



## Recruitment passes half way point: 77 patients registered onto the study

77 patients have been recruited into the study so far, with others being screened.

Patients from the following countries have been recruited: -

Australia	2
Belgium	2
Canada	11
France	2
Israel	2
Italy	4
Japan	10
The Netherlands	3
Norway	1
Spain	4
UK	8
USA	28

In February 2007 there were 86 centres in 25 countries with ethical approval for the ITI study and ready to enrol patients. Several centres are in contract negotiation and new centres and countries are still joining the study.

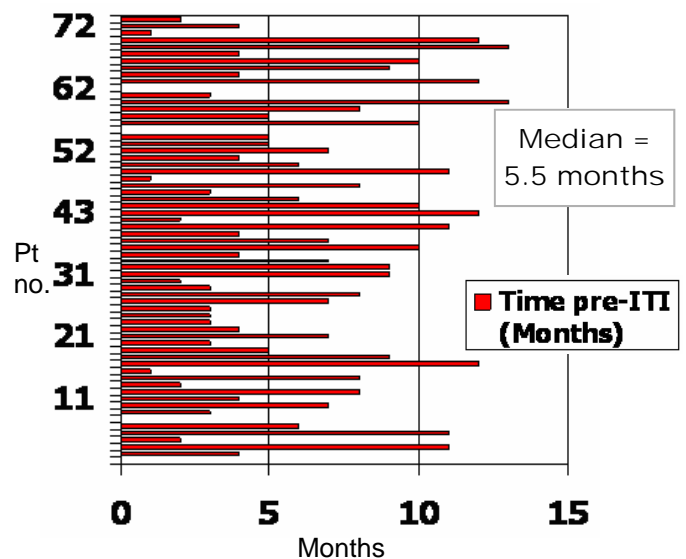
After recruitment to the study with an inhibitor titre >10 BU, patients took a median of 7 months for the inhibitor to decline to <10 BU, at which point they were randomised and started ITI

Of the 67 patients randomised to ITI on study (at a mean age of 27 months, range 6-80 months), 32 have so far achieved a negative inhibitor titre after a mean 8.8 months, 25 have achieved a normal recovery after a mean of 11 months and 22 are tolerant after a mean 14.7 months.

Eight patients fulfilled failure criteria because of a failure of the inhibitor to decline, and 10 were withdrawn for various reasons and 3 were defined by PK parameters as partial responders despite no breakthrough bleeding on prophylaxis.

Eight further patients were withdrawn for various reasons *before* being randomised or starting ITI.

### Time from inhibitor diagnosis to decline to <10BU



Of 138 patients from participating centres who were **not** recruited to the study, 101 did not fulfil the entry criteria, most commonly because they had long standing inhibitors and in some cases had undergone previous attempts at ITI. Of the 37 patients **not** recruited to the study who did fulfil the entry criteria, 21 did not participate because the parents refused randomization and in 16 cases the clinician refused, usually because the patient had very poor venous access. Randomisation remains the biggest barrier to study participation

Charles Hay and Janet Goldstone



## Investigators Meeting Report: Orlando December 2006

Almost 60 investigators attended the Study investigators meeting at ASH in Orlando on 10-Dec-06. The format of inviting all investigators rather than just steering committee members seems popular, and we have gained considerably more feedback and active discussion as a result. The results were reviewed. Recruitment was discussed. We suspect that up to 50% of eligible patients are being lost because of resistance to randomisation. New countries are expected to participate in the next year, however, including Argentina, Brazil, Chile and Mexico. Product subsidies have been negotiated for most of these countries and for Japan.

Potential protocol amendments were discussed. It was agreed that we should collect extended data of patients meeting failure criteria, by means of a separate registry, to determine whether they fulfil partial response criteria, as set down in the protocol, or not. These patients are currently lost from the study once they fulfil failure criteria. Many of the patients who do not fulfil criteria for success nevertheless have low titre inhibitors and respond well to factor VIII. These are partial responders.

One patient had died before randomisation from a traumatic intracerebral bleed. We discussed whether to emphasise the need for the patient's optimal management to take precedence over the study protocol in life-threatening situations at

length, but the consensus view was that this was self-evident and did not need to be re-stated in the protocol.

Data safety was reviewed and it was agreed that the study should continue.

The ITI study has also become an important framework for a growing number of important satellite studies (see pages 3 and 4). This is, in fact, one of the more important functions of the ITI study, since these studies will advance our understanding of the mechanisms underlying immune tolerance, and hopefully lead to evidence based advances in the approach to tolerance induction. The satellite studies Currently in progress or in the planning stage include the genotype study (A Thompson), the factor VIII memory B-cell study (B. Reipert), the RESIST Study (A. Gringeri), a study of B-cell inhibitor epitopes (C. Konigs), and a low level inhibitor study (B. Verbruggen). These studies are reviewed briefly on the next two pages and protocols and further details are available on the website:

[www.itistudy.com](http://www.itistudy.com) .

