35 | NT |
| G-16-11 | 56 | NT | 57 | 56 | NT |
| G-16-12 | 37 | 35 | 56 | 49 | NT |
| G-16-13 | 16 | NT | 39 | 38 | NT |
| G-16-14 | NT | 27 | 28 | 23 | NT |
| G-16-15 | 61 | 76 | NT | 100 | NT |
| G-16-16 | 95 | 95 | 76 | 30 | NT |
| G-16-17 | NT | NT | NT | NT | NT |
| G-16-18 | NT | NT | 37 | 33 | NT |
| G-16-19 | 81 | 28 | 42 | 42 | NT |
| G-16-21 | NT | NT | 35 | NT | NT |
| G-16-22 | NT | 64 | 78 | 56 | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| G-16-23 | 51 | 130 | NT | 56 | NT |
| G-16-24 | NT | 135 | NT | NT | NT |
| G-16-26 | 47 | NT | 42 | 69 | NT |
| G-16-28 | 16 | 15 | 15 | 17 | NT |
| G-16-29 | 66 | 135 | NT | 135 | NT |
| G-16-31 | 140 | NT | 140 | 125 | NT |
| G-16-32 | 51 | NT | 115 | 165 | NT |
| G-16-33 | NT | NT | NT | NT | NT |
| G-16-34 | 61 | NT | 53 | 61 | NT |
| G-16-35 | 18 | NT | NT | NT | NT |
| G-16-36 | NT | 30 | NT | 21 | NT |
| G-16-37 | 12 | NT | NT | NT | NT |
| G-16-38 | 7 | NT | 10 | 10 | NT |
| G-16-39 | NT | NT | 32 | 88 | NT |
| G-16-41 | 18 | NT | NT | NT | NT |
| G-16-42 | 36 | NT | NT | NT | NT |
| I-16-01 | NT | NT | NT | 8 | NT |
| I-16-02 | 23 | 17 | 14 | 15 | NT |
| I-16-03 | 66 | 74 | 87 | NT | NT |
| I-16-04 | 22 | 25 | 21 | 26 | NT |
| I-16-05 | 7 | NT | 5 | 7 | NT |
| I-16-07 | 143 | 124 | NT | NT | NT |
| I-16-08 | 29 | NT | 33 | 22 | NT |
| I-16-09 | 50 | 21 | 27 | 21 | NT |
| Y-16-02 | NT | NT | 40 | NT | NT |
| Y-16-03 | NT | NT | NT | 22 | 32 |
| Y-16-04 | NT | NT | 22 | 22 | 28 |
| Y-16-05 | NT | NT | 16 | 17 | 14 |
| Y-16-07 | 20 | NT | 19 | 21 | 18 |
| Y-16-08 | NT | NT | NT | 15 | 24 |
| Y-16-09 | NT | NT | NT | 22 | 16 |
| Y-16-10 | NT | NT | NT | 17 | NT |
| Y-16-11 | NT | 18 | NT | NT | NT |
| Y-16-12 | NT | NT | NT | 19 | 28 |
| Y-16-13 | NT | NT | NT | NT | NT |
| Y-16-14 | NT | 19 | 18 | 18 | NT |
| Y-16-15 | NT | NT | 19 | NT | NT |
| Y-16-16 | NT | NT | 18 | 17 | NT |
| Y-16-17 | NT | 18 | 18 | 17 | 21 |
| Y-16-18 | NT | NT | NT | 16 | 15 |
| Y-16-20 | NT | 20 | 19 | NT | 15 |
| Y-16-22 | 16 | 14 | 14 | 16 | NT |
| Y-16-24 | 24 | NT | 20 | NT | 20 |
| Y-16-25 | NT | NT | NT | NT | NT |
| Y-16-26 | NT | NT | NT | NT | 14 |
| DM-16-02 | 18 | NT | NT | NT | NT |
| DM-16-03 | NT | NT | NT | 167 | NT |

# TABLE 4: SERUM ALKALINE PHOSPHATASE LEVELS IN PATIENTS ON SNBTS HP016 CLINICAL TRIAL

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTH |
|---|---|---|---|---|---|
| A-16-01 | 214 | 197 | 209 | 243 | NT |
| A-16-02 | 171 | 116 | 259 | 289 | NT |
| A-16-03 | 202 | 206 | 252 | 261 | NT |
| A-16-04 | 210 | 204 | NT | NT | NT |
| A-16-05 | 272 | 279 | 425 | 379 | NT |
| A-16-06 | NT | 315 | 293 | 227 | NT |
| A-16-07 | 149 | 181 | 162 | 173 | NT |
| A-16-10 | 270 | NT | 179 | 174 | NT |
| A-16-12 | 117 | 91 | 91 | NT | NT |
| A-16-13 | 38 | 49 | 33 | 50 | NT |
| A-16-14 | 87 | 142 | 103 | 109 | NT |
| A-16-15 | NT | NT | 106 | NT | NT |
| A-16-16 | 75 | 85 | 66 | 77 | NT |
| A-16-17 | 110 | 722 | 72 | NT | NT |
| A-16-18 | 27 | 21 | 31 | NT | NT |
| A-16-20 | 296 | 219 | 211 | NT | NT |
| B-16-01 | 121 | 106 | NT | 122 | NT |
| B-16-02 | NT | 146 | 117 | 155 | 128 |
| B-16-03 | NT | NT | 87 | 94 | 78 |
| B-16-04 | 71 | 77 | NT | 67 | NT |
| B-16-05 | 102 | NT | 74 | 86 | 82 |
| B-16-06 | 94 | 90 | NT | NT | NT |
| B-16-07 | 74 | 77 | NT | 78 | 68 |
| B-16-08 | 119 | 106 | 123 | 114 | NT |
| B-16-09 | 117 | 111 | 116 | 120 | 117 |
| B-16-10 | 57 | 80 | 82 | 86 | 70 |
| B-16-11 | 73 | 64 | NT | 69 | NT |
| B-16-12 | 97 | NT | NT | 105 | NT |
| B-16-14 | 84 | 75 | 82 | NT | NT |
| B-16-15 | 305 | 198 | 211 | 223 | 259 |
| B-16-16 | 98 | 88 | 40 | 91 | 109 |
| B-16-17 | 90 | 69 | 81 | 92 | 76 |
| B-16-18 | 54 | NT | 63 | NT | 53 |
| B-16-19 | 82 | 68 | 72 | 83 | 79 |
| B-16-20 | 133 | 127 | 129 | 102 | 85 |
| B-16-21 | 117 | 116 | 99 | 172 | 99 |
| B-16-22 | 103 | NT | 81 | 79 | NT |
| B-16-23 | 55 | NT | NT | 59 | 76 |
| B-16-24 | 89 | NT | 86 | 76 | 77 |
| B-16-25 | 108 | 103 | 117 | 160 | NT |
| B-16-26 | 138 | 138 | 115 | 95 | NT |
| B-16-27 | 347 | NT | 290 | 332 | 273 |
| B-16-28 | 326 | NT | 303 | 351 | 292 |
| B-16-29 | 190 | NT | NT | 221 | 262 |
| B-16-30 | 295 | 253 | 307 | 341 | NT |
| B-16-31 | 157 | 147 | NT | 169 | 185 |
| B-16-32 | 443 | NT | 340 | 388 | NT |
| B-16-33 | 166 | 150 | 171 | 178 | 189 |
| B-16-34 | 217 | 202 | 266 | NT | NT |
| B-16-36 | 190 | 171 | NT | 159 | NT |
| B-16-37 | 253 | 292 | 316 | NT | 362 |
| B-16-38 | NT | NT | 167 | 178 | NT |
| B-16-39 | 55 | 55 | 54 | NT | NT |
| B-16-40 | 182 | 132 | 126 | 104 | 113 |
| B-16-41 | 223 | NT | 178 | 239 | 283 |
| B-16-42 | 197 | 161 | NT | NT | NT |
| B-16-43 | NT | 161 | NT | 157 | NT |
| B-16-44 | 175 | NT | 184 | 205 | 195 |
| D-16-01 | 160 | 160 | 192 | 149 | 192 |
| D-16-02 | 215 | 222 | 233 | 224 | 217 |
| D-16-03 | 88 | 112 | 95 | NT | NT |
| D-16-04 | 122 | NT | 136 | 98 | NT |
| D-16-05 | 41 | NT | 53 | NT | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| D-16-06 | 67 | NT | 68 | 63 | NT |
| D-16-07 | NT | NT | 101 | 61 | NT |
| D-16-08 | 96 | NT | 76 | 65 | NT |
| D-16-09 | 68 | NT | 68 | NT | NT |
| D-16-10 | 160 | 59 | 84 | NT | NT |
| D-16-21 | 253 | NT | NT | NT | NT |
| D-16-22 | 167 | NT | NT | NT | NT |
| D-16-23 | 349 | 538 | 108 | NT | NT |
| D-16-24 | 176 | 171 | NT | 195 | NT |
| D-16-25 | 203 | 377 | NT | NT | NT |
| E-16-01 | NT | NT | 459 | 166 | 151 |
| E-16-02 | 84 | 85 | 87 | 80 | 69 |
| E-16-03 | NT | NT | NT | 725 | NT |
| E-16-04 | 345 | 295 | 195 | 153 | 126 |
| E-16-05 | 79 | 62 | 85 | 73 | 60 |
| E-16-06 | 505 | NT | 143 | 150 | 132 |
| E-16-07 | 342 | 182 | NT | 170 | NT |
| E-16-08 | 102 | 93 | 102 | 71 | 71 |
| E-16-09 | 104 | NT | 103 | 87 | 90 |
| E-16-10 | 48 | 58 | 71 | 66 | NT |
| E-16-11 | 107 | 162 | 287 | 164 | NT |
| E-16-12 | 397 | 215 | 230 | 249 | 222 |
| E-16-13 | 421 | 167 | NT | 157 | NT |
| E-16-14 | 493 | 183 | 174 | 153 | NT |
| E-16-15 | 503 | NT | 210 | NT | 196 |
| E-16-16 | 344 | NT | 169 | 333 | NT |
| E-16-17 | 449 | 166 | 167 | 342 | 156 |
| E-16-18 | 221 | 172 | 138 | 132 | NT |
| E-16-19 | 75 | NT | 73 | 65 | NT |
| E-16-20 | 117 | 113 | 133 | 110 | NT |
| E-16-21 | 119 | 120 | 111 | 358 | NT |
| E-16-22 | 349 | 538 | 108 | NT | 100 |
| E-16-23 | 452 | NT | 660 | NT | NT |
| E-16-24 | 101 | NT | NT | 82 | NT |
| E-16-25 | 117 | 157 | 140 | NT | NT |
| E-16-26 | 92 | 78 | NT | NT | NT |
| E-16-27 | 39 | NT | NT | NT | NT |
| E-16-28 | 64 | 76 | 69 | NT | NT |
| E-16-29 | 60 | 59 | NT | NT | NT |
| E-16-30 | 80 | 106 | 73 | 65 | NT |
| E-16-31 | 59 | NT | NT | NT | NT |
| E-16-32 | 57 | 62 | 61 | NT | NT |
| E-16-33 | 113 | 109 | 107 | 124 | 114 |
| E-16-34 | 63 | 57 | NT | NT | NT |
| G-16-01 | 590 | 700 | 470 | 510 | NT |
| G-16-02 | 215 | NT | NT | 170 | NT |
| G-16-03 | 200 | 150 | 130 | 200 | NT |
| G-16-04 | 185 | NT | 160 | NT | NT |
| G-16-05 | 275 | NT | 175 | 215 | NT |
| G-16-06 | 420 | 480 | 475 | 510 | NT |
| G-16-08 | 130 | 130 | 140 | 125 | NT |
| G-16-11 | 185 | NT | 175 | 185 | NT |
| G-16-12 | 235 | 275 | 250 | 345 | NT |
| G-16-13 | 180 | NT | 165 | 190 | NT |
| G-16-14 | NT | 155 | 155 | 175 | NT |
| G-16-15 | 240 | 195 | NT | 230 | NT |
| G-16-16 | 135 | 135 | 85 | 100 | NT |
| G-16-17 | NT | 175 | 155 | 190 | 200 |
| G-16-18 | NT | NT | 190 | 200 | NT |
| G-16-19 | 215 | 200 | 200 | 215 | NT |
| G-16-21 | NT | NT | 225 | NT | NT |
| G-16-22 | NT | 560 | 690 | 420 | NT |
| G-16-23 | 240 | 295 | NT | 240 | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| G-16-24 | NT | 255 | NT | NT | NT |
| G-16-26 | 295 | NT | 275 | 295 | NT |
| G-16-28 | 235 | 255 | 175 | 205 | NT |
| G-16-29 | 260 | 255 | NT | 250 | NT |
| G-16-31 | 285 | NT | 290 | 305 | NT |
| G-16-32 | 165 | NT | 180 | 230 | NT |
| G-16-33 | NT | NT | NT | NT | NT |
| G-16-34 | 195 | NT | 190 | 185 | NT |
| G-16-35 | 195 | NT | NT | NT | NT |
| G-16-36 | NT | 215 | 235 | NT | NT |
| G-16-37 | 265 | NT | NT | NT | NT |
| G-16-38 | 120 | NT | 130 | 125 | NT |
| G-16-39 | NT | NT | 210 | 290 | NT |
| G-16-41 | 145 | NT | NT | NT | NT |
| G-16-42 | 180 | NT | NT | NT | NT |
| I-16-01 | NT | NT | NT | 142 | NT |
| I-16-02 | 185 | 140 | 130 | 120 | NT |
| I-16-03 | 116 | 87 | 79 | NT | NT |
| I-16-04 | 105 | 101 | 100 | 97 | NT |
| I-16-05 | 294 | NT | 286 | 344 | NT |
| I-16-07 | 89 | 88 | NT | NT | NT |
| I-16-09 | 120 | 93 | 103 | 95 | NT |
| Y-16-02 | 164 | 135 | 181 | 142 | 187 |
| Y-16-03 | 142 | 211 | 202 | 193 | 204 |
| Y-16-04 | 179 | 171 | 149 | 171 | 174 |
| Y-16-05 | 113 | 113 | 124 | 115 | 113 |
| Y-16-07 | 167 | 192 | 191 | 194 | 224 |
| Y-16-08 | 151 | 148 | 148 | 164 | 177 |
| Y-16-09 | 165 | 149 | 161 | 156 | 172 |
| Y-16-10 | 169 | 152 | 162 | 151 | 133 |
| Y-16-11 | 212 | 225 | 211 | 203 | NT |
| Y-16-12 | 188 | 199 | 185 | 206 | 188 |
| Y-16-13 | 138 | 148 | 169 | NT | 155 |
| Y-16-14 | 241 | 221 | 219 | 219 | 307 |
| Y-16-15 | 174 | 209 | NT | 208 | 236 |
| Y-16-16 | 169 | 176 | 190 | 153 | 174 |
| Y-16-17 | 210 | 208 | 208 | 290 | 195 |
| Y-16-18 | 195 | 218 | 200 | 210 | 193 |
| Y-16-20 | 246 | 215 | 216 | 242 | 169 |
| Y-16-22 | 200 | 188 | 206 | 163 | NT |
| Y-16-24 | 186 | NT | 173 | NT | 272 |
| Y-16-25 | 205 | NT | NT | 215 | NT |
| Y-16-26 | 163 | NT | NT | NT | 157 |
| DM-16-02 | 186 | 204 | 171 | 173 | 186 |
| DM-16-03 | 300 | 318 | 247 | 242 | 251 |

