APPENDIX TWENTY

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE
Headquarters Unit
Ellen's Glen Road
ÍO/f Edinburgh EH 17 7QT
031-664 2317
6th January 1983
Dr C D Forbes
Consultant Physician . ,
University Department of Medicine
10 Alexandra Parade
GLASGOW
G31 2ER

Dear Charles
New SNBTS Factor VIII Concentrates
I thought I ought to let you know, in advance, that we (PFC) hope to have a new factor VIII concentrate available by the late Spring of 1983 for preliminary studies (in vivo yield and half-life). The new product will be one which is of a higher potency than the existing intermediate preparation, and will have a much lower fibrinogen content that the latter. The production methods have to remain a secret at the moment until patenting

NOT RELEVANT 08/06/2010

formalities have been finalised. However, prior to the initiation of the clinical studies the basis of the methods will be discussed with you.
It is our intention, once this new product has been shown to have an ¿n vivo yield and J life comparable to the intermediate VIII concentrate, to come to you soon thereafter with the same preparation, but which has now been heat-treated. Once again we would wish to examine the in vivo yield and i life of the heat-treated product.
I therefore write to enquire, in advance, whether you would be prepared to collaborate with us and undertake the necessary studies. I had envisaged that we would probably need only a total of 5 severe patients for this work - ideally the same 5 getting both the new and heat-treated preparations - and wonder whether you would liaise with Christopher Ludlam as I have also written to him. Perhaps Glasgow could provide 3 patients and Edinburgh 2 patients.
Finally, I would very much value your thoughts on doing a similar exercise on a couple of severe von Willebrand Syndrome patients. I am most anxious that at the end of the day we know, or not, whether we have a "safer" product for the von Willebrand patients as a whole.
Best wishes for 1983. /' \
Kindest regards, \
Yours sincerely
National Medicai Director. Dr John D.Cash National Administrator Miss Morag Corr.

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE
Headquarters Unit
Ellen's Glen Road
Edinburgh EH17 7QT
031-664 2317
T3fh June 1983

JDC/EP
Dr C A Ludlam
Consultant Haematologist
Royal Infirmary
EDINBURGH

Dear Chris

Heat Treatment of Factor VIII Concentrate
I promised to follow up our telephone conversation with a note which would include a proposed protocol and information which may be of interest to you and the Infirmary Ethics Committee, /W-W'k p.f /
T '
Perhaps I should first emphasise that the plan I^proposed at the last Scottish Haemophilia/BTS Directors' WP still stands - wé intend to come back to you and Charles Forbes with a matched pair (heated/unheated) of factor VIII concentrates. We had, in fact, hoped to be able to move forward at this time but unfortunately the unheated part of the pair proved to be unacceptably pyrogenic in the rabbit test. Thus we have at the moment a small amount of heat treated material only.
John Watt and I feel that it would be most unfortunate not to use this first heat treated batch on its own. If you were able to show in 2 or 3 patients that its behaviour was broadly similar to previous data you, Chris and Frank have collected on cryoppt. and intermediate VIII then it would

considerably boost the confidence of the PFC team and, I should hasten to add, the Licensing Authority within Medicines Division who are being kept fully briefed on the work up here (thus no Clinical Trial Certificate or Exemption required).
Finally, in this preamble, I would turn your attention to the point you rightly raised.with regard to the possibility of molecular damage during . the heat treatment process. John and I would be delighted if you wished to f take a couple of the available vials and test them in your own laboratory against your known antibodies. You will be interested in the enclosed information produced by Dr Dawes. Her data suggest, using immunoassays, that there does not appear to be damage following heat treatment with respect of VIII:CAg, VIII:RAg, thrombospondin, BTG and PF4.
I enclose a suggested protocol and the profile of batch NY.761. The only comment with regard to the profile is that the osmolality is higher than existing products (it will be suitably adjusted in future batches). We suggest that you make each vial of this batch (NY.761) up with a volume of 25 ml. distilled water. I've suggested a dose of 20 i.u./Kg. which for a 70 Kg. patient will require 10 vials of this particular batch. Thus you will have more than enough to do 3 patients.

National Medica! Director Dr John D.Cash
National Administrator Miss Morag Corrie

Dr C A Ludlam 13th June 1983
I've sent Frank Boulton a copy of this letter and enclosures as he has kindly agreed to co-ordinate matters on my behalf. Frank will liaise with you closely, as before, and will make the necessary arrangements to get the vials of batch NY.761 down to you when you are ready to go.

