

Welcome: C. Hay

Dr Hay welcomed the attendees, thanked Grifols for sponsoring the meeting

ITI study update: C. Hay

Recruitment as of 21Nov 2008: 120 registered (of target enrollment of 150)

4 currently pre-ITI phase, 105 randomized (56 on study, 49 off study), 11 off study in pre-ITI phase

Registration by year: 2002 = 5; 2003 = 18; 2004 = 18; 2005 = 16; 2006 = 16; 2007 = 25; 2008 = 22 (Consistent enrollment over 2007 and 2008)

Randomization by year: 2002 = 4; 2003 = 15; 2004 = 16; 2005 = 13; 2006 = 17; 2007 = 20; 2008 = 20

Recruitment by country: Argentina 1, Australia 2, Belgium 3, Canada 17, France 3, Israel 2, Italy 6, Japan 17, The Netherlands 3, New Zealand 4, Norway 2, Spain 5, UK 10, USA 45

Reasons for non-eligibility: n=118 (some with more than 1 reason)

Age \geq 8yrs =33, FVIII \geq 0.01IU/ml =5, Inhibitor >12 months (original protocol) = 30, Inhibitor <5 BU = 41, Inhibitor >200 BU =20, Previous ITI=10, Unable to comply with protocol =3

Reasons for non-enrollment of eligible patients: n =55 (some with more than 1 reason)

Clinician refusal (usually access issue) 13, Patient refusal to randomize 30, Venous access 4, Other 15

Reasons for non-randomization:

Enrolled subjects taken off study pre randomization 11, Exceeded eligible duration time of inhibitor 4, no NHS funding 1, no consent for line insertion 1, inability to comply with protocol 1, physician decision 2, inhibitor rose to > 200 BU 1, death (ICH) 1

Time from inhibitor diagnosis to decline to <10 BU (n =105)

Median time is 5 months (0-23 months) (these demographics stable over course of study)

Subject Demographics for randomized patients (21st Nov08) n=105

	Median	(Range)
Randomisation age (months)	23.0	(3 - 80)
Diagnostic Inhibitor Titre	10.0	(0.6 - 175)
Peak Historical titre	19.7	(5 - 198)
Titre at start of ITI	5.1	(0.6 - 9.8)
Peak inhibitor titre on ITI	23.7	(0 - 5600)

(these demographics stable over course of study)

Progress on Study: Randomised Subjects

	Median	(Range)
Months from diagnosis to < 10 BU (n=105)	5.0	(0-23)
Months on ITI (n=105)	13.0	(0.8-36)
Months to negative titre (n=50)	6.0	(1.0 - 26.0)
Months ITI start to normal recovery (n=42)	8.0	(2.0 - 32.0)
Months from ITI start to tolerance (n=41)	15.0	(3.0- 30.0)

On-study subjects: Current Status n=56

With inhibitor 34, negative inhibitor 2, negative inhibitor and normal recovery 2, normal half-life 18

Off Study Subjects: (n= 49)

Tolerant = 23 (15: successes, 5: relapses that are also partial successes, 3 removed post tolerance (1: Lost to FU, 1: MD decision, 1: non-compliance))

Partial Success =2

Failure =11 (6: due to <20% decline in inhibitor in 6 months; 5: due to positive inhibitor after 33 months)

Withdrawal =13 (2: MD decision, 2: family decision, 4: protocol deviation, 5: non-compliance)

Relapses and Partial Successes

5 relapsed on prophylaxis

- 3/5 negative inhibitor but shortened half-life/recovery

- 2 subsequently normalised PK and negative inhibitor on prophylaxis

- Demographically similar to non-relapsers

- All meet criteria for a partial success

- All responding to treatment with no anamnestic increase in inhibitor

2 subjects 33 months on study without normal recovery but with negative Bethesda titre

- Responding to factor VIII

Discussion:

Dr Rivard –asked if it was possible to get the slides. Dr DiMichele-responded that the data on the slides would be included in the minutes. The slides themselves would be available to steering committee members to promote the study

Dr Klaassen suggested that non-compliant subjects shouldn't be taken off study, because that is what happens in the real world.

Dr Hay agreed that non-compliance with immune tolerance does occur in clinical practice.

Dr Aledort added that maintaining such subjects in the analysis depended on the percent of treatment that did adhere to protocol and that study endpoints must remain consistent once they are established.