# TABLE 5: SERUM BILIRUBIN LEVELS IN PATIENTS ON SNBTS HP016 CLINICAL TRIAL

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| A-16-01 | 6 | 5 | 5 | 7 | NT |
| A-16-02 | 10 | 6 | 5 | NT | NT |
| A-16-03 | 5 | 7 | 5 | 4 | NT |
| A-16-04 | 8 | 7 | NT | NT | NT |
| A-16-05 | 15 | 9 | 9 | 4 | NT |
| A-16-06 | NT | 9 | 10 | 13 | NT |
| A-16-07 | 9 | 5 | 9 | 9 | NT |
| A-16-10 | 8 | NT | 8 | 11 | NT |
| A-16-12 | 12 | 12 | 12 | NT | NT |
| A-16-13 | 22 | 17 | 20 | 21 | NT |
| A-16-14 | 8 | 7 | 6 | 8 | NT |
| A-16-15 | NT | NT | 19 | NT | NT |
| A-16-16 | 24 | 18 | 12 | 13 | NT |
| A-16-17 | 9 | 8 | 8 | NT | NT |
| A-16-18 | 8 | 7 | 6 | NT | NT |
| A-16-20 | 4 | 2 | 1 | NT | NT |
| B-16-01 | 10 | 11 | NT | 25 | NT |
| B-16-02 | NT | 7 | 18 | 23 | 21 |
| B-16-03 | NT | NT | 8 | 16 | 13 |
| B-16-04 | 14 | 11 | NT | 15 | NT |
| B-16-05 | 7 | NT | 11 | 10 | 8 |
| B-16-06 | 13 | 9 | NT | NT | NT |
| B-16-07 | 12 | 10 | NT | NT | 20 |
| B-16-08 | 24 | 22 | 27 | 29 | NT |
| B-16-09 | 11 | 12 | 11 | 17 | 12 |
| B-16-10 | 16 | 14 | 12 | 16 | 11 |
| B-16-11 | 7 | 9 | NT | 10 | NT |
| B-16-12 | 9 | NT | 13 | NT | NT |
| B-16-14 | 7 | 9 | 8 | NT | NT |
| B-16-15 | NT | NT | 7 | 7 | 4 |
| B-16-16 | 7 | 3 | 7 | 9 | 11 |
| B-16-17 | 14 | 5 | 7 | 17 | 12 |
| B-16-18 | 9 | NT | NT | 12 | NT |
| B-16-19 | 11 | 13 | 12 | 14 | 19 |
| B-16-20 | 25 | 32 | 39 | 52 | 56 |
| B-16-21 | 10 | 10 | 9 | 14 | 8 |
| B-16-22 | 8 | NT | 7 | 15 | 9 |
| B-16-23 | 22 | NT | NT | 14 | 11 |
| B-16-24 | 13 | 23 | 23 | 23 | 22 |
| B-16-25 | 16 | 26 | 28 | 22 | NT |
| B-16-26 | 15 | 21 | 8 | 14 | NT |
| B-16-27 | 4 | NT | 3 | 3 | 9 |
| B-16-28 | 5 | NT | 8 | 5 | 12 |
| B-16-29 | 7 | 6 | 5 | 5 | 1 |
| B-16-30 | 31 | 25 | 33 | 13 | NT |
| B-16-31 | 5 | 7 | NT | 4 | 4 |
| B-16-32 | 8 | NT | 9 | 7 | NT |
| B-16-33 | 8 | 4 | 6 | 2 | 6 |
| B-16-34 | 12 | 15 | 12 | NT | NT |
| B-16-35 | 10 | 1 | 1 | 14 | 18 |
| B-16-36 | 4 | 4 | NT | 2 | NT |
| B-16-37 | 5 | 9 | 6 | NT | 8 |
| B-16-38 | NT | NT | 7 | 4 | NT |
| B-16-39 | 13 | 16 | 14 | NT | NT |
| B-16-40 | 8 | 7 | 11 | 14 | 10 |
| B-16-41 | 6 | NT | 3 | 4 | 7 |
| B-16-42 | 2 | 11 | NT | NT | NT |
| B-16-43 | 4 | | | | |
| B-16-44 | 7 | NT | 9 | 12 | 18 |
| D-16-01 | 6 | 6 | 9 | 9 | 9 |
| D-16-02 | 23 | 36 | 33 | 51 | 32 |
| D-16-03 | 46 | 25 | 56 | NT | NT |
| D-16-04 | 6 | NT | 7 | 6 | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| D-16-05 | 11 | NT | 10 | NT | NT |
| D-16-06 | 9 | NT | 14 | 12 | NT |
| D-16-07 | NT | NT | 6 | 5 | NT |
| D-16-08 | 16 | NT | 21 | 24 | NT |
| D-16-09 | 10 | NT | 10 | NT | NT |
| D-16-10 | 8 | 6 | 8 | NT | NT |
| D-16-21 | 5 | NT | NT | NT | NT |
| D-16-22 | 5 | NT | NT | NT | NT |
| D-16-23 | 5 | 10 | 6 | NT | NT |
| D-16-24 | NT | 7 | NT | 5 | NT |
| D-16-25 | 6 | 5 | NT | NT | NT |
| E-16-01 | 14 | 7 | 2 | 1 | 2 |
| E-16-02 | 9 | 6 | 16 | 7 | 3 |
| E-16-03 | 4 | NT | NT | 4 | NT |
| E-16-04 | 4 | 5 | 1 | 2 | 1 |
| E-16-05 | 7 | NT | 11 | 7 | 4 |
| E-16-06 | 16 | NT | 7 | 3 | 1 |
| E-16-07 | NT | 4 | NT | 4 | NT |
| E-16-08 | 21 | 22 | 21 | 15 | 28 |
| E-16-09 | 7 | NT | 4 | 8 | 1 |
| E-16-10 | 13 | 7 | 12 | 8 | NT |
| E-16-11 | 19 | 13 | 10 | 5 | NT |
| E-16-12 | 15 | 1 | 2 | 4 | 5 |
| E-16-13 | 11 | 1 | NT | 1 | NT |
| E-16-14 | 10 | 3 | 3 | 2 | NT |
| E-16-15 | 9 | NT | 2 | NT | 2 |
| E-16-16 | 5 | NT | 5 | 8 | NT |
| E-16-17 | 5 | 3 | 1 | 7 | 1 |
| E-16-18 | 9 | 7 | 3 | 5 | NT |
| E-16-19 | 8 | NT | 9 | 15 | NT |
| E-16-20 | 7 | 9 | 9 | 6 | NT |
| E-16-21 | 7 | 8 | 5 | 7 | NT |
| E-16-22 | 5 | 10 | 6 | NT | 1 |
| E-16-23 | 3 | NT | NT | NT | NT |
| E-16-24 | 14 | NT | NT | 7 | NT |
| E-16-25 | 5 | 3 | 3 | NT | NT |
| E-16-26 | 7 | 10 | NT | NT | NT |
| E-16-27 | 9 | NT | NT | NT | NT |
| E-16-28 | 11 | 11 | 8 | NT | NT |
| E-16-29 | 4 | 9 | NT | NT | NT |
| E-16-30 | 3 | 11 | 4 | 5 | NT |
| E-16-31 | 11 | NT | NT | NT | NT |
| E-16-32 | 18 | 10 | 15 | NT | NT |
| E-16-33 | 11 | 8 | 2 | 9 | 8 |
| E-16-34 | 14 | 13 | NT | NT | NT |
| G-16-01 | 15 | 13 | 18 | 29 | NT |
| G-16-03 | 6 | 6 | 6 | 10 | NT |
| G-16-04 | 9 | NT | 10 | NT | NT |
| G-16-05 | 11 | NT | 13 | 13 | NT |
| G-16-06 | 9 | 14 | 12 | 10 | NT |
| G-16-08 | 7 | 4 | 10 | 8 | NT |
| G-16-11 | 14 | NT | 12 | 14 | NT |
| G-16-12 | 5 | 4 | 6 | 6 | NT |
| G-16-13 | 10 | NT | 12 | 10 | NT |
| G-16-14 | NT | 17 | 10 | 12 | NT |
| G-16-15 | 9 | 12 | NT | 14 | NT |
| G-16-16 | 8 | 8 | 9 | 7 | NT |
| G-16-17 | NT | 9 | NT | 6 | NT |
| G-16-18 | NT | NT | 11 | 12 | NT |
| G-16-19 | 18 | 17 | 14 | 12 | NT |
| G-16-21 | NT | NT | 16 | NT | NT |
| G-16-22 | NT | 27 | 22 | 14 | NT |
| G-16-23 | 8 | 8 | NT | 14 | NT |



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| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| G-16-24 | NT | 11 | NT | NT | NT |
| G-16-26 | 4 | NT | 9 | 12 | NT |
| G-16-28 | 11 | 11 | 7 | 12 | NT |
| G-16-29 | 10 | 11 | NT | 12 | NT |
| G-16-31 | 35 | NT | 33 | 39 | NT |
| G-16-32 | 38 | NT | 19 | 22 | NT |
| G-16-33 | NT | NT | NT | NT | NT |
| G-16-34 | 14 | | 15 | 10 | NT |
| G-16-35 | 5 | NT | NT | NT | NT |
| G-16-36 | NT | 13 | NT | 13 | 10 |
| G-16-37 | 25 | NT | NT | NT | NT |
| G-16-38 | 12 | NT | 13 | 10 | NT |
| G-16-39 | NT | NT | 8 | 9 | NT |
| G-16-41 | 18 | NT | NT | NT | NT |
| G-16-42 | 13 | NT | NT | NT | NT |
| I-16-01 | NT | NT | NT | 5 | NT |
| I-16-02 | 5 | 9 | 8 | 8 | NT |
| I-16-03 | 9 | 10 | 7 | NT | NT |
| I-16-04 | 5 | 14 | 7 | 13 | NT |
| I-16-05 | 5 | NT | 9 | 2 | NT |
| I-16-07 | 11 | 12 | NT | NT | NT |
| I-16-08 | 8 | NT | 9 | 7 | NT |
| I-16-09 | 10 | 11 | 8 | 8 | NT |
| Y-16-02 | 6 | 6 | 8 | 11 | 8 |
| Y-16-03 | 12 | 11 | 8 | 14 | 12 |
| Y-16-04 | 7 | 9 | 9 | 13 | 9 |
| Y-16-05 | 8 | 5 | 8 | 9 | 10 |
| Y-16-07 | 10 | 10 | 10 | 16 | 11 |
| Y-16-08 | 6 | 10 | 11 | 9 | 9 |
| Y-16-09 | 4 | 19 | 6 | 11 | 12 |
| Y-16-10 | 12 | 12 | 12 | 15 | 14 |
| Y-16-11 | 8 | 8 | 9 | 12 | NT |
| Y-16-12 | 7 | 10 | 10 | 11 | 12 |
| Y-16-13 | 8 | 4 | 5 | NT | 3 |
| Y-16-14 | 11 | 9 | 12 | 12 | 12 |
| Y-16-15 | 4 | 7 | 6 | 9 | 9 |
| Y-16-16 | 6 | 9 | 8 | 9 | 8 |
| Y-16-17 | 18 | 16 | 16 | 19 | 12 |
| Y-16-18 | 8 | 13 | 12 | 16 | 9 |
| Y-16-20 | 40 | 6 | 7 | 5 | 5 |
| Y-16-22 | 4 | 7 | 9 | 4 | NT |
| Y-16-24 | 10 | NT | 11 | NT | 4 |
| Y-16-25 | 8 | NT | NT | 8 | NT |
| Y-16-26 | NT | NT | NT | NT | 4 |
| DM-16-02 | 12 | 10 | 5 | 9 | 9 |
| DM-16-03 | 8 | 7 | 4 | 4 | 4 |