The next investigators meeting will be held on **Sunday, 8th July 2007** in Room E of the congress centre of the ISTH Meeting in Geneva between 1.00 and 2.15. All investigators are very welcome.

## Study Sponsorship CRM Hay

The original contracts for study sponsorship from **Baxter, Bayer, ZLB and Wyeth** all came up for renewal in 2006/7 and the principal investigators entered into negotiation to extend funding for possibly five more years. These negotiations have either been completed successfully or are close to being agreed. We are extremely grateful to these manufacturers for their continued support of the study.

When the study started, we had assumed that almost all subjects would be tolerised using

recombinant factor VIII, since that was the usual treatment for children in the participating countries at that time. However, there has been increased interest in tolerance induction using plasma-derived products and for that reason, we have negotiated sponsorship contracts also with **Grifols** and **Octapharma**. **Grifols** have generously also agreed to provide a product subsidy, providing factor VIII to tolerise 12 patients in Argentina, Chile and Mexico. We are very grateful to these manufacturers for their support.



# Satellite Studies

## CRM Hay and DM Di Michele

### **The RESIST Study:**

This satellite study is complementary to the International ITI Study. The study has been much delayed by regulatory negotiations in relation to the European Directive. This directs that studies be conducted to GCP/FDA standards and free concentrate be provided. This condition makes such an investigator-led study impossible to fund and conduct. France and Italy have negotiated an exemption for this study which would provide a template for other countries to apply for exemption so that the study may take place in other European countries. The European directive is, of course, no bar to the study starting outside Europe but there may be further regulatory hurdles in the USA.

The study aims to evaluate the potential role of von Willebrand factor-containing factor VIII concentrates in inducing immune tolerance in patients with a poor prognosis. This study, named "RESIST" (REScue Immunotolerance STudy), will include patients that are not eligible for the main International ITI Study: i.e. Starting titre >10 Bu, Peak titre >200 BU, age >8 or previous failed ITI.

These poor prognosis (or high risk) patients will be randomised to ITI with high-dose recombinant or plasma-derived VWF-containing concentrate. The power calculation suggests that 150 patients will be required. Follow-up and response evaluation methods will be exactly the same of the main study.

Patients who have failed ITI will not be randomised given a fixed dose of 200 IU/Kg daily, but will be randomized to use either a recombinant/monoclonally purified FVIII concentrate or a VWF-containing FVIII concentrate.

Patients who have failed previous ITI will not be randomised but will be tolerised with 200 IU/Kg of a VWF-containing FVIII concentrate daily.

**For further information, contact Dr. A Gringeri**

**([alessandro.gringeri@unimi.it](mailto:alessandro.gringeri@unimi.it)) or view the website [www.itistudy.com](http://www.itistudy.com)**

### **Factor VIII Genotyping Study:**

Art Thompson is investigating the influence of haemophilia genotype on ITI outcome. He requires either samples for DNA analysis or evidence of genotype for patients who come from a kindred in which the genotype is already established.

All participating ITI centres are encouraged to also participate in this study which may require separate agreement with their Research and Contracts office on this point, while continuing to emphasise the low anticipated enrolment, the investigator-initiated nature of the study, Dr Thompson's research budget does not include funds for additional subject enrolment and IRB fees. Consequently each center will need to submit this as an amendment to the main study protocol. Separate consent is usually required for genotyping even in normal clinical practice, and a paragraph in the main consent mentioning the optional study having a separate consent. If you would like to obtain a sample consent or require any assistance with the submission of this protocol, please contact Ilene Goldberg.

**For more information about Dr. Thompson's companion study, please contact Charles Cooper, RN at [charlesc@psbc.org](mailto:charlesc@psbc.org) or view the website [www.itistudy.com](http://www.itistudy.com)**



## Further Satellite Studies

### **FVIII-Memory B-Cell Study: Birgit Reipert, Vienna**

Dr Birgit Reipert will analyse the dynamics of the factor VIII specific memory B-cells during the course of ITI. This will answer the questions :-

- 1.) Is there a correlation between levels of FVIII specific memory B-cells in peripheral blood and inhibitor levels.
- 2.) Is the disappearance of FVIII specific memory cells associated with tolerance.
- 3.) Are factor VIII specific memory B-cells absent after successful ITI?

Three ml. samples are required before and during ITI. These may be divided and could double up for one of the other studies (e.g. Low level inhibitor study, see below). 20 subjects are required for the study.

Further sampling may be an IRB issue and US centres will require a research contract. Dr Reipert will help with this and any funding issues that may arise. The full protocol and sampling protocol are available on the web-site [www.itistudy.com](http://www.itistudy.com) and from Dr Reipert.