Dr Klaassen indicated that the delay in receiving the official study half-life determinations has been creating some confusion at his center about how to proceed with the subject. Drs DiMichele and Hay agreed that the half-life results should be sent to the centers promptly and will explore the reasons for the past delays.

Data Safety Report: L. Aledort

Dr Aledort reported that the DSMB will meet in June to go over some unresolved issues. The DSMB has acknowledged that success rates to date on the study are lower than in published reports, but that the study is ongoing and final outcomes are unknown. All hospitalizations are SAEs. Port infections are a major issue but it is as yet unclear what role they play in inhibiting success in the study (in both arms).

Serious Adverse Events (SAEs): n=227 (226 hospitalisations)

28 study related; 25 catheter-related SAEs (including 9 infections in 6 patients); 1 subclavian thrombosis; 1 trauma; 1 possible allergic reaction to factor product

Dr Aledort- If the clinician put the catheter in for a clinical reason the SAE is non-study related. There is a questionnaire to determine this at each port event.

199 non-study related; 101 catheter related SAEs (5 catheter related bleeds, 54 catheter infections in 18 patients, 34 insertions and/or removals, 4 haematomas, 1 PUO and 3 other catheter related problems); 58 bleeds in 25 patients; 6 infections in 6 patients; 1 death; others (3 hematomas; 1 subclavian thrombosis; 1 ear infection; 2 dental extractions; 9 traumas; 2 surgeries; 4 PUO; 2 bronchospasms; 1 possible reaction to factor product; 7 hospitalisations for other reasons)

Catheter placement –

86/120 enrolled subjects have or had 144 catheters

63 (73%) were placed pre-registration

48/56 on study subjects currently have catheters

There has so far been a median of 1 catheter per subject (range 1-8): Mean of 2 catheters per subject

Number of catheters inserted per patient

1 in 59 patients, 2 in 13 patients, 3 in 8 patients, 4 in patients, 5 in 1 patient, 6 in 0 patients, 7 in 2 patient, 8 in 1 patient

Catheter complications-

88 line infections in 30 subjects (1-11/subject)

-Many with apparently repeated infection had several episodes with single organism.

-Some treated with oral antibiotic outpatient

- May represent a single infection incompletely eliminated

4 haematomas/swelling around ports in 4 patients

2 subclavian thrombosis

46 line insertions/removals in 27 subjects (1-5/subject); 2 due to ruptured suture site

Catheter infections

144 catheters placed in 86/120 registered subjects

81 Port a cath, 28 Broviac/ Hickman, 22 PICCS, 13 unknown

From 72 completed questionnaires: 57 catheters entered for clinical reasons and 15 for study needs

Catheter infection developed in 30/86 subjects after a median of 196 days (11-996 days)
Median age at randomization of infected and uninfected subjects was 21 and 25 months respectively

Infected subjects had a median of 3 (1-11) infections

Infected subjects had a median of 2 (1-8) catheters

Number of infections/subject

1/11 subjects, 2/6 subjects, 3/6 subjects, 4/1 subject, 5/3 subjects, 6/0, 7/1 subject, 8/0, 9/0, 10/1 subject, 11/1 subject

Catheter infections- causative agents (15 double infections and 3 triple infections)

Gram +ve: 13 Staph epidermis, 18 Staph Aureus, 3, MRSA, 15 unspecified staph, 8 Streptococcus, 1 Rhodococcus, 3 Bacillus cereus, 1 Mycobacterium Fortuitum, 5 unspecified

Gram -ve: 3 Pseudomonas, 2 Klebsiella, 6 Enterobacter, 7 Acinetobacter, 3 Achromobacter, 1; Serratia, 3 Enterobacter, 3 Agrobacterium, 3 Stentrophomonas, 3 Flavobacterium, 1 Alcaligenes xylosoxidans, 1 unspecified

Other: 4 Candida, 2 unknown

Kaplan Meir Plot of first catheter survival for 10 Broviacs and 50 Port a caths:
Broviac survival was shorter than that of port a caths (0.059)

Non-Serious Adverse Events: Catheter-Related

52 catheter related events in 20 subjects

13 for swelling around port site, 8 for irritation around site, 16 for blocked/stiff line, 5 for discharge around catheter, 4 for cracked lines, 1 for pain around catheter, 5 haematoma after catheter use

Non-Serious Adverse Events: Intercurrent Haemorrhages

724 bleeds in 71 subjects reported

median (range) per subject	8 (1 - 64)
median (range) per subject/yr on ITI	7 (0.6 – 29.0)
median (range) per subject/yr on ITI for patients on study (n=24)	7 (1.4 – 29.0)

Total haemarthroses: 341, Muscle bleeds: 144, Face/head (Minor trauma):117, Nose: 19, Mouth: 49, Port/Broviac: 55, Other: 8, Unspecified: 9

Dr Aledort indicated that it was still unclear how the SAE's would impact tolerization.