# APPENDIX 3

# VIROLOGY RESULTS FOR SNBTS CLINICAL TRIAL HP016

# TABLE 1: HEPATITIS A ANTIGEN RESULTS FOR PATIENTS ON SNBTS HP016 CLINICAL TRIAL

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| A-16-01 | N | N | N | NT | NT |
| A-16-02 | N | N | N | N | NT |
| A-16-03 | Y | Y | Y | Y | Y |
| A-16-04 | Y | Y | Y | Y | Y |
| A-16-05 | N | N | N | N | NT |
| A-16-06 | N | N | N | N | NT |
| A-16-07 | N | N | N | N | NT |
| A-16-10 | Y | Y | Y | Y | Y |
| A-16-12 | Y | Y | Y | Y | Y |
| A-16-13 | Y | Y | Y | Y | Y |
| A-16-14 | Y | Y | Y | Y | Y |
| A-16-15 | N | N | N | NT | NT |
| A-16-16 | NT | NT | NT | Y | Y |
| A-16-17 | N | NT | NT | NT | NT |
| A-16-18 | N | N | N | NT | NT |
| A-16-20 | N | NT | N | NT | NT |
| B-16-01 | Y | Y | Y | Y | Y |
| B-16-02 | Y | Y | Y | Y | Y |
| B-16-03 | Y | Y | Y | Y | Y |
| B-16-04 | N | N | N | N | Y |
| B-16-05 | Y | Y | Y | Y | Y |
| B-16-06 | Y | Y | Y | Y | Y |
| B-16-07 | Y | Y | Y | Y | Y |
| B-16-08 | N | N | N | N | NT |
| B-16-09 | N | N | N | N | N |
| B-16-10 | N | N | N | N | Y |
| B-16-11 | Y | Y | Y | Y | Y |
| B-16-12 | N | NT | NT | NT | NT |
| B-16-14 | Y | Y | Y | Y | Y |
| B-16-15 | N | N | N | NT | NT |
| B-16-16 | N | N | N | N | NT |
| B-16-17 | Y | Y | Y | Y | Y |
| B-16-18 | Y | Y | Y | NT | Y |
| B-16-19 | N | N | N | Y | Y |
| B-16-20 | N | N | N | N | N |
| B-16-21 | Y | Y | Y | Y | Y |
| B-16-22 | Y | Y | Y | Y | Y |
| B-16-23 | Y | Y | Y | Y | Y |
| B-16-24 | N | N | N | Y | Y |
| B-16-25 | N | N | N | Y | Y |
| B-16-26 | Y | Y | Y | Y | Y |
| B-16-27 | N | N | N | N | NT |
| B-16-28 | N | N | N | N | NT |
| B-16-29 | N | N | N | NT | NT |
| B-16-30 | N | N | N | NT | NT |
| B-16-31 | N | N | N | NT | NT |
| B-16-32 | N | N | N | NT | NT |
| B-16-33 | N | N | NT | NT | NT |
| B-16-34 | N | N | NT | NT | NT |
| B-16-35 | N | N | N | N | NT |
| B-16-36 | N | N | N | NT | NT |
| B-16-37 | N | N | N | NT | NT |
| B-16-40 | N | N | N | Y | Y |
| D-16-01 | N | N | N | N | N |
| D-16-02 | N | N | N | N | NT |
| D-16-03 | N | Y | Y | N | NT |
| D-16-04 | N | N | N | N | NT |
| D-16-05 | N | Y | Y | Y | Y |
| D-16-06 | N | Y | Y | Y | Y |
| D-16-07 | N | N | N | NT | NT |
| D-16-08 | Y | Y | Y | Y | Y |
| D-16-09 | N | N | N | N | NT |
| D-16-10 | NT | NT | NT | NT | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| D-16-21 | N | N | N | NT | NT |
| D-16-22 | N | NT | Y | Y | Y |
| D-16-23 | N | N | N | N | NT |
| D-16-24 | Y | N | N | N | NT |
| D-16-25 | N | N | NT | NT | NT |
| E-16-01 | N | N | N | N | N |
| E-16-02 | N | N | N | Y | Y |
| E-16-03 | N | N | N | N | NT |
| E-16-04 | N | N | N | N | N |
| E-16-05 | N | N | N | Y | Y |
| E-16-06 | N | N | N | N | N |
| E-16-07 | N | N | N | N | NT |
| E-16-08 | Y | Y | Y | Y | Y |
| E-16-09 | N | N | N | Y | N |
| E-16-10 | Y | Y | Y | Y | Y |
| E-16-11 | Y | Y | Y | Y | Y |
| E-16-12 | N | N | N | N | N |
| E-16-13 | N | N | NT | N | NT |
| E-16-14 | N | N | N | N | NT |
| E-16-15 | N | N | N | NT | N |
| E-16-16 | N | N | N | NT | N |
| E-16-17 | N | NT | N | N | N |
| E-16-18 | Y | Y | Y | Y | Y |
| E-16-19 | N | N | N | N | NT |
| E-16-20 | N | Y | Y | Y | Y |
| E-16-21 | Y | Y | Y | Y | Y |
| E-16-22 | N | N | N | N | N |
| E-16-23 | N | N | N | NT | NT |
| E-16-24 | N | NT | NT | N | NT |
| E-16-25 | Y | Y | Y | Y | Y |
| E-16-26 | Y | Y | Y | Y | Y |
| E-16-27 | N | NT | NT | NT | NT |
| E-16-28 | Y | Y | Y | Y | Y |
| E-16-29 | Y | Y | Y | Y | Y |
| E-16-30 | N | NT | NT | Y | Y |
| E-16-31 | N | N | NT | NT | NT |
| E-16-32 | Y | Y | Y | Y | Y |
| E-16-33 | N | N | NT | N | NT |
| E-16-34 | Y | Y | Y | Y | Y |
| G-16-01 | Y | Y | Y | Y | Y |
| G-16-02 | NT | NT | NT | NT | NT |
| G-16-03 | N | N | N | NT | NT |
| G-16-05 | NT | NT | NT | NT | NT |
| G-16-06 | N | N | NT | NT | NT |
| G-16-08 | N | N | N | NT | NT |
| G-16-11 | N | N | N | NT | NT |
| G-16-12 | NT | Y | Y | Y | Y |
| G-16-13 | NT | NT | NT | NT | NT |
| G-16-14 | Y | Y | Y | Y | Y |
| G-16-15 | Y | Y | Y | Y | Y |
| G-16-16 | Y | Y | Y | Y | Y |
| G-16-17 | Y | Y | Y | Y | Y |
| G-16-18 | Y | Y | Y | Y | Y |
| G-16-19 | N | N | N | NT | NT |
| G-16-21 | N | N | N | NT | NT |
| G-16-22 | N | N | N | N | N |
| G-16-23 | N | N | NT | NT | NT |
| G-16-26 | Y | Y | Y | Y | Y |
| G-16-28 | N | N | NT | NT | NT |
| G-16-29 | Y | Y | Y | Y | Y |
| G-16-31 | N | NT | NT | NT | NT |
| G-16-32 | Y | Y | Y | Y | Y |
| G-16-33 | N | N | N | NT | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| G-16-34 | Y | Y | Y | Y | Y |
| G-16-36 | N | N | NT | NT | NT |
| G-16-37 | Y | Y | Y | Y | Y |
| G-16-38 | N | NT | NT | NT | NT |
| G-16-39 | Y | Y | Y | Y | Y |
| I-16-01 | N | NT | NT | N | NT |
| I-16-02 | N | N | N | N | NT |
| I-16-03 | Y | Y | Y | Y | Y |
| I-16-04 | N | N | N | N | NT |
| I-16-05 | N | NT | NT | N | NT |
| I-16-07 | N | N | NT | NT | NT |
| I-16-08 | N | N | N | N | NT |
| I-16-09 | Y | N | N | N | NT |
| Y-16-02 | N | N | N | NT | N |
| Y-16-03 | N | N | N | N | NT |
| Y-16-04 | N | N | N | N | NT |
| Y-16-05 | N | N | N | N | N |
| Y-16-07 | N | N | N | N | NT |
| Y-16-08 | N | N | N | N | N |
| Y-16-09 | N | N | N | N | N |
| Y-16-10 | N | N | N | N | N |
| Y-16-11 | N | N | N | NT | NT |
| Y-16-12 | N | N | N | N | N |
| Y-16-13 | N | N | N | NT | NT |
| Y-16-14 | N | N | N | NT | NT |
| Y-16-15 | N | N | N | N | N |
| Y-16-16 | N | N | N | N | NT |
| Y-16-17 | N | N | N | N | N |
| Y-16-18 | N | N | NT | N | N |
| Y-16-20 | N | N | N | N | NT |
| Y-16-22 | N | N | N | N | NT |
| Y-16-24 | N | N | N | N | NT |
| Y-16-25 | NT | N | N | NT | NT |
| Y-16-26 | N | N | NT | NT | NT |
| DM-16-02 | N | N | NT | NT | NT |
| DM-16-03 | N | N | N | N | NT |

# TABLE 2: HEPATITIS B SURFACE ANTIGEN RESULTS FOR PATIENTS ON SNBTS HP016 CLINICAL TRIAL

| STUDY NUMBER | PREINF | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| A-16-01 | N | N | N | NT | NT |
| A-16-02 | N | N | N | N | NT |
| A-16-03 | N | N | N | N | NT |
| A-16-04 | N | N | NT | NT | NT |
| A-16-05 | N | N | N | N | NT |
| A-16-06 | N | N | N | N | NT |
| A-16-07 | N | N | N | N | NT |
| A-16-10 | N | N | N | N | NT |
| A-16-12 | N | N | N | NT | NT |
| A-16-13 | N | N | N | N | NT |
| A-16-14 | N | N | N | N | NT |
| A-16-15 | N | N | N | NT | NT |
| A-16-16 | NT | NT | N | N | NT |
| A-16-17 | N | N | N | NT | NT |
| A-16-18 | N | N | N | NT | NT |
| A-16-20 | N | NT | N | NT | NT |
| B-16-01 | N | N | N | N | NT |
| B-16-02 | N | N | N | N | N |
| B-16-03 | N | N | N | N | N |
| B-16-04 | N | N | N | N | N |
| B-16-05 | N | N | N | N | N |
| B-16-06 | Y | Y | Y | Y | Y |
| B-16-07 | N | N | N | N | N |
| B-16-08 | N | N | N | N | NT |
| B-16-09 | N | N | N | N | N |
| B-16-10 | N | N | N | N | N |
| B-16-11 | N | N | N | N | NT |
| B-16-12 | N | NT | NT | NT | NT |
| B-16-14 | N | N | N | NT | NT |
| B-16-15 | N | N | N | NT | NT |
| B-16-16 | N | N | N | N | NT |
| B-16-17 | N | N | N | N | N |
| B-16-18 | N | N | N | NT | N |
| B-16-19 | N | N | N | N | N |
| B-16-20 | N | N | N | N | N |
| B-16-21 | N | N | N | N | N |
| B-16-22 | N | N | N | N | N |
| B-16-23 | N | N | N | N | N |
| B-16-24 | N | N | N | N | N |
| B-16-25 | N | N | N | N | NT |
| B-16-26 | N | N | N | N | NT |
| B-16-27 | N | N | N | N | NT |
| B-16-28 | N | N | N | N | NT |
| B-16-29 | N | N | N | NT | NT |
| B-16-30 | N | N | N | NT | NT |
| B-16-31 | N | N | N | NT | NT |
| B-16-32 | N | N | N | NT | NT |
| B-16-33 | N | N | NT | NT | NT |
| B-16-34 | N | N | NT | NT | NT |
| B-16-35 | N | N | N | N | NT |
| B-16-36 | N | N | N | NT | NT |
| B-16-37 | N | N | N | NT | N |
| B-16-40 | N | N | N | N | N |
| D-16-01 | N | N | N | N | N |
| D-16-02 | N | N | N | N | NT |
| D-16-03 | N | N | N | N | NT |
| D-16-04 | N | N | N | N | NT |
| D-16-05 | N | N | NT | NT | NT |
| D-16-06 | N | N | NT | N | NT |
| D-16-07 | N | N | N | N | NT |
| D-16-08 | N | NT | N | N | NT |
| D-16-09 | N | N | N | N | NT |
| D-16-10 | N | N | N | NT | NT |

| STUDY NUMBER | PREINF | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| D-16-21 | N | N | Y | NT | NT |
| D-16-22 | N | NT | N | N | NT |
| D-16-23 | NT | NT | NT | NT | NT |
| D-16-24 | N | N | N | N | NT |
| D-16-25 | N | N | NT | NT | NT |
| E-16-01 | N | N | N | N | N |
| E-16-02 | N | N | N | N | N |
| E-16-03 | N | N | N | N | NT |
| E-16-04 | N | N | N | N | N |
| E-16-05 | N | N | N | N | N |
| E-16-06 | N | NT | N | N | NT |
| E-16-07 | N | N | N | NT | NT |
| E-16-08 | N | N | N | N | N |
| E-16-09 | N | N | N | N | N |
| E-16-10 | N | N | N | N | NT |
| E-16-11 | N | N | NT | N | NT |
| E-16-12 | N | N | N | N | N |
| E-16-13 | N | N | NT | N | NT |
| E-16-14 | N | N | N | N | NT |
| E-16-15 | N | NT | NT | NT | N |
| E-16-16 | N | N | N | NT | NT |
| E-16-17 | N | N | N | N | N |
| E-16-18 | N | N | N | N | NT |
| E-16-19 | N | N | N | N | NT |
| E-16-20 | N | N | N | N | NT |
| E-16-21 | N | N | N | N | NT |
| E-16-22 | NT | NT | NT | N | N |
| E-16-23 | N | NT | N | NT | NT |
| E-16-24 | N | NT | NT | N | NT |
| E-16-25 | N | N | N | NT | NT |
| E-16-26 | N | N | NT | NT | NT |
| E-16-27 | N | NT | NT | NT | NT |
| E-16-28 | N | N | N | NT | NT |
| E-16-29 | N | N | N | NT | NT |
| E-16-30 | N | N | N | N | NT |
| E-16-32 | N | N | N | NT | NT |
| E-16-33 | N | N | NT | NT | N |
| E-16-34 | N | N | NT | NT | NT |
| G-16-01 | N | N | N | NT | NT |
| G-16-02 | NT | NT | NT | NT | NT |
| G-16-03 | N | NT | NT | NT | NT |
| G-16-05 | NT | NT | N | NT | NT |
| G-16-06 | N | N | NT | NT | NT |
| G-16-08 | N | NT | NT | NT | NT |
| G-16-11 | NT | NT | NT | NT | NT |
| G-16-12 | N | N | N | NT | NT |
| G-16-13 | NT | NT | NT | NT | NT |
| G-16-14 | NT | NT | NT | NT | NT |
| G-16-15 | N | NT | NT | NT | NT |
| G-16-16 | N | N | N | NT | NT |
| G-16-17 | NT | N | NT | NT | NT |
| G-16-18 | N | N | N | NT | NT |
| G-16-19 | NT | NT | NT | NT | NT |
| G-16-21 | N | NT | NT | NT | NT |
| G-16-22 | N | N | NT | NT | NT |
| G-16-23 | N | N | NT | NT | NT |
| G-16-26 | N | NT | NT | NT | NT |
| G-16-28 | N | NT | NT | NT | NT |
| G-16-29 | NT | NT | NT | NT | NT |
| G-16-31 | N | NT | NT | NT | NT |
| G-16-32 | NT | NT | NT | NT | NT |
| G-16-33 | NT | NT | NT | NT | NT |
| G-16-34 | NT | NT | NT | NT | NT |



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| STUDY NUMBER | PREINF | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| G-16-36 | N | NT | NT | NT | NT |
| 16-37 | N | NT | NT | NT | NT |
| G-16-38 | N | NT | NT | NT | NT |
| G-16-39 | NT | NT | NT | NT | NT |
| I-16-01 | N | NT | NT | N | NT |
| I-16-02 | N | N | N | N | NT |
| I-16-03 | N | N | N | NT | NT |
| I-16-04 | N | N | N | N | NT |
| I-16-05 | N | N | N | N | NT |
| I-16-08 | N | N | N | N | NT |
| I-16-09 | N | N | N | NT | NT |
| Y-16-08 | N | N | NT | NT | NT |
| Y-16-09 | N | N | N | NT | NT |
| Y-16-10 | N | N | NT | N | NT |
| Y-16-11 | N | NT | N | N | N |
| Y-16-12 | N | N | NT | N | NT |
| Y-16-13 | N | N | N | NT | NT |
| Y-16-14 | NT | N | N | NT | N |
| Y-16-15 | NT | N | N | N | N |
| Y-16-16 | N | N | N | N | NT |
| Y-16-17 | N | NT | NT | N | NT |
| Y-16-18 | N | N | N | N | NT |
| Y-16-20 | NT | N | N | NT | NT |
| Y-16-22 | N | N | N | NT | NT |
| Y-16-24 | N | NT | NT | NT | NT |
| Y-16-25 | NT | NT | NT | NT | NT |
| Y-16-26 | N | N | NT | NT | NT |
| DM-16-02 | N | N | NT | NT | NT |
| DM-16-03 | N | N | N | N | NT |