Sincere thanks, good luck and best wishes.
Yours sincerley
John D Cash

p-s-: We would much appreciate it if, after you've done the 3 severe haemophiliacs and if there was a sufficient number of vials from batch NY.761 left over, you would consider giving an infusion into a Von Willebrand's Syndrome patient. We would all like to know whether it is efficacious.
Enel.
Copy to :
Dr Boulton
Mr Watt
Dr Foster

--

PROPOSED PROTOCOL FOR NY.761: CLINICAL STUDIES
(a) Patients: (i) Maximum number required 3.
(ii) All severe haemophiliacs,
(iii) If possible (not essential) patients are those

on whom data has already been generated with
regard to cryoppt. and/or intermediate VIII.
(b) Infusion dose: 20 i.u./kg. b.w.
(c) Infusion time: 20 minutes
(d) Sampling times:
Before infusion
End of infusion (+ 20 minutes)
+ 60 minutes
+ 180 minutes
+ 360 minutes
24 hours after
+ 10 days
(e) Measurements:
(i) Essential:
(ii) Optional:
Factor VIII:C
Factor VIII:CAg
Factor VIII:RAg
Temp: BP: Pulse (i hourly)
VIII inhibitor bioassays (as appropriate)
? Look for ppt. lines (? Dawes' assays) for inhibitors
to VIII and other proteins.
? Look for acute increase in T-cell suppressor cells.
? Anti-HBs (rise in titre of patient already +ve).

ANALYTICAL PROFILE OF HEAT TREATED FACTOR VIII BATCH NO. 761
When reconstituted with 25ml of Water for Injections Factor VIII 761
will have the following analytical profile:-

Factor VIII:C Content	145 I.U.
Total Protein	14.4 g/litre
Fibronogen	5.2 g/litre
Sodium	40.4 mmol/1
Potassium	0.01 mmol/1
Chloride	11.9 mmol/1
Citrate	12.3 mmol/1
pH	6.8
Sorbitol	54 g/litre
Osmolality	509
Zinc	3.6 ppm
Cellulose Acetate Electrophoresis	
Rabbit Pyrogen Test	
Limulus Pyrogen Test (endotoxin equiv.)	
Normal	

3.8°/6 rabbits
▪^0.5 ng/ml
Acute Toxicity
HBsAg
Sterility Test
Pass
Negative
Pass
Isoagglutinin (.Indirect Coombs Test)
Aj A2 B 0
1/8 1/4 1/8 Negative

RJP/ÎMCK 31st October 1983
Dr F Boulton - Edinburgh BTS (8 vials)
Dr R Crawford - Glasgow & West of Scotland (21 vials)

I have just dispatched vials of the most recent batch of heat treated FVIII to yourself as previously arranged by Dr Cash.
Below is a summary of the analytical profile of this batch of material.
FVIII Content 155 IÜ
Reconstitution Volume 10 ml
Pyrogen 2.5 in 3 rabbits
Acute Toxicity Test Pass
Sterility Test Pass
Total Protein 31.2 g/litre
Fibrinogen 7.8 g/litre
% Clot 25
Sodium 248 mmol/1
Chloride 137 mmol/1
Citrate 50.4 mmol/1
pH 6.78
Zinc 1.9 ppm
Osmolality 429 raOSm/kg
You will note that the sodium level is higher than the limit of 200 mmol/1 and citrate and pH values are on the borderline (in-house limits of 50 mmol/1 are 6.8 - 7.4). Since these limits are those applied to the existing intermediate concentrate and in the absence of a formal specification for the new product I have taken the view that this batch of material is sutiable for issue.
I think, however that it may be prudent if, as a clinical trial material, this decision be confirmed by yourself prior to issue of the material to the clinician responsible for administration.
With kind regards
Yours sincerely

Dr R J PERRY
cc Mr J G Watt •

RJP/LAB
9th November,1983
Dr. R... Crawford,
Glasgow & West of Scotland
Blood Transfusion Service,
Law Hospital,
CARLUKE,
Lanarkshire.
Dear Bob,
HEAT TREATED FVIII - 2HT 004
Further to my recent letter regarding this material giving details of the timshed product analytical specification, it was sointed out to me that I omnutted the sorbitol result from this data.
The residual sorbitol concentration in the product reconstituted with 10r-l 2HT So" InJections is 1.35g/100ml which compares with 1.70g/100ral for
With kind regards.