Discussion:

Dr Aledort indicated that it will be important to publish catheter data separately to understand what is happening to patients during ITI.

Dr Valentino added that his metaanalysis published in 2004 demonstrated similar results

Dr Tarantino asked if the study was collecting treatment data on the infections such as the antibiotics used and ethanol locks.

Dr Hay- responded that although the study does collect antibiotic information, these data do not include ethanol locks since these were not used at the beginning of the study.

Satellite studies: C. Hay

The following are now able to be added to the study as satellites now that MTA's have been completed or almost completed.

Low Level Inhibitor Study - B. Verbruggen: Nijmegen

Inhibitor epitope study - C. Königs /Kreuz: Frankfurt

Proteomics Study - W. van Heerde; Nijmegen

The need for these as the study progresses has up until now significantly delayed the start date for these studies that will not be part of the upcoming amendment.

Materials Transfer Agreements (MTAs)

Introduced in the UK September 2006 (with similar timing in the US), these are agreements between investigating centres and the PIs centres to transfer samples from one to the other.

These are simple contracts about sample handling and storage plus intellectual property rights.

All *new* studies involving central testing should now have MTA language in their contract; old studies may not need this.

Cell samples are even far more regulated by the Human Tissue Act.

Current Status of MTAs and Satellite Studies

MTAs agreed between listed satellite studies separately in the UK and US.

MTAs between sample repositories and central inhibitor testing lab now being negotiated; this will NOT be required between study centres and repositories.

Unfortunately, neither CMMC nor Cornell felt they were able to negotiate MTAs for the Reipert Study which involves a transfer of samples between two 3rd parties over which they have no control.

Amended Protocol and Re-consent: C. Hay

For these satellite studies we will require as many samples as possible including key samples for central testing as well as any monthly samples that have been stored.

Re-consenting for this collection and use will be necessary where not originally specified, i.e. in the international protocol and in some US center IRB protocol submissions.

Amended protocol will be sent out to all participants for ethical (IRB) approval in January 2009.

When all international centres who wish to participate have ethical approval and re-consents where necessary, Manchester can collect the samples for central testing and the satellite studies. *Dr DiMichele added that in the US, the Cornell coordinating center controls the repository, and will get this approval on behalf of US centers to share samples from subjects who have agreed in their main consent to store and use them for*

future research. Since these are retrospectively- collected samples, separate consent for participation in the satellite studies should not be necessary.

Protocol Amendments: C.Hay

The amended protocol will include 1) all satellite studies; 2) amendment to include collection of pre-ITI bleeding data and off study data on subjects' ITI status; 3) the redefinition of *Partial Success*; 4) collection of known genotype data; and 5) removal of Hepatitis B vaccination from eligibility criteria.

S&P Committee Update: T. Kisker and G. Rivard

There have not been any publications at this time.

Dr Van Heerde's satellite study has been approved.

Discussion:

Dr Kisker suggested that there could be a role for publishing interim study data without breaking the randomization code.

Dr Aledort countered that it is may be scientifically invalid to publish interim data without breaking the code, because the data now could be very different when the code is broken.

Dr Rivard agreed with Dr Aledort.

Dr Kisker questioned the suitability of samples stored at the institutions.

Dr DiMichele answered that the centres are given specific protocol instructions about sample storage conditions.

Dr Carcao asked whether due to the number of subject withdrawals the study might need to recruit additional subjects. He added that it would be a shame to terminate enrollment and not have enough evaluable subjects.

Dr Hay responded that the statistician and DSMB would continue to look at this. And he encouraged ongoing enrollment.

Final Comments: C. Hay

Acknowledgement and thanks given to all industry sponsors and Grifols in particular for sponsoring the meeting; the DSMB for their diligence, and the participating centres for their enormous efforts on behalf of the study.

It was announced that the RESIST study meeting would follow this meeting and that the next investigators meeting will be during ISTH in Boston, date and venue to be arranged. The ITI study meeting was adjourned at 13:30

Minutes submitted by Ilene Goldberg RN and Donna DiMichele, MD