# TABLE 3: HEPATITIS B CORE ANTIGEN RESULTS FOR PATIENTS ON SNBTS HP016 CLINICAL TRIAL

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| A-16-01 | N | NT | NT | NT | NT |
| A-16-02 | Y | Y | Y | Y | Y |
| A-16-03 | Y | Y | Y | Y | Y |
| A-16-04 | Y | Y | Y | Y | Y |
| A-16-05 | NT | NT | NT | NT | NT |
| A-16-06 | N | NT | NT | NT | NT |
| A-16-07 | NT | NT | NT | NT | NT |
| A-16-10 | Y | Y | Y | Y | Y |
| A-16-12 | N | Y | Y | Y | Y |
| A-16-13 | NT | Y | Y | Y | Y |
| A-16-14 | N | N | N | N | NT |
| A-16-15 | N | NT | Y | Y | Y |
| A-16-16 | NT | NT | Y | Y | Y |
| A-16-17 | N | N | N | NT | NT |
| A-16-18 | NT | Y | Y | Y | Y |
| A-16-20 | NT | NT | NT | NT | NT |
| B-16-01 | Y | Y | Y | Y | Y |
| B-16-02 | Y | Y | Y | Y | Y |
| B-16-03 | Y | Y | Y | Y | Y |
| B-16-04 | Y | Y | Y | Y | Y |
| B-16-05 | Y | Y | Y | Y | Y |
| B-16-06 | N | N | NT | NT | NT |
| B-16-07 | Y | Y | Y | Y | Y |
| B-16-08 | Y | Y | Y | Y | Y |
| B-16-09 | Y | Y | Y | Y | Y |
| B-16-10 | N | N | N | N | N |
| B-16-11 | Y | Y | Y | Y | Y |
| B-16-12 | N | NT | NT | NT | NT |
| B-16-14 | N | N | N | NT | NT |
| B-16-15 | Y | Y | Y | Y | Y |
| B-16-16 | Y | Y | Y | Y | Y |
| B-16-17 | Y | Y | Y | Y | Y |
| B-16-18 | Y | Y | Y | Y | Y |
| B-16-19 | Y | Y | Y | Y | Y |
| B-16-20 | Y | Y | Y | Y | Y |
| B-16-21 | Y | Y | Y | Y | Y |
| B-16-22 | Y | Y | Y | Y | Y |
| B-16-23 | N | N | N | N | N |
| B-16-24 | Y | Y | Y | Y | Y |
| B-16-25 | Y | Y | Y | Y | Y |
| B-16-26 | N | N | N | N | NT |
| B-16-27 | Y | Y | Y | Y | Y |
| B-16-28 | Y | Y | Y | Y | Y |
| B-16-29 | Y | Y | Y | Y | Y |
| B-16-30 | Y | Y | Y | Y | Y |
| B-16-31 | Y | Y | Y | Y | Y |
| B-16-32 | Y | Y | Y | Y | Y |
| B-16-33 | Y | Y | Y | Y | Y |
| B-16-34 | Y | Y | Y | Y | Y |
| B-16-35 | Y | Y | Y | Y | Y |
| B-16-36 | Y | Y | Y | Y | Y |
| B-16-37 | Y | Y | Y | Y | Y |
| B-16-40 | Y | Y | Y | Y | Y |
| D-16-01 | Y | Y | Y | Y | Y |
| D-16-02 | Y | Y | Y | Y | Y |
| D-16-03 | Y | Y | Y | Y | Y |
| D-16-04 | Y | Y | Y | Y | Y |
| D-16-05 | N | N | NT | NT | NT |
| D-16-06 | N | N | NT | N | NT |
| D-16-07 | Y | NT | N | Y | Y |
| D-16-08 | N | NT | N | N | NT |
| D-16-09 | Y | Y | Y | Y | Y |
| D-16-10 | Y | NT | N | NT | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| D-16-21 | Y | Y | Y | Y | Y |
| D-16-22 | N | NT | N | N | NT |
| D-16-23 | N | Y | Y | N | NT |
| D-16-24 | Y | Y | Y | Y | Y |
| D-16-25 | N | N | NT | NT | Y |
| E-16-01 | Y | Y | Y | Y | Y |
| E-16-02 | Y | Y | Y | Y | Y |
| E-16-03 | N | N | Y | N | Y |
| E-16-04 | Y | Y | Y | Y | Y |
| E-16-05 | Y | Y | Y | Y | Y |
| E-16-06 | Y | Y | Y | Y | Y |
| E-16-07 | Y | Y | Y | Y | Y |
| E-16-08 | Y | Y | Y | Y | Y |
| E-16-09 | Y | Y | N | Y | Y |
| E-16-10 | N | N | N | NT | NT |
| E-16-11 | Y | Y | Y | Y | Y |
| E-16-12 | Y | Y | Y | Y | Y |
| E-16-13 | Y | Y | NT | Y | Y |
| E-16-14 | Y | Y | Y | Y | Y |
| E-16-15 | Y | Y | Y | NT | Y |
| E-16-16 | NT | Y | Y | Y | Y |
| E-16-17 | N | Y | Y | Y | Y |
| E-16-18 | N | N | NT | Y | Y |
| E-16-19 | Y | Y | Y | Y | Y |
| E-16-20 | Y | Y | Y | Y | Y |
| E-16-21 | Y | Y | Y | Y | Y |
| E-16-22 | N | Y | Y | Y | Y |
| E-16-23 | Y | Y | Y | Y | Y |
| E-16-24 | Y | NT | NT | Y | Y |
| E-16-25 | Y | Y | Y | Y | Y |
| E-16-26 | Y | Y | Y | Y | Y |
| E-16-27 | Y | NT | NT | NT | Y |
| E-16-28 | Y | Y | Y | Y | Y |
| E-16-29 | Y | Y | Y | Y | Y |
| E-16-30 | Y | Y | Y | Y | Y |
| E-16-32 | N | N | N | NT | NT |
| E-16-33 | Y | Y | Y | Y | Y |
| E-16-34 | Y | Y | NT | NT | Y |
| G-16-01 | Y | Y | Y | Y | Y |
| G-16-02 | Y | Y | Y | Y | Y |
| G-16-03 | Y | Y | Y | Y | Y |
| G-16-04 | Y | Y | Y | Y | Y |
| G-16-05 | Y | Y | Y | Y | Y |
| G-16-06 | NT | NT | NT | NT | |
| G-16-08 | Y | Y | Y | Y | Y |
| G-16-11 | NT | NT | NT | NT | NT |
| G-16-12 | Y | Y | Y | Y | Y |
| G-16-13 | NT | NT | NT | NT | NT |
| G-16-14 | NT | NT | NT | NT | NT |
| G-16-15 | NT | NT | NT | NT | NT |
| G-16-16 | N | Y | Y | Y | Y |
| G-16-17 | NT | NT | NT | NT | NT |
| G-16-18 | Y | Y | Y | Y | Y |
| G-16-19 | Y | Y | Y | Y | Y |
| G-16-21 | NT | NT | NT | NT | NT |
| G-16-22 | Y | Y | Y | NT | Y |
| G-16-23 | N | N | NT | NT | NT |
| G-16-26 | NT | NT | NT | NT | NT |
| G-16-28 | NT | NT | NT | NT | NT |
| G-16-29 | NT | NT | NT | NT | NT |
| G-16-31 | NT | NT | NT | NT | NT |
| G-16-32 | N | NT | NT | NT | NT |
| G-16-33 | NT | NT | NT | NT | NT |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| G-16-34 | NT | NT | NT | NT | NT |
| G-16-36 | Y | Y | NT | NT | NT |
| G-16-37 | NT | NT | NT | NT | NT |
| G-16-38 | Y | Y | Y | Y | Y |
| G-16-39 | NT | NT | NT | NT | NT |
| I-16-01 | Y | NT | NT | Y | Y |
| I-16-02 | Y | Y | Y | Y | Y |
| I-16-03 | Y | Y | Y | Y | Y |
| I-16-04 | Y | Y | Y | Y | Y |
| I-16-05 | N | NT | NT | N | NT |
| I-16-08 | Y | Y | Y | Y | Y |
| I-16-09 | N | N | N | N | NT |
| Y-16-02 | Y | Y | Y | Y | Y |
| Y-16-03 | Y | Y | Y | Y | Y |
| Y-16-04 | Y | Y | Y | Y | Y |
| Y-16-05 | Y | Y | Y | Y | Y |
| Y-16-07 | Y | Y | Y | Y | Y |
| Y-16-08 | Y | Y | Y | Y | Y |
| Y-16-09 | Y | Y | Y | Y | Y |
| Y-16-10 | Y | Y | Y | Y | Y |
| Y-16-11 | Y | Y | Y | Y | Y |
| Y-16-12 | Y | Y | Y | Y | Y |
| Y-16-13 | Y | Y | Y | Y | Y |
| Y-16-14 | Y | Y | Y | Y | Y |
| Y-16-15 | Y | Y | Y | Y | Y |
| Y-16-16 | Y | Y | Y | Y | Y |
| Y-16-17 | Y | Y | Y | Y | Y |
| Y-16-18 | Y | Y | Y | Y | Y |
| Y-16-20 | Y | Y | Y | Y | Y |
| Y-16-22 | Y | Y | Y | Y | Y |
| Y-16-24 | Y | NT | Y | Y | Y |
| Y-16-25 | NT | NT | Y | Y | Y |
| Y-16-26 | NT | NT | NT | NT | NT |
| DM-16-02 | Y | Y | NT | NT | NT |
| DM-16-03 | Y | Y | Y | Y | Y |



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# TABLE 4: HEPATITIS C ANTIGEN RESULTS FOR PATIENTS ON SNBTS HP016 CLINICAL TRIAL

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| A-16-01 | N | N | N | NT | NT |
| A-16-02 | N | N | N | N | NT |
| A-16-03 | N | N | N | N | NT |
| A-16-04 | N | N | NT | NT | NT |
| A-16-05 | Y | Y | Y | Y | Y |
| A-16-06 | Y | Y | Y | Y | Y |
| A-16-07 | Y | Y | Y | Y | Y |
| A-16-10 | Y | Y | Y | Y | Y |
| A-16-12 | Y | Y | Y | Y | Y |
| A-16-13 | Y | Y | Y | Y | Y |
| A-16-14 | Y | Y | Y | Y | Y |
| A-16-15 | Y | Y | Y | Y | Y |
| A-16-16 | NT | NT | Y | Y | NT |
| A-16-17 | Y | Y | Y | Y | Y |
| A-16-18 | Y | Y | Y | Y | Y |
| A-16-20 | N | NT | N | NT | NT |
| B-16-01 | Y | Y | Y | Y | Y |
| B-16-02 | Y | Y | Y | Y | Y |
| B-16-03 | Y | Y | Y | Y | Y |
| B-16-04 | Y | Y | Y | Y | Y |
| B-16-05 | Y | Y | Y | Y | Y |
| B-16-06 | Y | Y | Y | Y | Y |
| B-16-07 | Y | Y | Y | Y | Y |
| B-16-08 | Y | Y | Y | Y | Y |
| B-16-09 | N | N | N | N | N |
| B-16-10 | Y | Y | Y | Y | Y |
| B-16-11 | Y | Y | Y | Y | Y |
| B-16-12 | N | NT | NT | NT | NT |
| B-16-14 | N | N | N | NT | NT |
| B-16-15 | N | N | N | NT | NT |
| B-16-16 | Y | Y | Y | Y | Y |
| B-16-17 | Y | Y | Y | Y | Y |
| B-16-18 | Y | Y | Y | Y | Y |
| B-16-19 | Y | Y | Y | Y | Y |
| B-16-20 | Y | Y | Y | Y | Y |
| B-16-21 | Y | Y | Y | Y | Y |
| B-16-22 | Y | Y | Y | Y | Y |
| B-16-23 | Y | Y | Y | Y | Y |
| B-16-24 | Y | Y | Y | Y | Y |
| B-16-25 | Y | Y | Y | Y | Y |
| B-16-26 | Y | Y | Y | Y | Y |
| B-16-27 | Y | Y | Y | Y | Y |
| B-16-28 | Y | Y | Y | Y | Y |
| B-16-29 | Y | Y | Y | Y | Y |
| B-16-30 | Y | Y | Y | Y | Y |
| B-16-31 | N | N | N | NT | NT |
| B-16-32 | Y | Y | Y | Y | Y |
| B-16-33 | N | N | NT | NT | NT |
| B-16-34 | N | N | NT | NT | NT |
| B-16-35 | Y | Y | Y | Y | Y |
| B-16-36 | N | N | N | NT | NT |
| B-16-37 | Y | Y | Y | Y | Y |
| B-16-40 | Y | Y | Y | Y | Y |
| D-16-01 | Y | Y | Y | Y | Y |
| D-16-02 | Y | Y | Y | Y | Y |
| D-16-03 | Y | Y | Y | Y | Y |
| D-16-04 | Y | Y | Y | Y | Y |
| D-16-05 | Y | Y | Y | Y | Y |
| D-16-06 | Y | Y | Y | Y | Y |
| D-16-07 | Y | Y | Y | Y | Y |
| D-16-08 | N | NT | Y | Y | Y |
| D-16-09 | Y | Y | Y | Y | Y |
| D-16-10 | Y | Y | Y | Y | Y |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| D-16-21 | Y | Y | Y | Y | Y |
| D-16-22 | N | NT | N | N | NT |
| D-16-23 | N | N | N | N | NT |
| D-16-24 | Y | Y | Y | Y | Y |
| D-16-25 | N | NT | NT | NT | NT |
| E-16-01 | N | N | N | N | N |
| E-16-02 | Y | Y | Y | Y | Y |
| E-16-03 | N | N | N | N | NT |
| E-16-04 | Y | Y | Y | Y | Y |
| E-16-05 | Y | Y | Y | Y | Y |
| E-16-06 | N | N | N | N | N |
| E-16-07 | N | N | N | N | N |
| E-16-08 | Y | Y | Y | Y | Y |
| E-16-09 | Y | Y | Y | Y | Y |
| E-16-10 | Y | Y | Y | Y | Y |
| E-16-11 | Y | Y | Y | Y | Y |
| E-16-12 | N | N | N | N | N |
| E-16-13 | N | N | NT | N | NT |
| E-16-14 | N | N | N | N | NT |
| E-16-15 | N | N | N | NT | NT |
| E-16-16 | N | N | N | N | NT |
| E-16-17 | N | N | N | N | N |
| E-16-18 | Y | Y | Y | Y | Y |
| E-16-19 | Y | Y | Y | Y | Y |
| E-16-20 | Y | Y | Y | Y | Y |
| E-16-21 | Y | Y | Y | Y | Y |
| E-16-22 | N | N | N | N | N |
| E-16-23 | Y | Y | Y | Y | Y |
| E-16-24 | Y | Y | Y | Y | Y |
| E-16-25 | Y | Y | Y | Y | Y |
| E-16-26 | Y | Y | Y | Y | Y |
| E-16-27 | Y | Y | Y | Y | Y |
| E-16-28 | Y | Y | Y | Y | Y |
| E-16-29 | Y | Y | Y | Y | Y |
| E-16-30 | Y | Y | Y | Y | Y |
| E-16-31 | Y | Y | Y | Y | Y |
| E-16-32 | Y | Y | Y | Y | Y |
| E-16-33 | Y | Y | Y | Y | Y |
| E-16-34 | Y | Y | Y | Y | Y |
| G-16-01 | Y | Y | Y | Y | Y |
| G-16-02 | Y | Y | Y | Y | Y |
| G-16-03 | Y | Y | Y | Y | Y |
| G-16-04 | Y | Y | Y | Y | Y |
| G-16-05 | Y | Y | Y | Y | Y |
| G-16-06 | Y | Y | Y | Y | Y |
| G-16-08 | Y | Y | Y | Y | Y |
| G-16-11 | Y | Y | Y | Y | Y |
| G-16-12 | Y | Y | Y | Y | Y |
| G-16-13 | Y | Y | Y | Y | Y |
| G-16-14 | Y | Y | Y | Y | Y |
| G-16-15 | Y | Y | Y | Y | Y |
| G-16-16 | Y | Y | Y | Y | Y |
| G-16-17 | Y | Y | Y | Y | Y |
| G-16-18 | Y | Y | Y | Y | Y |
| G-16-19 | Y | Y | Y | Y | Y |
| G-16-21 | Y | Y | Y | Y | Y |
| G-16-22 | Y | Y | Y | Y | Y |
| G-16-23 | Y | Y | Y | Y | Y |
| G-16-26 | Y | Y | Y | Y | Y |
| G-16-28 | Y | Y | Y | Y | Y |
| G-16-29 | Y | Y | Y | Y | Y |
| G-16-31 | Y | Y | Y | Y | Y |
| G-16-32 | Y | Y | Y | Y | Y |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| G-16-33 | Y | Y | Y | Y | Y |
| G-16-34 | Y | Y | Y | Y | Y |
| G-16-36 | Y | Y | Y | Y | Y |
| G-16-37 | Y | Y | Y | Y | Y |
| G-16-38 | Y | Y | Y | Y | Y |
| G-16-39 | Y | Y | Y | Y | Y |
| I-16-01 | N | NT | NT | N | NT |
| I-16-02 | Y | Y | Y | Y | Y |
| I-16-03 | Y | Y | Y | Y | Y |
| I-16-04 | Y | Y | Y | Y | Y |
| I-16-05 | N | NT | NT | N | NT |
| I-16-07 | Y | Y | Y | Y | Y |
| I-16-08 | Y | Y | Y | Y | Y |
| I-16-09 | Y | Y | Y | Y | Y |
| Y-16-02 | Y | Y | Y | Y | Y |
| Y-16-03 | Y | Y | Y | Y | Y |
| Y-16-04 | Y | Y | Y | Y | Y |
| Y-16-05 | N | N | N | N | N |
| Y-16-07 | Y | Y | Y | Y | Y |
| Y-16-08 | Y | Y | Y | Y | Y |
| Y-16-09 | N | N | N | N | N |
| Y-16-10 | Y | Y | Y | Y | Y |
| Y-16-11 | N | NT | NT | N | NT |
| Y-16-12 | Y | Y | Y | Y | Y |
| Y-16-13 | N | N | N | NT | NT |
| Y-16-14 | Y | Y | Y | Y | Y |
| Y-16-15 | Y | Y | Y | Y | Y |
| Y-16-16 | N | N | N | N | N |
| Y-16-17 | Y | Y | Y | Y | Y |
| Y-16-18 | N | N | N | N | N |
| Y-16-20 | Y | Y | Y | Y | Y |
| Y-16-22 | N | N | N | N | N |
| Y-16-24 | N | N | N | N | NT |
| Y-16-25 | NT | Y | Y | Y | Y |
| Y-16-26 | N | N | NT | NT | NT |
| DM-16-02 | Y | Y | Y | Y | Y |
| DM-16-03 | Y | Y | Y | Y | Y |



