CLINICAL TRIAL DESIGN FOR HEMOPHILIA

A PROJECT GROUP

of the FVIII/IX SUBCOMMITTEE

DONNA DI MICHELE MD

FOR

CLINICAL TRIAL DESIGN FOR HEMOPHILIA PROJECT GROUP

WFH Global Forum

September 22, 2011
<table>
<thead>
<tr>
<th>Conflict</th>
<th>Disclosure – if conflict of interest exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support</td>
<td>None</td>
</tr>
<tr>
<td>Director, Officer, Employee</td>
<td>None</td>
</tr>
<tr>
<td>Shareholder</td>
<td>None</td>
</tr>
<tr>
<td>Honoraria</td>
<td>None</td>
</tr>
<tr>
<td>Advisory Committee</td>
<td>None</td>
</tr>
<tr>
<td>Consultant</td>
<td>None</td>
</tr>
</tbody>
</table>
Issues Underlying Committee Mandate-Pragmatic

- Multiple products entering into pre-registration clinical trials simultaneously

- Limited availability of hemophilia subjects for these trials, given current regulatory enrollment requirements
  - Issue amplified in product trials for even rarer disorders

- Industry, regulators, clinicians and patients demanding trial simplification without compromising safety/efficacy assessment
Issues Underlying Project Group Mandate-Regulatory

- Currently, variable requirements between regulatory agencies for pre- & post-registration safety and efficacy assessment of CFCs.

- Underlying philosophy of ensuring the safety and efficacy of biologics well appreciated; but scientific basis for many requirements unclear.

- Most agree on the value of discussing and harmonizing regulatory requirements among major regulators.
To determine the optimal prospective pre-licensure and observational post-licensure trial designs for new clotting factor concentrates (CFCs) for hemophilia on the basis of:

- harmonized safety and efficacy data required by regulators for product registration and by the hemophilia community at large post-licensure;

- anticipated available study population;

- innovative clinical trial design suitable for rare diseases such as hemophilia.
Proposed Plan of Action

Project members will review current endpoint definitions and clinical trial requirements with guidance from all stakeholders:

- FVIII/IX SSC Definitions Project Group
- US and European regulators*
- Industry representatives
- Scientific and methodological experts*
- Clinical investigators*
Members

Dr. Donna DiMichele (NIH, Chair)
Dr. Nisha Jain (FDA)
Dr. Anneliese Hilger (EMA)
Dr. Alok Srivastava (ISTH/WFH)
Dr. Flora Peyvandi (ISTH)
Dr. Sebastien Lacroix-Desmazes (Immunology Consultant)
Dr. Frits Rosendaal (Clinical Trial Design)
Dr. John Scott (FDA; Statistician)
Plan:

- Develop or refine consensus CLINICAL OUTCOME ENDPOINT definitions

  Clinical Severity; Prophylaxis; Inhibitors; Bleed; Response to Treatment

- Optimize clinical trial design requirements:

  Numbers and types of subjects
  - Safety / Efficacy trials
  - Surgery trials

  Study duration; exposure requirements

  Assay methodology
  - Inhibitor and global hemostasis assays?
Project Timeline

- **February 2011**: Design of Clinical Trials in Hemophilia Project Group began deliberations

- **Feb–Sept 2011**: Eight teleconferences One in person–meeting

- **June/July 2013**: Final report to FVIII/IX Subcommittee anticipated
Next Steps

- Alternative clinical trial design and statistical modeling will be applied to 5 types of PTP (and potentially PUP) trials:
  - FVIII biosimilar and novel biologics
  - FIX biosimilar and novel biologics
  - FVIII/IX novel bypassing agents

- Industry input will be solicited during this process

- SSC input solicited during Kyoto ISTH meeting
CFC pre-registration trial design optimization:

- Modifying safety rather than efficacy endpoints (esp. product neoantigenicity) is greater design challenge

- No alternatives to the traditional inhibitor assay yet ready for clinical trials; mechanistic studies needed

- Unique solutions may or may not be needed for:
  - FVIII vs FIX products (Biosimilar vs novel biologics)
  - FVIII/IX Bypassing agents (novel biologics)

- Complimentary role of prospective observational post-registration studies needs to be further explored
Current Activities

- Clinical Trial Design and Statistical Modeling Sub-Group:
  - Nisha Jain (FDA)
  - Anneliese Hilger (EMA)
  - Frits Rosendaal (Epidemiology, clinical trial design)
  - John Scott (FDA, Small clinical trial design)
  - Sebastien Lacroix-Desmazes (Immunology)

- Will re-examine PTP immunogenicity clinical trial requirements for FVIII and IX biosimilars, using currently known neoantigenicity data; applicability to novel products will be further deliberated once early data from first novel CFC trials are available

- Will explore potential inclusion of mechanistic studies into future trials to evaluate other sensitive and biologically representative early detection assays for product immunogenicity

- Relevant industry input will be solicited
Current Activities

- **Clinical Endpoints and PROM Sub-Group:**
  - Flora Peyvandi (ISTH, NHLBI Global Assay Working Group)
  - Alok Srivastava (FVIII/IX Subcommittee Clinical Definitions PG, WFH)

- Will liaison with all stakeholders to ascertain precise consensus definitions for relevant objective clinical efficacy endpoints, as well as patient-reported outcome measures.

- These data will be incorporated into future PG deliberations on applicable alternative clinical trial design methodology for pre- and post-registration efficacy trials.
Questions and group input welcome ......