[birgit\\_reipert@baxter.com](mailto:birgit_reipert@baxter.com)

### **Low level Inhibitor Study: Bert Verbruggen, Nijmegen**

Bert Verbruggen from Nijmegen has proposed to use the ITI study to validate a refinement of the Nijmegen modification of the Bethesda assay. Like the Nijmegen modification, this variant is more sensitive at lower inhibitor titres than the original Bethesda method and it is hoped that this new variant will be sufficiently sensitive and specific to distinguish between very low level inhibitors leading to a reduced half-life and truly negative samples.

Patients undergoing ITI are particularly useful for such studies because they are pharmacokinetically well characterised. Samples taken pre-infusion prior to recovery or for half-life estimations towards the end of

tolerance would be suitable for this study. Samples from 8 patients are required for the study. Only 1 ml may be required and a frozen and thawed sample would be acceptable. Since no additional blood will need to be drawn, no IRB issues arise. Indeed US repository samples may be used. Samples may have to be transported on dry ice at Dr Verbruggen's expense but this is still under discussion. This study has just been approved by the Scientific and Publications committee.

### **Mapping of B-cell Inhibitor Epitopes: Christoph Konigs and Wolfhart Kreuz, Frankfurt.**

Dr Konigs is an associate of the Frankfurt group. He wishes to map inhibitor B-cell epitopes at intervals before and during ITI. This is an ELISA test looking at IGG subclass distribution, which is thought to change during successful ITI. Immunoglobulin from each sample will be immobilised and incubated with random peptide libraries. Peptides that bind will be isolated and, in a second step, this peptide pool will be incubated with an inhibitor negative plasma pool to remove peptides binding to non-relevant antibodies. In an ELISA, isolated single peptides will be tested for inhibitor binding to separate peptide binders from background. Such binding peptides represent an inhibitor epitope, so called mimeotopes. The sequence of these peptides can then be compared to the primary sequence of FVIII to identify the epitope.

This requires only a 1 ml plasma sample and so no additional sampling may be required. The study should not, therefore, require ethical approval. This study has just been approved by the Scientific and Publications Subcommittee and the protocol will shortly be posted on our website.



# Frequently asked questions

**Matt Foulkes and Ilene Goldberg**

- ◆ *When should a patient be registered onto the study?*
- ◆ As soon as possible after consent is obtained; please do not wait for the patient's inhibitor titres to drop to below 10BU as this pre immune tolerance induction period is one of the areas the study is collecting data on.
- ◆ *How do I randomise a patient?*
- ◆ In order for the patient to be randomised they must have inhibitor titres of <10BU within a month of each other. As soon as these are entered into the electronic case report form (eCRF), the system will automatically assign the patient to a study arm. You will then be asked to enter data regarding titre results at diagnosis, study entry and the maximum historical inhibitor titre along with some basic patient demographics.
- ◆ *When is a washout period needed during the study?*
- ◆ A 72 hour washout period is necessary when determining the patient's factor VIII inhibitor, and when recovery or half life studies are done.
- ◆ *Should washout periods be recorded as interruptions in ITI?*
- ◆ No. Washout periods are part of the protocol so they are not considered interruptions of ITI

- ◆ *If a patient is on Novoseven/FEIBA prophylaxis should that information be recorded?*

- ◆ Yes. It should be entered as concomitant therapy in the monthly time period with the prophylactic dose as the total daily dose and reason prophylaxis i.e. FEIBA 1000 iu tiw.

For a patient to be considered tolerant both the half life and the recovery component must be considered normal; the factor VIII must be >66% of expected and the half life must be >6 hours. (see protocol p.19)

Any event where a patient is hospitalised/ treated as an inpatient qualifies as Serious Adverse Event. Please ensure that hospitalisations are reported promptly as they must be reviewed by the Data Safety Committee.

Any hospitalisations that are regarding catheter placements, removals or infections will also require a catheter questionnaire to be reviewed; if a questionnaire hasn't been completed or updated for the patient, please ask your local coordinating centre for one.

Factor VIII given as per study requirements should be reported on the monthly treatment section of the eCRF; any factor given as treatment for a bleed should be reported separately in the intercurrent bleeds section.

Please ensure a weight assessment is performed whenever prompted by the protocol, as this is necessary when checking recoveries and factor usage.

# The ITI Study in the USA

## DM Di Michele and Ilene Goldberg

Enthusiasm and participation in the US for the international ITI study has continued to be steady! Currently 37 US HTC's have final ethical (IRB) approval with at least 4 other centres in the process of protocol submission. To date, seventy-seven subjects have been enrolled in the study worldwide. Twenty-eight US subjects have been enrolled and 24 of them have been randomised.