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# TABLE 5: PARVOVIRUS (B19) ANTIGEN RESULTS FOR PATIENTS ON SNBTS HP016 CLINICAL TRIAL

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| A-16-01 | N | N | N | NT | NT |
| A-16-02 | Y | Y | Y | Y | NT |
| A-16-03 | Y | Y | Y | Y | NT |
| A-16-04 | N | NT | NT | NT | NT |
| A-16-05 | Y | Y | Y | Y | NT |
| A-16-06 | NT | NT | NT | NT | NT |
| A-16-07 | NT | NT | NT | NT | NT |
| A-16-10 | NT | NT | NT | NT | NT |
| A-16-12 | Y | Y | Y | Y | NT |
| A-16-13 | N | Y | Y | Y | NT |
| A-16-14 | NT | Y | Y | Y | NT |
| A-16-15 | Y | Y | Y | Y | NT |
| A-16-16 | NT | NT | Y | Y | NT |
| A-16-17 | N | N | N | NT | NT |
| A-16-18 | NT | Y | Y | NT | NT |
| A-16-20 | N | NT | NT | NT | NT |
| B-16-01 | Y | Y | Y | Y | Y |
| B-16-02 | Y | Y | Y | Y | Y |
| B-16-03 | Y | Y | Y | Y | Y |
| B-16-04 | Y | Y | Y | Y | Y |
| B-16-05 | Y | Y | Y | Y | Y |
| B-16-06 | Y | Y | NY | Y | Y |
| B-16-07 | Y | Y | Y | Y | Y |
| B-16-08 | Y | Y | Y | Y | Y |
| B-16-09 | Y | Y | Y | Y | Y |
| B-16-10 | Y | Y | Y | Y | Y |
| B-16-11 | Y | Y | Y | Y | Y |
| B-16-12 | Y | NT | NT | NT | Y |
| B-16-14 | Y | Y | Y | NT | Y |
| B-16-15 | Y | Y | Y | NT | Y |
| B-16-16 | Y | Y | Y | Y | Y |
| B-16-17 | Y | Y | Y | Y | Y |
| B-16-18 | N | N | N | NT | N |
| B-16-19 | Y | Y | Y | Y | Y |
| B-16-20 | N | N | N | N | N |
| B-16-21 | Y | Y | Y | Y | Y |
| B-16-22 | Y | Y | Y | Y | Y |
| B-16-23 | Y | Y | Y | Y | Y |
| B-16-24 | Y | Y | Y | Y | Y |
| B-16-25 | Y | Y | Y | Y | Y |
| B-16-26 | Y | Y | Y | Y | Y |
| B-16-27 | Y | Y | Y | Y | Y |
| B-16-28 | Y | Y | Y | Y | Y |
| B-16-29 | Y | Y | Y | Y | Y |
| B-16-30 | Y | Y | Y | Y | Y |
| B-16-31 | Y | Y | Y | NT | Y |
| B-16-32 | Y | Y | Y | NT | Y |
| B-16-33 | N | Y | NT | NT | NT |
| B-16-34 | N | Y | NT | NT | Y |
| B-16-35 | Y | Y | Y | Y | Y |
| B-16-36 | N | N | Y | Y | Y |
| B-16-37 | Y | Y | Y | Y | Y |
| B-16-40 | Y | Y | Y | Y | Y |
| D-16-01 | Y | Y | Y | Y | Y |
| D-16-02 | Y | Y | Y | Y | Y |
| D-16-03 | Y | Y | Y | Y | Y |
| D-16-04 | Y | Y | Y | Y | Y |
| D-16-05 | Y | Y | NT | NT | Y |
| D-16-06 | Y | Y | Y | Y | Y |
| D-16-07 | Y | NT | N | NT | Y |
| D-16-08 | Y | Y | Y | Y | Y |
| D-16-09 | N | N | N | Y | Y |
| D-16-10 | NT | NT | Y | NT | Y |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| D-16-21 | Y | Y | Y | NT | Y |
| D-16-22 | N | NT | Y | Y | Y |
| D-16-23 | N | NT | NT | Y | Y |
| D-16-24 | Y | Y | Y | Y | Y |
| D-16-25 | NT | NT | NT | NT | NT |
| E-16-01 | Y | Y | Y | Y | Y |
| E-16-02 | Y | Y | Y | Y | Y |
| E-16-03 | N | N | N | NT | NT |
| E-16-04 | Y | Y | Y | Y | Y |
| E-16-05 | Y | Y | Y | Y | Y |
| E-16-06 | Y | Y | Y | Y | Y |
| E-16-07 | Y | Y | Y | Y | Y |
| E-16-08 | NT | NT | NT | NT | N |
| E-16-09 | Y | Y | Y | Y | Y |
| E-16-10 | Y | Y | Y | Y | Y |
| E-16-11 | Y | Y | Y | Y | Y |
| E-16-12 | Y | Y | Y | Y | Y |
| E-16-13 | N | NT | Y | Y | Y |
| E-16-14 | Y | Y | Y | Y | Y |
| E-16-15 | N | NT | N | NT | Y |
| E-16-16 | N | N | Y | Y | Y |
| E-16-17 | N | NT | Y | Y | Y |
| E-16-18 | Y | Y | Y | Y | Y |
| E-16-19 | Y | Y | Y | Y | Y |
| E-16-20 | Y | Y | Y | Y | Y |
| E-16-21 | Y | Y | Y | Y | Y |
| E-16-22 | N | NT | NT | N | N |
| E-16-23 | NT | NT | Y | Y | Y |
| E-16-24 | Y | Y | Y | Y | Y |
| E-16-25 | Y | Y | Y | Y | Y |
| E-16-26 | Y | Y | NT | NT | Y |
| E-16-27 | Y | NT | NT | NT | Y |
| E-16-28 | NT | Y | Y | NT | Y |
| E-16-29 | Y | Y | Y | NT | Y |
| E-16-30 | Y | NT | NT | Y | Y |
| E-16-32 | Y | Y | Y | NT | Y |
| E-16-33 | NT | NT | NT | Y | Y |
| E-16-34 | Y | Y | NT | NT | Y |
| G-16-01 | Y | Y | Y | NT | Y |
| G-16-02 | NT | NT | NT | NT | Y |
| G-16-03 | Y | Y | Y | NT | Y |
| G-16-05 | NT | NT | Y | NT | Y |
| G-16-06 | Y | Y | NT | NT | Y |
| G-16-08 | N | NT | NT | NT | N |
| G-16-11 | N | NT | NT | NT | N |
| G-16-12 | NT | NT | NT | NT | N |
| G-16-13 | NT | NT | NT | NT | N |
| G-16-14 | Y | Y | Y | NT | Y |
| G-16-15 | Y | Y | Y | NT | Y |
| G-16-16 | Y | Y | Y | NT | Y |
| G-16-17 | Y | Y | Y | NT | Y |
| G-16-18 | Y | Y | Y | NT | Y |
| G-16-19 | Y | Y | Y | NT | Y |
| G-16-21 | Y | Y | Y | NT | Y |
| G-16-22 | NT | NT | NT | NT | NT |
| G-16-23 | NT | NT | NT | NT | NT |
| G-16-26 | N | NT | NT | NT | NT |
| G-16-28 | Y | Y | Y | NT | Y |
| G-16-29 | Y | Y | Y | NT | Y |
| G-16-31 | Y | Y | Y | NT | Y |
| G-16-32 | Y | Y | Y | NT | Y |
| G-16-33 | N | N | N | NT | NT |
| G-16-34 | Y | Y | Y | NT | Y |

| STUDY NUMBER | PREINFUSION | 3 MONTHS | 6 MONTHS | 12 MONTHS | 18 MONTHS |
|---|---|---|---|---|---|
| G-16-36 | N | NT | NT | NT | NT |
| G-16-37 | NT | NT | NT | NT | NT |
| G-16-38 | Y | Y | Y | NT | Y |
| G-16-39 | Y | Y | Y | NT | Y |
| I-16-01 | Y | NT | NT | N | NT |
| I-16-02 | Y | N | N | N | NT |
| I-16-03 | N | N | N | NT | NT |
| I-16-04 | Y | Y | Y | Y | Y |
| I-16-05 | Y | Y | Y | N | NT |
| I-16-08 | Y | Y | Y | N | NT |
| I-16-09 | Y | Y | Y | Y | Y |
| Y-16-02 | Y | Y | Y | Y | Y |
| Y-16-03 | Y | Y | Y | Y | Y |
| Y-16-04 | Y | Y | Y | Y | Y |
| Y-16-05 | Y | Y | Y | Y | Y |
| Y-16-07 | Y | Y | Y | Y | Y |
| Y-16-08 | Y | Y | Y | Y | Y |
| Y-16-09 | NT | Y | Y | Y | Y |
| Y-16-10 | Y | Y | Y | Y | Y |
| Y-16-11 | Y | Y | Y | NT | Y |
| Y-16-12 | Y | Y | Y | Y | Y |
| Y-16-13 | NT | Y | Y | NT | Y |
| Y-16-14 | N | N | NT | NT | Y |
| Y-16-15 | NT | NT | Y | Y | Y |
| Y-16-16 | Y | Y | Y | Y | Y |
| Y-16-17 | Y | Y | Y | Y | Y |
| Y-16-18 | N | Y | Y | Y | Y |
| Y-16-20 | N | N | NT | NT | Y |
| Y-16-22 | N | NT | NT | NT | Y |
| Y-16-24 | NT | NT | NT | NT | Y |
| Y-16-25 | NT | NT | NT | NT | Y |
| Y-16-26 | NT | NT | NT | NT | Y |
| DM-16-02 | N | N | NT | NT | Y |
| DM-16-03 | Y | Y | Y | N | NT |