Yours sincerely,
R.J. PERRY

Quality Control Inspector

THE ROYAL INFIRMARY OF EDINBURGH
HAEMATOLOGY DEPARTMENT
Dr. A. C. Parker (Ext. GRO:C) LAURISTON PLACE
Dr. C. A. Ludlam (Ext. GRO:C) EDINBURGH EH3 9YW
Senior Chief M.L.S.O.
Mr. P. F. J. Newman (Ext. GRO:C)
Telephone: 031-229 2477
Your Ref.:
Oar Ref.: CAL/PMW
Ilth January, 1984
Dr. J.D. Cash,
Blood Transfusion Service,
Ellen's Glen Road,
Edinburgh.
Dear John,
Heat Treated Factor VIII Batch NY76I
I write to let you know the outcome of infusing the heat treated factor VIII. The above batch of material was given to a single severe haemophiliac on three separate occasions. I enclose a copy of the results that Chris Prowse obtained but we have confirmatory studies from our own Department. As you can see the recoveries and survival times were reasonable.
Infusions were accompanied by reactions on all three occasions. On the first the recipient had a short episode of diarrhoea beginning an hour after the infusion. On the second and third occasion he felt ill towards the end of each infusion. He developed transient central chest pain, pallor and wretching. There was no change in his pulse, BP or temperature. To ascertain whether this was likely to be an organic reaction to the concentrate we gave him a 'placebo' infusion of ordinary SNBTS factor VIII. He was told that it was the heated material and the infusion protocol was identical. He had no adverse reaction to this standard product. I therefore have to

conclude that this batch of material genuinely gave rise to significant and unacceptably adverse reactions in the recipient.
I hope this information is of use to you in the further development of hepatitis reduced factor VIII concentrates.
With best wishes,

Yours sincerely, C.A. Ludlam

Consultant Haematologist
o.e. Dr. C.V. Prowse
Dr. F.E. Boulton
Mr. J. Watt J
Dr. CD. Forbes

JDC/MM 16th January 1984
Dr C Ludlam
Department of Haematology
Royal Infirmary
EDINBURGH

Dear Christopher

Your letter of the 11th January arrived as I was about to write to you to convey ray thanks for your continued support and assistance.
The information contained in your letter is important and Ï am bound, at the present time, to share your conclusions. The absence of changes in the pulse/BP temperature are a little mystifying but may indicate that the problem could have been due to the unusual sorbitol content of this particular batch.
It is our- hope that by April 1984 we will have a further batch of material for you: -with further improvements on heat treatment and low sorbitol content.
Again, sincere thanks for your help.
Best wishes for 1984.
Kindest regards.
Yours sincerely

John D Cash
Dr Boulton

THE ROYAL INFIRMARY OF EDINBURGH
HAEMATOLOGY DEPARTMENT
Db A C Parker
Dr. C. A. Ludlam
(Ext. GRO:C)
(Ext. GRO:C
Senior Chief M.L.S.O.
Mr. P. F. J. Newman (Ext. GRO:C
Your Ref. :

Our Ref.: CAL/PMW
LAURISTON PLACE
EDINBURGH EH3 9YW
Telephone: 031-229 2477

I4th February, 1984

Dr.P.R. Foster,
Scottish National
Blood Transfusion Service,
P.F.C.
Ellen's Glen Road,
Edinburgh.

Dear Peter,

Thank you for your letter of loth February. I note the data on the new factor VIII product. I will need to think about it further.
So far as Batch I of the heat treated material is concerned, I personally think that it is not worth the effort to try and establish the cause of the reaction in my patient. The project has moved on since these infusions and I think that it is more important that we concentrate on the final product.
Thank you very much looking out the immunoglobulin data. I look forward to receiving results on Defix as soon as they are available.

With best wishes,
Yours sincerely

C.A. Ludlam
Consultant Haematologist
PROTEIN FRACTIONATION CENTRE
Received:
File No: 2-in <p\MH
Refer to
Action taken

ANALYTICAL PROFILE OF HEAT TREATED FACTOR VIII BATCH NO. ZHT004
When reconstituted with 10ml of Water for Injections Factor VIII
ZHT004 will have the following analytical profiler-
Factor VIII:C Content
Total Protein
Fibrinogen
Sodium
Potassium
Chloride
Citrate
pH
Sorbitol
Osmolality
Zinc
Acute Toxicity
HBsAg