One US subject has been successfully tolerated, 1 has relapsed, 4 have not been tolerated, and 7 subjects have been withdrawn, due to social, venous access, death or eligibility issues. The study data on US subjects is included in Dr Hay's ITI study progress report in the newsletter. We continue to thank all ongoing new and potential investigators for their interest and important collaboration!

Site	Investigator	Subject	Site	Investigator	Subject
UAB, AL	Watts/ Noa	1	Children's Mercy Hospital, MO	Wicklund/ Mehrhof	3
Children's Hospital, AZ	Recht/ Schultz		UNC, NC	Monahan/ Nielsen	2
CHOC, CA	Nugent/ Birschbaum, McDaniel		Hackensack UMC, NJ	Flug/ Falls	
City of Hope, CA	Ewing/ DeGuzman	1	Newark BI, NJ	Cohen/ White	1
Mountain State HTC, CO	Manco-Johnson/ Smith	2	St Michaels's, NJ	Guron/Pietsch	
All Children's Hospital, FL	Ayala/Cardenas	1	U of New Mexico, NM	Mathew/Schwartz	
Emory, GA	Dunn/ Bryant	3	Mount Sinai, NY	Hurlet/ McCarthy	
U of Iowa, IA	DiPaola/ Lammer		NYPH, NY	Di Michele/ Goldberg	
Children's Memorial Hosp. IL	Allen/ Brummel		Akron Children's Hospital, OH	Hord/Ali	
Comp. Bleeding Disorder Center, IL	Tarantino/ Lucas		Ohio State U, OH	Kerlin/Pedue	
RUSH, IL	Valentino/ Howard	3	CHOP, PA	Manno/ Kiefer	
Indiana H&T Center, IN	Shapiro/ Chong		HTC of Western PA, PA	Ragni/ Jaworski	
Tulane, LA	Leissinger/ Schmidt	1	St. Christopher's, PA	Shafer/ O'Brien	1
Children's Hospital, MA	Neufeld/ Barry	1	St. Jude, TN	Reiss/ Grant	2
Tufts-NEMC, MA	Rosenfield/Hailey		Vanderbilt, TN	Domm/ Hudson	
U Mass, MA	Brettler/ Forsberg		Gulf States H & T Center, TX	Hoots/Moynahan/ Cantini	
Michigan SU, MI	Scott-Emuakpor/ Carlson		CHKD, VA	Werner/ Stewart	2
U of Michigan, MI	Pipe/ Hauke	1	BC of SW Wisconsin, WI	Gill/ Gavin	1
Children's Hospital MN	Heisel/ Gorlin	2			

**If there are any centres who would like to participate in the study, but do not have the personnel to put through the submission, please contact Ilene Goldberg and she will assist you with your submission.**



## The ITI Study in the USA

# Protocol Reminder

The study is collecting data on non-enrolled patients to monitor for selection bias. In accordance with HIPAA guidelines in the US complete dates should not be used, only the **year** of birth and inhibitor diagnosis should be provided. Please be sure to collect and store all plasma samples required by protocol for inhibitor confirmation. The required time points are the initial pre ITI inhibitor, the first 2 negative inhibitors on ITI and the final assay 12 months after the end of ITI. Extra plasma obtained during inhibitor testing can also be saved and sent to the US repository for use in future studies, as per your institutional IRB study approval. Subject samples will be shipped to the repository once a subject has completed the study or sooner if necessary.

The US sample repository is Kam Tek, not RTI, Danny Ringer is the contact person for sending the samples to the repository and his contact information has been changed to [dringer@rti.org](mailto:dringer@rti.org): (301-230-4678).

# Research Contracts

As a reminder, please note that the study reimburses investigators at a rate of 2,000.00 \$US per study subject enrolled (indirect costs included). However, a limited additional subsidy for IRB fees can also be negotiated on a case by case basis. Please continue to initiate all research contract negotiations directly with Janet Goldstone in Manchester (contact details on back page). However, do not hesitate to contact Donna DiMichele for any assistance you require with research and contract –specific funding issues.

# ITI Contacts

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## Problems?

For problems with ethical submissions in the US contact Donna Di Michele or Ilene Goldberg. Investigators in other countries should contact Dr Charles Hay or Janet Goldstone. Contractual issues should be addressed initially to Janet Goldstone.

Any problems with the website should be referred to Matt or to Rob Hollingsworth (Email [rob.hollingsworth@cmmc.nhs.uk](mailto:rob.hollingsworth@cmmc.nhs.uk))

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## Finance and Contracts:

Financial support is available to cover the cost of administering the study. This is paid in instalments. There is a standard financial contract template available for centres to use. This can be obtained by e-mail from Janet Goldstone.

Most centres have used the template without alteration but if you or your contracts department wish to make changes or additions, please send Janet a draft copy for approval by our Research and Development Department before having it authorised.

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