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# APPENDIX 4

# LYMPHOCYTE SUBSET FOR SNBTS CLINICAL TRIAL HP016

Lymphocyte subsets in haemophilia A patients without antibodies to HIV prior to treatment with Liberate and 3, 6 , 12 and 18 months thereafter (counts x 10^9/l)

| | PRE-INFUSION | | | 3 MONTHS | | | 6 MONTHS | | | 12 MONTHS | | | 18 MONTHS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PATIENT | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 |
| A-16-01 | 0.87 | 0.39 | 2.23 | 0.90 | 0.42 | 0.48 | 1.14 | 0.58 | 1.97 | 0.62 | 0.31 | 0.20 | | | |
| A-16-02 | 1.45 | 0.88 | 1.65 | 1.70 | 0.76 | 2.24 | 1.76 | 0.74 | 2.38 | 1.88 | 1.11 | 1.69 | | | |
| A-16-03 | 1.26 | 0.58 | 2.17 | | | | 1.47 | 0.45 | 3.27 | 1.26 | 0.51 | 2.47 | | | |
| A-16-04 | 0.99 | 0.68 | 1.46 | 1.10 | 0.48 | 2.29 | | | | | | | | | |
| A-16-05 | 0.69 | 0.47 | 1.47 | 0.87 | 0.49 | 1.78 | 0.88 | 0.59 | 1.49 | 0.94 | 0.56 | 1.68 | | | |
| A-16-06 | | | | 0.67 | 0.43 | 1.56 | 0.82 | 0.66 | 1.24 | | | | | | |
| A-16-07 | 0.85 | 0.29 | 2.93 | 1.07 | 0.32 | 3.34 | 0.73 | 0.24 | 3.04 | 0.94 | 0.49 | 1.92 | | | |
| A-16-10 | 0.61 | 0.25 | 2.44 | | | | 0.70 | 0.37 | 1.89 | 1.05 | 0.63 | 1.67 | | | |
| A-16-12 | 1.58 | 0.65 | 2.43 | 1.37 | 0.55 | 2.49 | 1.37 | 0.55 | 2.49 | | | | | | |
| A-16-13 | 1.10 | 0.69 | 1.59 | 1.24 | 0.58 | 2.14 | 1.06 | | | 1.09 | 0.75 | 1.45 | | | |
| A-16-14 | 0.89 | 0.41 | 2.17 | 1.31 | 0.49 | 2.67 | 0.69 | 0.24 | 2.88 | 1.34 | 0.59 | 2.77 | | | |
| A-16-15 | 0.81 | 0.57 | 1.42 | | | | 0.90 | 0.66 | 1.36 | | | | | | |
| A-16-16 | 1.30 | 0.84 | 1.55 | 0.62 | 0.46 | 1.35 | 0.76 | 0.52 | 1.46 | 0.88 | 0.67 | 1.31 | | | |
| A-16-17 | 1.42 | 0.46 | 3.09 | 1.18 | 0.43 | 2.74 | 1.18 | 0.43 | 2.74 | | | | | | |
| A-16-18 | | | | 1.05 | 0.61 | 1.72 | 1.05 | 0.61 | 1.72 | | | | | | |
| A-16-20 | 3.09 | 0.95 | | | | | | | | | | | | | |
| B-16-01 | 0.54 | 0.67 | 0.81 | 0.63 | 0.80 | 0.79 | | | | 0.84 | 1.06 | 0.83 | 0.56 | 0.69 | 0.81 |
| B-16-02 | 0.62 | 0.44 | 1.41 | 0.67 | 0.95 | 0.71 | 0.75 | 0.52 | 1.44 | 0.94 | 0.77 | 1.22 | 0.96 | 1.07 | 0.90 |
| B-16-03 | 0.98 | 0.72 | 1.36 | | | | 0.86 | 0.62 | 1.39 | 0.88 | 0.65 | 1.35 | | | |
| B-16-04 | 0.99 | 0.70 | 1.41 | 0.62 | 0.51 | 1.22 | | | | 0.76 | 0.47 | 1.61 | | | |
| B-16-05 | 1.26 | 0.63 | 2.00 | 0.45 | 0.29 | 1.55 | 0.54 | 0.30 | 1.80 | 0.68 | 0.31 | 2.19 | 0.62 | 0.25 | 2.48 |
| B-16-06 | 0.68 | 0.79 | 0.86 | 0.67 | 0.64 | 1.05 | | | | | | | | | |
| B-16-07 | 0.51 | 0.86 | 0.59 | 0.52 | 0.53 | 0.98 | | | | | | | 0.46 | 0.44 | 1.04 |
| B-16-08 | 0.41 | 0.40 | 1.03 | 0.47 | 0.43 | 1.09 | 0.47 | 0.38 | 1.24 | 0.40 | | | | | |
| B-16-09 | 0.72 | 0.28 | 2.57 | 1.29 | 0.35 | 3.69 | 1.12 | 0.36 | 3.11 | 0.95 | 0.34 | 2.79 | 1.13 | 0.31 | 3.64 |
| B-16-10 | | | | 0.36 | 0.20 | 1.80 | 0.65 | 0.40 | 1.62 | 0.54 | 0.41 | 1.32 | | | |
| B-16-11 | 0.66 | 0.57 | 1.16 | 0.56 | 0.49 | 1.14 | | | | 0.66 | 0.40 | 1.65 | | | |
| B-16-12 | 1.51 | 1.02 | 1.48 | | | | | | | 0.93 | 0.57 | 1.63 | | | |
| B-16-14 | 0.66 | 0.22 | 3.00 | 0.53 | 0.22 | 2.41 | 0.57 | 0.24 | 2.38 | | | | | | |
| B-16-15 | 1.85 | 1.00 | 1.85 | 1.12 | 0.76 | 1.47 | 1.64 | 0.53 | 3.09 | | | | | | |
| B-16-16 | | | | 0.34 | 0.48 | 0.71 | 0.45 | 0.50 | 0.90 | 0.45 | 0.62 | 0.72 | 0.40 | 0.69 | 0.58 |
| B-16-17 | 0.60 | 0.32 | 1.88 | 0.74 | 0.33 | 2.24 | 2.02 | 0.47 | 4.28 | 0.95 | 0.30 | 3.17 | | | |
| B-16-18 | | | | | | | 0.33 | 0.48 | 0.69 | | | | 0.38 | 0.43 | 0.88 |
| B-16-19 | | | | 0.72 | 0.70 | 1.03 | 0.63 | 0.55 | 1.15 | 0.88 | 0.64 | 1.38 | 0.69 | 0.61 | 1.13 |
| B-16-20 | 0.72 | 0.68 | 1.06 | 0.77 | 0.58 | 1.33 | 0.70 | 0.40 | 1.75 | 0.77 | 0.65 | 1.18 | 0.84 | 0.61 | 1.38 |
| B-16-21 | 0.30 | 0.36 | 0.83 | 0.37 | 0.27 | 1.37 | 0.30 | 0.16 | 1.88 | 0.31 | 0.23 | 1.34 | 0.39 | 0.25 | 1.56 |
| B-16-24 | 0.42 | 0.31 | 1.35 | | | | 0.57 | 0.20 | 2.85 | 0.73 | 0.39 | 1.87 | 0.64 | 0.34 | 1.88 |
| B-16-23 | | | | | | | | | | 0.85 | 0.61 | 1.39 | | | |
| B-16-24 | 1.15 | 0.49 | 2.35 | 1.35 | 0.23 | 5.87 | 1.40 | 0.37 | 3.78 | 1.28 | 0.37 | 3.46 | 1.34 | 0.41 | 3.27 |
| B-16-25 | 0.52 | 0.43 | 1.21 | 0.57 | 0.28 | 2.04 | 0.60 | 0.27 | 2.22 | 0.55 | 0.21 | 2.62 | | | |
| B-16-26 | 0.88 | 0.93 | 0.95 | 0.42 | 0.31 | 1.35 | | | | 0.59 | 0.36 | 1.64 | | | |
| B-16-27 | 0.80 | 1.14 | 0.70 | | | | | | | | | | | | |
| B-16-28 | 0.84 | 0.95 | 0.88 | | | | | | | | | | | | |
| B-16-29 | 0.61 | 0.35 | 1.74 | 0.96 | 0.44 | 2.18 | | | | | | | | | |
| B-16-30 | 0.30 | 0.43 | 0.70 | | | | | | | | | | | | |
| B-16-31 | 0.97 | 0.66 | 1.47 | | | | | | | | | | | | |
| B-16-32 | 0.82 | 0.27 | 3.04 | | | | | | | | | | | | |
| B-16-33 | 1.11 | 0.33 | 3.36 | 1.12 | 0.24 | 4.67 | | | | | | | | | |
| B-16-34 | 1.14 | 0.51 | 2.24 | 0.94 | 0.39 | 2.41 | | | | | | | | | |
| B-16-35 | 0.84 | 0.55 | 1.53 | 0.94 | 0.54 | 1.74 | | | | | | | | | |

| | PRE-INFUSION | | | 3 MONTHS | | | 6 MONTHS | | | 12 MONTHS | | | 18 MONTHS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PATIENT | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 |
| B-16-37 | 0.98 | 0.52 | 1.88 | 0.54 | 0.28 | 1.93 | | | | | | | | | |
| B-16-38 | | | | | | | | | | | | | | | |
| B-16-39 | 0.76 | 0.22 | 3.45 | 0.74 | 0.29 | 1.62 | 0.91 | 0.35 | 2.60 | | | | | | |
| B-16-40 | | | | 0.65 | 0.57 | 1.14 | 0.69 | 0.42 | 1.64 | 0.71 | 0.51 | 1.39 | | | |
| B-16-41 | 1.12 | 0.86 | 1.30 | | | | | | | | | | | | |
| B-16-42 | | | | | | | | | | | | | | | |
| B-16-43 | | | | | | | | | | | | | | | |
| B-16-44 | | | | | | | | | | | | | | | |
| D-16-01 | 0.97 | 0.70 | 1.39 | 0.74 | 0.58 | 1.28 | 1.18 | 0.84 | 1.40 | 0.61 | 0.75 | 0.81 | 0.63 | 0.83 | 0.76 |
| D-16-02 | 0.32 | 0.13 | 2.46 | 0.34 | 0.14 | 2.43 | 0.37 | 0.42 | 0.88 | 0.27 | 0.15 | 1.80 | 0.24 | 0.13 | 1.85 |
| D-16-03 | 1.09 | 0.60 | 1.82 | 0.87 | 0.55 | 1.58 | 0.36 | 0.94 | 0.38 | | | | | | |
| D-16-04 | 44% | 27% | | | | | 0.66 | 0.44 | 1.50 | | | | | | |
| D-16-05 | 40% | 38% | | | | | 0.67 | 0.48 | 1.40 | | | | | | |
| D-16-06 | | | | | | | 0.83 | 0.61 | 1.36 | 0.77 | 0.63 | 1.22 | | | |
| D-16-07 | | | | | | | 0.90 | 1.13 | 0.80 | | | | | | |
| D-16-08 | | | | | | | | | | | | | | | |
| D-16-09 | | | | | | | | | | | | | | | |
| D-16-10 | | | | | | | 1.52 | 1.05 | 1.45 | | | | | | |
| D-16-21 | | | | | | | | | | | | | | | |
| D-16-22 | | | | | | | | | | | | | | | |
| D-16-23 | 5.71 | 1.86 | 3.07 | | | | | | | | | | | | |
| D-16-24 | | | | | | | | | | 0.80 | 0.71 | 1.13 | | | |
| D-16-25 | | | | | | | | | | | | | | | |
| E-16-01 | | | | | | | 1.30 | 1.56 | 0.83 | 1.55 | 1.77 | 0.88 | 0.53 | 0.49 | 1.08 |
| E-16-02 | 0.50 | 0.57 | 0.88 | 1.33 | 0.57 | 2.33 | 0.35 | 0.45 | 0.78 | 0.59 | 0.97 | 0.61 | 0.82 | 0.62 | 1.33 |
| E-16-03 | | | | | | | | | | 4.76 | 2.77 | 1.72 | | | |
| E-16-04 | 0.84 | 1.12 | 0.75 | 1.25 | 1.38 | 0.91 | 0.66 | 0.70 | 0.94 | 0.91 | 1.02 | 0.89 | 0.41 | 0.34 | 1.21 |
| E-16-05 | 0.66 | 0.44 | 1.50 | | 1.09 | 0.00 | 1.09 | 0.44 | 2.48 | 0.41 | 0.29 | 1.41 | 1.06 | 0.61 | 1.74 |
| E-16-06 | 2.39 | 1.09 | 2.19 | | | | 1.83 | 0.82 | 2.23 | 1.97 | 0.96 | 2.05 | | | |
| E-16-07 | | | | 1.19 | 1.05 | 1.13 | 0.68 | 0.50 | 1.36 | 0.85 | 0.83 | 1.02 | | | |
| E-16-08 | 1.01 | 0.43 | 2.35 | 0.77 | 0.36 | 2.14 | 0.68 | 0.34 | 2.00 | 0.79 | 0.41 | 1.93 | 0.97 | 0.34 | 2.85 |
| E-16-09 | 0.92 | 0.53 | 1.74 | | | | 0.42 | 0.25 | 1.68 | 1.20 | 0.53 | 2.26 | 0.97 | 0.44 | 2.20 |
| E-16-10 | 0.64 | 0.43 | 1.49 | 0.87 | 0.55 | 1.58 | 0.57 | 0.89 | 0.64 | 1.12 | 0.56 | 2.00 | | | |
| E-16-11 | 0.72 | 0.63 | 1.14 | 0.47 | 0.38 | 1.24 | | | | 0.48 | 0.35 | 1.37 | | | |
| E-16-12 | | | | 2.38 | 1.44 | 1.65 | 1.86 | 1.09 | 1.71 | 2.09 | 0.99 | 2.11 | 1.18 | 0.44 | 2.68 |
| E-16-13 | 2.51 | 1.09 | 2.30 | 2.59 | 1.32 | 1.96 | | | | | | | | | |
| E-16-14 | | | | 1.32 | 0.87 | 1.52 | 2.46 | 2.35 | 1.05 | | | | | | |
| E-16-15 | 1.96 | 0.94 | 2.09 | | | | 1.58 | 1.12 | 1.41 | | | | 1.06 | 0.61 | 1.74 |
| E-16-16 | | | | 0.71 | 0.94 | 0.76 | 0.59 | 0.71 | 0.83 | 1.36 | 1.79 | 0.76 | | | |
| E-16-17 | | | | 1.19 | 0.79 | | 1.19 | 0.78 | 1.52 | 1.35 | 0.98 | 1.38 | 0.98 | 0.65 | 1.51 |
| E-16-18 | 0.34 | 0.42 | 0.81 | 0.46 | 0.69 | 0.67 | | | | 0.52 | 0.65 | 0.80 | | | |
| E-16-19 | 0.49 | 0.67 | 0.73 | | | | 0.92 | 0.88 | 1.05 | 0.52 | 0.60 | 0.87 | | | |
| E-16-20 | 1.15 | 0.88 | 1.31 | 1.05 | 0.96 | 1.09 | 1.16 | 0.71 | 1.63 | 0.98 | 0.49 | 2.00 | | | |
| E-16-21 | 1.96 | 1.29 | 1.52 | 1.16 | 0.66 | 1.76 | 1.14 | 0.66 | 1.72 | 2.32 | 1.02 | 2.27 | | | |
| E-16-22 | 5.71 | 1.86 | 3.07 | | | | | | | | | | 2.42 | 1.07 | 2.26 |
| E-16-23 | 1.30 | 1.00 | 1.30 | | | | 1.08 | 0.70 | 1.54 | | | | | | |
| E-16-24 | 0.62 | 0.58 | 1.07 | | | | | | | 1.06 | 0.82 | 1.29 | | | |
| E-16-25 | 0.52 | 0.19 | 2.74 | 0.70 | 0.29 | 2.41 | 0.62 | 0.19 | 3.26 | | | | | | |
| E-16-26 | 0.85 | 0.43 | 1.98 | 0.68 | 0.17 | 4.00 | | | | | | | | | |
| E-16-27 | 0.84 | 0.59 | 1.42 | | | | | | | | | | | | |
| E-16-28 | 0.91 | 0.64 | 1.42 | 0.92 | 0.51 | 1.80 | 0.86 | 0.72 | 1.19 | | | | | | |
| E-16-29 | 0.89 | 0.60 | 1.48 | 0.82 | 0.51 | 1.61 | | | | | | | | | |
| E-16-30 | 1.02 | 0.89 | 1.15 | 0.65 | 0.71 | 0.91 | 0.94 | 0.83 | 1.13 | 1.04 | 0.93 | 1.11 | | | |
| E-16-31 | 0.85 | 0.38 | 2.24 | 0.79 | 0.48 | 1.65 | | | | | | | | | |