Sterility Test
15.5 IU/ml
31.2 g/litre
7.8 g/litre
248 mmol/1
0.16mmol/l
137 mmol/1
50.4 mmol/1
6.78
13.5 g/litre
429 mOsm/kg
1.9 ppm
Cellulose Acetate Electrophoresis Normal
Rabbit Pyrogen Test 2.5°/3 rabbits
Limulus Pyrogen Test (Endotoxin equiv.) °" 4.5 ng/ml
Pass
Negative
Pass
Isoagglutinin (Indirect Coombs Test)
Ai, A2 B 0
1/64 1/8 1/16 Negative

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE
Headquarters Unit
Ellen's Glen Road
Edinburgh EH17 7QT
031-664 2317
13th March 1984
Dr C D Forbes
University Department of Medicine
Royal Infirmary
10 Alexandra Parade
GLASGOW
G31 2ER

Dear Charles

I have just received preliminary results of your heat treated factor VIII infusion studies. I would be most grateful if you would convey my sincere thanks to your colleagues for all the effort that they have put into this study.
Three comments:
1. Could we please have the doses given to each of the three patients, their respective body weights and the batch numbers?
2. You will recall that Christopher Ludlam's patient had some unexplained clinical symptoms with batch 1. Did any of your patients react adversely to the product?
3. Is '>'}'4flHnP> a mild/mod haemophiliac? candidate for follow-up of LFTs?
If so, I wonder if he is a
Kindest regards,
Yours sincerely
John D Cash
Copy to:

Dr Perry
'FÎ0TEIN FRACTIONATION CENTiUC -5
1 £ KAR 1984
National Medical Director Dr John D Cash
National Administrator Miss Morag Corni

UNIVERSITY OF GLASGOW
Haemostasis and Thrombosis
Research Unit
Regional Haemophilia
Reference Centre
University Department of Medicine
Royal Infirmary
10 Alexandra Parade
Glasgow G31 2ER
Tel: 041-552 3535 Ext. GRO:C

15th March, 1984.

Dr.J.D. Cash,

Scottish National Blood Transfusion Service,
Headquarters Unit,
Ellen's Glen Road,
Edinburgh. EH17 7QT.
Dear John,
The following points from your letter -
„is a severely affected patient.
You will have had multiple infusions since the material
was given and probably not worthwile following from that
point of view. In any case, we are following the liver
function tests routinely in all our patients now.
Point 2 - none of the patients had any reactions
whatsoever and we certainly saw nothing like what Chris Ludlam
had.
Point 1
Wt 86Kg Batch No. ZHT004 6 vials
:: Wt 62Kg Batch No. ZHT004 5 vials
Wt 60Kg Batch No ZHT004 5 vials
Recedo 0 2 APR 1984 |
r.C.D.Forbes.

EDINBURGH AND SOUTH-EAST SCOTLAND REGIONAL BLOOD TRANSFUSION SERVICE
Ref: FEB/LñP
23 March 1984
Or J D Cash
National Medicai Director
S N B T S
Headquarters Unit
Ellen's Glen Road
EDINBURGH

Dear John
REGIONAL CENTRE
ROYAL INFIRMARY
EDINBURGH EH3 9HB
Telephones
Department: 031-229 2585
Telex 72163
J
FURTHER FOLLOW-UP TO SORBITOL IN FACTOR »III
Irurírk I366 fr0m the C0Py of .Christ°Pher's letter, that he also thinks his symptoms in the same way that an oral dose would^^^^^^^^^^
You mill also see that he is asking questions about the amount of Sorbitol that is present in the newer products, particularly with a view to high dose therapy in patients with inhibitors etc. You will also see just a little bit of information in the copy of the letter from me from Mrs Irvine in Pharmacy, which indeed indicates that my calculation of an infusion rate of between 1Û and 15g of Sorbitol per hour is what goes in those TPN solutions which contain the Sorbitol. I understand that when such solutions are given, it is most unusual for there to be any form of reaction, such as that which NYF11
experienced.
Kindest regards.
Yours sincerely

Dr F E Boulton
Director: Dr. D. B. L. MCCLELLAND
Consultant: Dr. ANNE SMITH
Consultant: Dr. P. L. YAP
Deputy Director: Dr. F. E. 80ULT0N
Principal MLSO: Mr. R. WILSON