SBTS0003795_062_0187

| | PRE-INFUSION | | | 3 MONTHS | | | 6 MONTHS | | | 12 MONTHS | | | 18 MONTHS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PATIENT | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 |
| E-16-32 | 0.51 | 0.33 | 1.54 | 0.52 | 0.37 | 1.40 | 0.87 | 0.69 | 1.26 | | | | | | |
| E-16-33 | | | | | | | | | | | | | | | |
| E-16-34 | | | | | | | | | | | | | | | |
| G-16-01 | | | | | | | 0.33 | 0.53 | 0.63 | 0.22 | 0.30 | 0.73 | | | |
| G-16-03 | 1.36 | 0.75 | 1.81 | 0.75 | 0.43 | 1.76 | 0.75 | 0.43 | 1.76 | 1.07 | 0.59 | 1.81 | | | |
| G-16-04 | | | | | | | 0.54 | 0.63 | 0.86 | | | | | | |
| G-16-05 | | | | | | | 0.54 | 0.94 | 0.58 | 0.55 | 0.97 | 0.57 | | | |
| G-16-06 | | | | 0.40 | 0.15 | 2.72 | 0.23 | 0.09 | 2.70 | 0.24 | 0.12 | 2.00 | | | |
| G-16-08 | 0.85 | 0.33 | 2.58 | 1.07 | 0.51 | 2.09 | 0.91 | 0.44 | 2.09 | 0.91 | 0.41 | 2.22 | | | |
| G-16-11 | | | | | | | 0.56 | 0.40 | 1.42 | 0.44 | 0.24 | 1.83 | | | |
| G-16-12 | | | | 0.70 | 0.81 | 0.87 | 0.44 | 0.59 | 0.74 | 0.82 | 1.13 | 0.73 | | | |
| G-16-14 | | | | 0.72 | 0.34 | 2.15 | 0.61 | 0.30 | 2.05 | 0.64 | 0.42 | 1.52 | | | |
| G-16-16 | 0.66 | 0.50 | 1.32 | | | | 0.33 | 0.19 | 1.76 | 0.26 | 0.23 | 1.13 | | | |
| G-16-17 | | | | 0.74 | 0.58 | 1.28 | | | | 0.53 | 0.36 | 1.47 | | | |
| G-16-19 | | | | | | | 0.49 | 0.39 | 1.25 | 0.55 | 0.40 | 1.38 | | | |
| G-16-21 | | | | | | | 0.78 | 0.59 | 1.32 | 0.86 | 0.57 | 1.51 | | | |
| G-16-22 | | | | | | | | | | 0.34 | 0.17 | 2.00 | | | |
| G-16-23 | | | | 1.27 | 0.79 | 1.61 | | | | 0.75 | 0.49 | 1.52 | | | |
| G-16-24 | | | | 1.28 | 0.81 | 1.59 | | | | 0.82 | 0.41 | 2.00 | | | |
| G-16-26 | 0.50 | 0.43 | 1.18 | | | | | | | 0.39 | 0.33 | 1.18 | | | |
| G-16-28 | | | | 1.22 | 1.36 | 0.90 | 1.00 | 0.86 | 1.17 | 1.25 | 1.62 | 0.77 | | | |
| G-16-29 | 1.00 | 0.72 | 1.39 | 1.28 | 0.81 | 1.59 | | | | 1.65 | 0.95 | 1.74 | | | |
| G-16-31 | 0.37 | 0.18 | 2.06 | | | | 0.32 | 0.17 | 1.84 | 0.32 | 0.11 | 2.90 | | | |
| G-16-32 | 0.47 | 0.58 | 0.80 | | | | | | | | | | | | |
| G-16-33 | | | | | | | 1.08 | 1.01 | 1.06 | | | | | | |
| G-16-34 | | | | | | | 0.62 | 0.41 | 1.52 | 0.64 | 0.47 | 1.36 | | | |
| G-16-35 | 0.30 | 0.38 | 0.78 | | | | | | | | | | | | |
| G-16-36 | | | | | | | | | | 0.49 | 0.37 | 1.32 | | | |
| G-16-37 | | | | | | | | | | | | | | | |
| G-16-38 | 0.65 | 0.72 | 1.18 | | | | 0.59 | 0.48 | 1.23 | 0.89 | 0.60 | 1.48 | | | |
| G-16-39 | | | | 0.49 | 0.28 | 1.74 | 0.50 | 0.30 | 1.66 | 0.48 | 0.23 | 2.09 | | | |
| G-16-41 | 0.51 | 0.16 | 3.27 | | | | | | | | | | | | |
| G-16-42 | 0.51 | 0.63 | 0.82 | | | | | | | | | | | | |
| I-16-01 | | | | | | | | | | 1.10 | 1.10 | 1.00 | | | |
| I-16-02 | 45% | 16% | | 43% | 29% | | 45% | 18% | | 0.9 | 0.48 | 1.88 | | | |
| I-16-03 | 38% | 21% | | | | | | | | | | | | | |
| I-16-04 | 52% | 28% | | 50% | 23% | | 49% | 21% | | 1.2 | 0.95 | 1.26 | | | |
| I-16-05 | 34% | 28% | | | | | 39% | 29% | | 1.2 | 0.95 | 1.26 | | | |
| I-16-07 | 49% | 29% | | | | | | | | | | | | | |
| I-16-08 | 49% | 25% | | 43% | 33% | | 39% | 37% | | 1.3 | 1.4 | 0.93 | | | |
| I-16-09 | 41% | 27% | | 32% | 21% | | 38% | 25% | | 0.64 | 0.53 | 1.21 | | | |
| Y-16-02 | 0.71 | 0.76 | 0.93 | 0.94 | 0.33 | 2.87 | 1.10 | 0.86 | 1.28 | 0.34 | 0.31 | 1.09 | 0.77 | 0.59 | 1.31 |
| Y-16-03 | 0.49 | 0.52 | 0.96 | 0.43 | 0.54 | 0.79 | 0.32 | 0.29 | 1.09 | 0.69 | 0.54 | 1.28 | 0.34 | 0.30 | 1.13 |
| Y-16-04 | 0.58 | 0.34 | 1.72 | 0.98 | 0.53 | 1.84 | 0.74 | 0.48 | 1.54 | 0.84 | | | 0.91 | 0.44 | 2.07 |
| Y-16-05 | 0.61 | 0.26 | 2.32 | 1.21 | 0.54 | 2.27 | 0.84 | 0.52 | 1.63 | 0.73 | 0.38 | 1.92 | 0.78 | 0.41 | 1.90 |
| Y-16-07 | 1.02 | 0.94 | 1.09 | 1.00 | 1.00 | 1.00 | 1.21 | 1.21 | 1.00 | 0.34 | 0.32 | 1.06 | | | |
| Y-16-08 | 0.77 | 0.41 | 1.88 | 0.79 | 0.47 | 1.68 | 0.75 | 0.57 | 1.31 | 0.82 | 0.51 | 1.60 | 0.66 | 0.42 | 1.57 |
| Y-16-09 | 0.88 | 0.59 | 1.48 | 0.99 | 0.76 | 1.30 | 1.22 | 0.82 | 1.48 | 0.75 | 0.61 | 1.23 | 0.34 | 0.30 | 1.13 |
| Y-16-10 | 0.52 | 0.51 | 1.02 | 32% | 39% | | 0.52 | 0.57 | 0.91 | 0.60 | 0.65 | 0.92 | 0.81 | 0.83 | 0.78 |
| Y-16-11 | 0.88 | 0.94 | 0.94 | 0.65 | 0.69 | 0.94 | 0.65 | 0.59 | 1.10 | 0.29 | 0.35 | 0.83 | | | |
| Y-16-12 | 0.94 | 0.57 | 1.64 | 1.11 | 0.55 | 2.00 | 1.08 | 0.46 | 2.32 | 0.46 | 0.25 | 1.84 | 1.11 | 0.59 | 1.88 |
| Y-16-13 | 1.64 | 0.69 | 2.37 | 42% | 17% | | 1.34 | 0.54 | 2.47 | | | | 0.70 | 0.39 | 1.79 |
| Y-16-14 | 0.40 | 0.27 | 1.45 | 0.39 | 0.22 | 1.72 | 0.48 | 0.29 | 1.68 | 0.41 | 0.29 | 1.41 | | | |
| Y-16-15 | 41% | 25% | | 0.86 | 0.74 | 1.17 | 1.12 | 0.82 | 1.37 | 0.38 | 0.24 | 1.58 | | | |

| | PRE-INFUSION | | | 3 MONTHS | | | 6 MONTHS | | | 12 MONTHS | | | 18 MONTHS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PATIENT | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 | CD4 | CD8 | CD4/CD8 |
| Y-16-16 | 0.84 | 0.77 | 1.09 | 0.85 | 0.75 | 1.13 | 0.88 | 0.71 | 1.24 | 1.00 | 0.97 | 1.03 | 0.97 | 0.77 | 1.26 |
| Y-16-17 | 0.79 | 0.74 | 1.07 | 0.99 | 0.85 | 1.16 | 0.77 | 0.92 | 0.84 | 0.30 | 0.30 | 1.00 | 1.28 | 1.31 | 0.98 |
| Y-16-18 | 0.36 | 0.19 | 1.89 | 0.36 | 0.19 | 1.89 | 0.36 | 0.19 | 1.89 | | | | 0.28 | 0.19 | 1.47 |
| Y-16-20 | 26% | 35% | | 1.29 | 1.62 | 0.80 | 1.32 | 1.32 | 1.00 | 0.29 | 0.32 | 0.91 | 1.15 | 1.46 | 0.79 |
| Y-16-22 | 1.64 | 0.80 | 2.04 | 1.54 | 0.71 | 2.18 | 0.50 | 0.23 | | 1.64 | 0.89 | 1.84 | | | |
| Y-16-24 | 0.86 | 1.09 | 0.79 | | | | 0.47 | 0.39 | 1.21 | | | | 0.69 | 0.46 | 1.50 |
| Y-16-25 | 1.04 | 0.84 | 1.24 | | | | | | | 0.38 | 0.24 | 1.58 | | | |
| Y-16-26 | | | | | | | | | | | | | 1.14 | 0.49 | 2.33 |
| DM-16-02 | | | | 0.44 | 0.28 | 1.58 | 0.53 | 0.33 | 1.61 | | | | 0.52 | 0.32 | 1.62 |
| DM-16-03 | | | | | | | 1.61 | 1.34 | 1.20 | 0.44 | 0.39 | 1.13 | 0.79 | 0.51 | 1.55 |
| MEAN | 0.94 | 0.59 | 1.60 | 0.86 | 0.56 | 1.53 | 0.84 | 0.57 | 1.46 | 0.85 | 0.62 | 1.39 | 0.80 | 0.55 | 1.61 |
| 95% CI | 0.13 | 0.06 | 0.13 | 0.09 | 0.07 | 0.19 | 0.10 | 0.08 | 0.13 | 0.42 | 0.28 | 0.19 | 0.12 | 0.09 | 0.21 |

# APPENDIX 5

# FACTOR VIII INHIBITOR RESULTS FOR SNBTS CLINICAL TRIAL HP016

# FACTOR VIII INHIBITOR RESULTS FOR SNBTS CLINICAL TRIAL HP016

| STUDY NUMBER | INHIBITORS (PREINF) | INHIBITORS (3m) | INHIBITORS (6m) | INHIBITORS (12m) | INHIBITORS (18m) |
|---|---|---|---|---|---|
| A-16-01 | Y (0.6) | N | N | N | NT |
| A-16-02 | N | Y (0.2) | N | NT | NT |
| A-16-03 | N | N | N | N | NT |
| A-16-04 | N | Y (0.2) | NT | NT | NT |
| A-16-05 | Y (0.6) | Y (0.4) | N | Y (1.0) | NT |
| A-16-06 | NT | N | N | N | NT |
| A-16-07 | Y (0.6) | Y (4.0) | Y (1.0) | N | NT |
| A-16-10 | N | NT | NT | N | NT |
| A-16-12 | NT | Y (0.4) | Y | NT | NT |
| A-16-13 | NT | NT | N | N | NT |
| A-16-14 | N | N | N | N | NT |
| A-16-15 | NT | N | NT | NT | NT |
| A-16-16 | N | NT | N | N | NT |
| A-16-17 | NT | NT | NT | NT | NT |
| A-16-18 | NT | NT | N | NT | NT |
| A-16-20 | NT | NT | NT | NT | NT |
| B-16-01 | N | N | N | N | NT |
| B-16-02 | N | N | N | N | N |
| B-16-03 | N | N | N | N | N |
| B-16-04 | N | N | N | N | NT |
| B-16-05 | N | N | N | N | N |
| B-16-06 | N | N | N | NT | NT |
| B-16-07 | N | N | N | N | N |
| B-16-08 | N | N | N | N | NT |
| B-16-09 | N | N | N | N | N |
| B-16-10 | N | N | N | N | N |
| B-16-11 | N | N | N | N | NT |
| B-16-12 | N | NT | NT | N | NT |
| B-16-14 | N | N | N | NT | NT |
| B-16-15 | N | N | N | N | N |
| B-16-16 | N | N | N | N | N |
| B-16-17 | N | N | N | N | N |
| B-16-18 | N | N | N | N | N |
| B-16-19 | N | N | N | N | N |
| B-16-20 | N | N | N | N | N |
| B-16-21 | N | N | Y | N | N |
| B-16-22 | N | NT | Y | N | N |
| B-16-23 | N | NT | NT | N | N |
| B-16-24 | N | N | N | N | N |
| B-16-25 | N | N | N | N | NT |
| B-16-26 | N | N | N | N | NT |
| B-16-27 | N | NT | N | N | N |
| B-16-28 | N | NT | N | N | N |
| B-16-29 | N | N | NT | N | N |
| B-16-30 | N | N | N | N | NT |
| B-16-31 | N | N | NT | N | N |
| B-16-32 | N | NT | N | N | NT |
| B-16-33 | N | N | N | N | N |
| B-16-34 | N | N | N | N | NT |
| B-16-35 | N | N | N | N | N |
| B-16-36 | N | N | NT | N | NT |
| B-16-37 | N | N | N | N | N |
| B-16-38 | NT | NT | N | N | NT |
| B-16-39 | N | N | N | NT | NT |
| B-16-40 | N | N | N | N | N |
| B-16-41 | N | NT | N | N | N |
| B-16-42 | N | N | NT | NT | NT |
| B-16-43 | NT | N | N | Y (0.3) | NT |
| B-16-44 | N | NT | N | N | N |
| D-16-01 | N | N | N | N | N |
| D-16-02 | N | N | N | N | N |
| D-16-03 | N | N | N | NT | NT |

| STUDY NUMBER | INHIBITORS (PREINF) | INHIBITORS (3m) | INHIBITORS (6m) | INHIBITORS (12m) | INHIBITORS (18m) |
|---|---|---|---|---|---|
| D-16-04 | N | NT | N | N | NT |
| D-16-05 | N | NT | N | NT | NT |
| D-16-06 | N | NT | N | N | NT |
| D-16-07 | NT | NT | N | N | NT |
| D-16-08 | N | NT | N | N | NT |
| D-16-09 | N | NT | N | NT | NT |
| D-16-10 | Y (0.4) | Y (0.4) | Y(0.34) | NT | NT |
| D-16-21 | N | NT | NT | NT | NT |
| D-16-22 | N | NT | NT | NT | NT |
| D-16-23 | N | NT | N | NT | NT |
| D-16-24 | NT | N | NT | NT | NT |
| D-16-25 | NT | NT | NT | NT | NT |
| E-16-01 | N | NT | N | N | N |
| E-16-02 | N | N | N | N | N |
| E-16-03 | NT | N | N | N | NT |
| E-16-04 | N | NT | N | NT | N |
| E-16-05 | Y(154) | Y(696) | Y(513) | Y(357) | NT |
| E-16-06 | N | NT | N | N | N |
| E-16-07 | N | N | N | N | NT |
| E-16-08 | N | N | N | N | N |
| E-16-09 | N | NT | N | N | N |
| E-16-10 | N | N | Y(21.7) | Y(2.1) | NT |
| E-16-11 | N | N | N | N | NT |
| E-16-12 | N | N | N | N | N |
| E-16-13 | N | N | NT | NT | NT |
| E-16-14 | N | N | N | N | NT |
| E-16-15 | N | NT | N | NT | N |
| E-16-16 | N | N | NT | N | NT |
| E-16-17 | NT | N | N | N | N |
| E-16-18 | N | N | N | N | NT |
| E-16-19 | N | NT | N | NT | NT |
| E-16-20 | N | N | N | N | NT |
| E-16-21 | N | N | N | N | NT |
| E-16-22 | N | NT | N | N | N |
| E-16-23 | Y(2.5) | NT | NT | NT | NT |
| E-16-24 | N | NT | NT | N | NT |
| E-16-25 | N | N | N | NT | NT |
| E-16-26 | N | N | NT | NT | NT |
| E-16-27 | N | NT | NT | NT | NT |
| E-16-28 | N | N | N | NT | NT |
| E-16-29 | N | N | N | NT | NT |
| E-16-30 | N | N | N | NT | NT |
| E-16-31 | N | N | NT | NT | NT |
| E-16-32 | N | N | N | NT | NT |
| E-16-33 | N | N | N | N | NT |
| E-16-34 | N | N | NT | NT | NT |
| G-16-01 | N | N | N | N | NT |
| G-16-02 | N | NT | NT | N | NT |
| G-16-03 | N | N | N | N | NT |
| G-16-04 | NT | NT | N | NT | NT |
| G-16-05 | N | NT | N | N | NT |
| G-16-06 | N | N | N | N | NT |
| G-16-08 | N | N | N | N | NT |
| G-16-11 | N | NT | N | N | NT |
| G-16-12 | N | N | N | N | NT |
| G-16-13 | N | NT | N | N | NT |
| G-16-14 | NT | NT | NT | N | NT |
| G-16-15 | N | N | NT | N | NT |
| G-16-16 | N | N | NT | N | NT |
| G-16-17 | NT | N | NT | N | NT |
| G-16-18 | NT | NT | N | N | NT |
| G-16-19 | N | N | N | N | NT |

| STUDY NUMBER | INHIBITORS (PREINF) | INHIBITORS (3m) | INHIBITORS (6m) | INHIBITORS (12m) | INHIBITORS (18m) |
|---|---|---|---|---|---|
| G-16-21 | NT | NT | N | N | NT |
| G-16-22 | NT | N | N | N | NT |
| G-16-23 | N | N | NT | N | NT |
| G-16-24 | NT | N | NT | NT | NT |
| G-16-25 | N | NT | NT | N | NT |
| G-16-26 | N | NT | N | N | NT |
| G-16-28 | N | N | NT | N | NT |
| G-16-29 | N | N | NT | N | NT |
| G-16-31 | NT | NT | N | N | NT |
| G-16-32 | N | NT | N | N | NT |
| G-16-33 | NT | NT | NT | NT | NT |
| G-16-34 | N | NT | N | N | NT |
| G-16-35 | N | NT | NT | NT | NT |
| G-16-36 | NT | N | NT | N | NT |
| G-16-37 | N | NT | NT | NT | NT |
| G-16-38 | N | NT | Y(4.41) | Y(4.4) | NT |
| G-16-39 | NT | N | N | N | NT |
| G-16-41 | N | NT | NT | NT | NT |
| G-16-42 | N | NT | NT | NT | NT |
| I-16-01 | NT | NT | NT | N | NT |
| I-16-02 | N | N | N | N | NT |
| I-16-03 | N | N | N | NT | NT |
| I-16-04 | N | N | N | N | NT |
| I-16-05 | N | NT | N | N | NT |
| I-16-07 | N | N | NT | NT | NT |
| I-16-08 | N | N | N | N | NT |
| I-16-09 | N | N | N | N | NT |
| Y-16-02 | N | N | N | N | N |
| Y-16-03 | N | N | N | N | N |
| Y-16-04 | N | N | N | N | N |
| Y-16-05 | N | N | N | N | N |
| Y-16-07 | N | N | N | N | N |
| Y-16-08 | N | N | N | N | N |
| Y-16-09 | Y | Y | Y | Y | N |
| Y-16-10 | N | N | N | N | N |
| Y-16-11 | N | N | N | N | NT |
| Y-16-12 | N | N | N | N | N |
| Y-16-13 | N | N | N | N | N |
| Y-16-14 | N | N | N | N | N |
| Y-16-15 | N | N | N | N | NT |
| Y-16-16 | N | N | N | N | N |
| Y-16-17 | N | N | N | N | N |
| Y-16-18 | N | N | N | N | N |
| Y-16-20 | N | N | N | N | N |
| Y-16-22 | N | N | N | N | NT |
| Y-16-24 | N | NT | N | N | NT |
| Y-16-25 | N | NT | NT | N | N |
| Y-16-26 | N | NT | NT | NT | NT |
| DM-16-02 | N | N | N | N | N |
| DM-16-03 | NT | NT | N | N | N |

# APPENDIX 6

# ADVERSE EVENT DATA FOR SNBTS CLINICAL TRIAL HP016

# ADVERSE EVENT REPORT

Product SNBTS HPVIII

Patient GRO-A Age 53

## Clinical Background

Mr. GRO-A has moderate haemophilia A with a basal factor VIII of 0.08iu/ml. For bleeds he has been treated over the years with cryoprecipitate, SNBTS Z8 and more recently SNBTS HPVIII. His first infusion of HPVIII was on 3rd February 1993 and until his operation in June 1993 he received 68 infusions. On 10th June he underwent arthroscopy of his right knee joint and a calcified loose body was removed. Pre-operatively he received a bolus infusion of HPVIII to secure haemostasis over surgery. Thereafter he received HPVIII (Batch 20365) by continuous infusion using a syringe pump until 6 days post-operatively. This procedure worked well and reasonable factor VIII levels were secured.

Mr. GRO-A was readmitted on 1st July with a large apparently spontaneous haematoma on his left forearm. Measurement of his factor VIII revealed that it had fallen to <0.01iu/ml and that an anti-factor VIII inhibitor of 18 BU/ml was present.

Since then he has received treatment with human and porcine factor VIII and Feiba.

## Comment

It is unusual for individuals with moderated haemophilia A to develop anti-factor VIII inhibitors particularly at Mr. GRO-A's age when he had received many previous infusions of factor VIII containing products. The inhibitor appears to have arisen in response to the factor VIII received to cover the surgery.

GRO-C

Christopher A. Ludlam,
Director, Haemophilia and Haemostasis Centre,
Royal Infirmary, Edinburgh.

1st November 1993

# ADVERSE EVENT REPORT

Product SNBTS HPVIII

Patient GRO-A (Born GRO-A 1991)

## Clinical Background

The patient has severe haemophilia A with a basal factor VIII of <0.01iu/ml. He also has phenylketonuria which is apparently being adequately controlled by dietary modification.

He received his first injection of factor VIII concentrate (SNBTS HPVIII) on 18th July 1992. Thereafter he received 8 infusions until March 1993.

On a routine inhibitor screening test on 25th March 1993 there was a suggestion that an anti-factor VIII inhibitor may have developed but the plasma sample was small and it is extremely difficult to obtain a further blood sample from the child. It appeared that the inhibitor was less than 1 BU/ml.

Further investigation on subsequent samples revealed the presence of an anti-factor VIII inhibitor with a maximum level of 6 BU/ml.

## Comment

There is nothing unusual about this child's anti-factor VIII inhibitor. As it typical of such inhibitors it arose after 9 infusions of HPVIII. I have no reason to suspect that it was due to a defect in the HPVIII which the child received.

GRO-C

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Director, Haemophilia and Haemostasis Centre,
Royal Infirmary, Edinburgh.

25th October 1993

# APPENDIX 7

# PROTOCOL FOR SNBTS CLINICAL TRIAL HP016

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
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GRO-C

SCOTTISH 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 Miss Jane Pelly
Scottish National Blood Transfusion Service
Product Services Department
Livingstone House
39 Cowgate
Edinburgh
EH1 1JR

Signed ..... Date .....

# CONTENTS

## 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 opinion 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°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.

## 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°C

### 6.2.2 *Follow Up Samples*

3 MONTHS, 6 MONTHS, 12 MONTHS POST FIRST INFUSION

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-HBc, anti-HCV, anti-parvovirus B19
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 report form 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 detrmine 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 Miss Jane Pelly 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 B Cuthbertson, PFC Quality Assurance Manager or his deputy (Tel No GRO-C GRO-C ). 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 Thera | Month 3 | Month 6 | Month 12 |
|---|---|---|---|---|
| Full Blood Count | X | X | X | |
| Serum Stored (5ml) | X | X | X | |
| Lymphocyte Subsets | X | X | X | |
| Factor VIII Inhibitors | 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.



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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.

# APPENDIX 8

# ADDENDUM TO PROTOCOL FOR SNBTS CLINICAL TRIAL HP016

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 (HP016)

**Participating Centres:**

Aberdeen
Belfast
Dundee
Edinburgh
Glasgow (GRI & Yorkhill)
Inverness
Dumfries & Galloway

## ADDENDUM TO PROTOCOL
**25 April, 1994**

**S. J. Pelly**
**SNBTS Product Services Manager**

**Tel:** GRO-C
**Fax:**

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

**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 (HP016)**

## Addendum to Protocol Dated: .....

**Clinical Investigator:**

Name .....

Title .....

Address .....

.....

Signed ..... Date .....

**Monitor:**

Ms S J Pelly
SNBTS Product Services Department
Livingstone House
39 Cowgate
Edinburgh
EH1 1JR

Signed: _____

Date: _____

## 1. Introduction

This Addendum to trial HP016 is to cover the period following the main trial until a product licence is granted. Patients receiving HP8 will be maintained on an adjunct to the trial under the conditions contained in this Addendum. This will be agreed by the clinical investigators and the SNBTS and will be signed in confirmation of such agreement. The Addendum will be approved by the SOHHD, Medicines Control Agency and the Local Ethics Committees.

## 2. Follow Up Samples

Samples at 3 months, 6 months and 12 months post first infusion will be taken as specified in the main protocol.

Thereafter samples should be taken at 6 monthly intervals.

1. Lymphocyte subsets.
2. Liver function test (including ALT or AST)
3. APTT screening test for Factor VIII inhibitors.
4. Virology (HBsAg, anti-HAV, anti-HBs, anti-HCV, anti-$B_{19}$) until 2 consecutive samples positive.
5. Serum sample stored at -40°C -5ml (for children <5 years 1ml).

A summary of this sampling schedule appears in Appendix 1.

## 3. Documentation

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 print out, signed and dated, is acceptable.

The Addendum Laboratory Report Form (Form $C_a$) shall be completed for each patient, on which the results of those tests required as stated in this Addendum shall be recorded.

The Addendum Virology Report Form (Form $D_a$) shall be completed for each patient, on which the results of those tests required as stated in this Addendum shall be recorded

## 4. Adverse Event Reporting

Any serious adverse event which occurs subsequent to the infusion of HP8 should be reported immediately to the Quality Assurance Manager, Protein Fractionation Centre, or his deputy (031-664-2317). A serious adverse event includes the death of any patient in the study from whatever causes even if apparently unrelated to the trial medication. This is necessary as the SNBTS must report such reaction to the Medicines Control Agency promptly. Minor adverse events would be reported at the next regular monitoring meeting.

APPENDIX I

# SAMPLING SCHEDULE

| | 18 MONT | 24 MONT | 30 MONT | 36 MONT |
|---|---|---|---|---|
| Lymphocyte Subsets | X | X | X | X |
| Liver Function Test (including ALTor AST) | X | X | X | X |
| APTT Screening Test -Factor VIII Inhibitors | X | X | X | X |
| Virology | X | X | X | X |
| Serum stored 5ml | X | X | X | X |

# SUMMARY TABLES



SBTS0003795_062_0215

# SEROCONVERSION TO PARVOVIRUS (B19)

**HP012**

Y-12-01 became positive to B19 at 12 months

Y-12-06 became positive to B19 at 3 months

**HP016**

A-16-13 became positive to B19 at 3 months

A-16-17 became positive to B19 at 12 months

B-16-33 became positive to B19 at 3 months

B-16-34 became positive to B19 at 3 months

B-16-36 became positive to B19 at 6 months

B-16-22 became positive to B19 at 3 months

E-16-13 became positive to B19 at 12 months

E-16-15 became positive to B19 at 18 months

E-16-16 became positive to B19 at 6 months

E-16-17 became positive to B19 at 6 months

E-16-22 became positive to B19 at 12 months

Y-22-18 became positive to B19 at 3 months

# FACTOR VIII INHIBITOR DEVELOPMENT

**HP013**

E-13-05 developed inhibitors to factor VIII (1.0 BU) at 6 months which were not present at 12 months

G-13-07 developed inhibitors to factor VIII at 12 months

G-13-18 developed inhibitors to factor VIII (1.3 BU) at 6 months which were still present at 12 months but had disappeared at 18 months.

**HP016**

A-16-02 developed inhibitors to factor VIII at 3 months which were not present at 6 months.

B-16-21 developed inhibitors to factor VIII at 6 months which were not present at 12 months

B-16-32 developed inhibitors to factor VIII at 6 months which were not present at 12 months

B-16-43 developed inhibitors to factor VIII at 6 months which were also seen at 12 months

E-16-03 developed inhibitors to factor VIII at 18 months

E-16-10 developed inhibitors to factor VIII at 12 months

G-16-38 developed inhibitors to factor VIII at 6 months which were also seen at 12 months