THE ROYAL INFIRMARY OF EDINBURGH
HAEMATOLOGY DEPARTMENT
Dr. A. C. Parker (Ext. GRO-C
Dr. C. A. Ludlam U 2099) LAURISTON PLACE
Senior Chief M.L.S.O,
Mr. P. F. 1. Newman (Ext. GRO-C
Your Ref.:
Our Ref.: CAL/PMW
EDINBURGH EH3 9YW
Telephone: 031-229 2477

21st March, 1984

Dr. F.E. Boulton,
B.T.S.
R.I.E.
Dear Dr. Boulton,
Thank you for your letter of I9th March as a follow-up to that from John Cash.
I agree entirely with your comments, that Dr. Hyam's study bears

little relationship to giving intravenous sorbitol. I think we have to view the unfortunate reactions thataQHfe had as history and I am not sure that we can do much more to investigate why he had them. My only concern is that"if the reactions were " ' " in some way related to Sorbitol,(although it is reassuring that the patients in Glasgow did not have such side-effects) this was with relatively small doses of factor VIII. It would be-important to know whether it was safe to give 10,000 units of the new heat-treated factor VIII intravenously safely. This would presumably contain an appreciable amount of Sorbitol.
I mention this large dose of factor VIII as an extreme example because John Cash has asked menthe new higher purity heat treated product would allow me to do without the necessity of keeping a reserve of high purity factor VIII. I cannot answer this question at present as Peter Poster is unable to give me an exact specification of the new proposed concentrate.
With best wishes.
Yours sincerely,

C.A. Ludlam
Consultant Haematologist

LOTHIAN HEALTH BOARD South Lothian District
Royal Infirmary of Edinburgh PN7
Principal Pharmacist lolhian Drug ,nrormation Cen(rej
Dorothy Anderson M.Sc, M.P.S. Department of Pharmacy
™-0il. 229 2477-t«. GRO:C The Roy.,1 lnli,m.,,v
Launslon l'1.m-
tilinburgh
til J 9VV\
Your Reference:
Our Reference:

22nd March I984
Er Bolton
Registrar
Blood Transfusion
Royal Infirmary
EDINBURGH
Dear Dr Bolton
Sorbitol is a hexa-hydric polyaloohol which is converted to fructose in the liver by sorbitol dehydrogenase. If infused in concentrated solutions at too rapid a rate, it can be converted to lactate instead of glucose, and has been known to cause lactic acidosis. It is still used as a calorie source (lg=4cals) in some combined Total Parenteral Nutrition solutions which are provided commercially - such as Aminoplex 5, where the quantities present are 125g sorbitol/l and 9$ ethanol, as the calorie cource. Sorbitol is used instead of glucose, only because the protein solution can be autoclaved in the presence of sorbitol, without charring, however there is no evidence to show sorbitol has any advantage, otherwise, over glucose, and in most centre T.P.N. is administered from simultaneous infusion of separate containers

of amino acids, glucose and fat, or as is done more frequently from the 3 litre 'big bag' whereby the solutions are aseptically mixed in pharmacy - immediately prior to use.
I hope this answers your question satisfactory.
Yours sincerely
SKA Irvine (Mrs)
Staff Pharmacist

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE
Headquarters Unit
Ellen's Glen Road
Edinburgh EH17 7QT
031-664 2317

28th March 1984

Dr C D Forbes
University Department of Medicine
Royal Infirmary
10 Alexandra Parade
GLASGOW
G31 2ER
Dear Charles
Very many thanks for the latest information on the heat treated product.
I'm now beginning to plan ahead with regard to getting our product put into SHS 'virgin' haemophilia A patients and to this end intend to put up, in due course, a proposal for consideration by the Scottish Haemophilia Centre/Transfusion Centre Directors' Working Party.
I believe it is important that we obtain from your good self the promised data you have on serial liver function tests in haemophilia A patients who have received only PFC material (and/or local cryoppt.).
You will recall you advised the WP that you had data which indicated that the results from the Oxford study (using BPL intermediate product) were identical to yours.
I'd be most grateful if you could let me have (in confidence) a summary of your results. The importance of this work, in the context of the proposed heat treated product studies, lies in the fact that we need to know whether your patients can be used as adequate retrospective controls. Clearly this has now emerged as a crucial factor in the current working in Oxford.
Kindest regards,
Yours sincerely
Copy to:
John D Cash
Dr G McDonald
Dr A E Bell
Dr R J Perry
■'atfonal Medical Director- Dr John D.Cash
National Administrator: Miss Morag Corne

It is clear that all these people knew there was a problem.

NOT RELEVANT 08/06/2010