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Design of Clinical Trials for New Products in Hemophilia: Recommendations of the Clinical Trials Project Group of the Factor VIII, Factor IX and Rare Coagulation Disorders Subcommittee, Scientific and Standardization Committee, International Society of Thrombosis and Hemostasis. D.M. DIMICHELE,* S. LACROIX-DESMAZES†, F. PEYVANDI§, A. SRIVASTAVA#, F.R. ROENDDAAL##

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INTRODUCTION

This report presents an alternative approach to the clinical trial design of pre-authorization trials for both ‘me-too’ and novel clotting factor in previously treated patients (PTPs). This approach is rooted in the overall regulatory goals for safety and efficacy determination prior to product registration, and incorporates both current immunological theories of neoantigenicity and consensus clinical efficacy endpoint definitions.

Clinical trial design for pre-authorization trials

Critical elements of clinical trial design: Clinical efficacy endpoints

Treatment efficacy has historically been ascertained using non-standardized four point scale patient-reported hemostatic outcomes evaluated in single arm, open label pre-authorization studies, and reported as descriptive statistics. Recent efforts identified objective criteria, tested by pre-specified statistical analyses, to establish product efficacy for episodic treatment, prophylaxis, and surgery (Supplementary Table 5). Science-based definitions of clinical safety and efficacy are crucial to the standardization of outcomes in all clinical trials.

Critical elements of clinical trial design: Safety endpoints

Key aspects of regulatory agency guidance for pre-authorization new product trials are summarized in Supplementary Table 2 (1-5). Pre-authorization trials are primarily sized to assess Factor VIII (FVIII) product immunogenicity in PTPs (defined as having previously had > 150 product exposure days (EDs). Currently, \( \leq 1 \) inhibitor in 80 subjects is required to rule out a 6.8% inhibitor cumulative incidence over 50 EDs, based on the upper level of the 95% confidence interval in a Poisson distribution, the current upper bound of cumulative incidence adopted at a 2003 FDA workshop (5). The current recommendation relaxes the cumulative incidence to be excluded to 8% /year, coupled with the exclusion of a rate of 4/100 person-years in the second phase of a biphasic study. These cut-offs are in the range of elevated epidemic (6) and endemic (7) rates reported in the literature. This would typically result in studies with < 100 subjects (representative of the target treatment population), to be completed in less than two years.

The post FVIII-exposure inhibitor incidence has a biphasic nature: an early exposure (15, IQR 10-20 EDs) high peak ‘epidemic’ rate of up to 30% in previously untreated patients (PUPs) (7) is followed by a
lifelong low ‘endemic’ incidence of 0.1 to 0.6% per patient-year, (8-10). Initial new product trials enroll PTPs who have already successfully transited the ‘epidemic phase’ without apparent inhibitor development. They aim to detect a higher than expected incidence of inhibitors that could either augment the ‘endemic rate’, or, alternatively, constitute another epidemic peak of antibody development due to product immunogenicity.

To detect a product-related ‘epidemic’ elevation in inhibitor incidence (6), the study is confined to the early product exposure period, the measured outcome is cumulative incidence (events/people), and the sample size is based on the predefined risk of inhibitor development to be excluded. This is similar to the methodology currently used in the design of FVIII trials. To detect an elevated ‘endemic’ rate of inhibitor development, the rate itself is the effect measure (events/person-time), and the sample size is dependent on both the predefined rate of inhibitor development to be excluded and the person-time accrued in the study.

Sample size requirements (to be pre-specified and unalterable in a registered protocol) are demonstrated in the Table. To rule out a cumulative incidence of 8% in the first phase, one would observe zero events in 45, one or less in 68, or two or less in 88 subjects. In this model, once an ‘epidemic rate’ of product immunogenicity is excluded, the observation period for subjects who completed study phase 1 can be extended into phase 2. The biphasic study can also be designed to include more subjects in both phases to allow person-years to accrue over a shorter time period. As the Table shows, zero inhibitors observed among 93 person-years, or ≤ one inhibitor over 140 person-years, would rule out an incidence of 4 per 100 per year. To accrue 140 person-years for example, one would have to follow 140 subjects for one year, or 70 for two years (or slightly more to account for censored subjects).

Additional considerations in study design

Reexamining the definition of PTP
Available evidence suggests that the highest risk of inhibitor development in PUPs occurs within 20 product exposures. The CTPG recommends the use of post-marketing surveillance for the continued epidemiological study of inhibitor risk in the interval between 50 and 150 EDs to better define the ‘PTP’.

Application to factor IX products
The proposed methodology is also recommended for hemophilia B trials. Since the frequency of inhibitor development is low, studies could be safely designed to observe zero events, reducing the subject requirements for each phase of the study such that 50 subjects followed for two years would suffice.

Application to long-acting products
The proposed study design is applicable to modified clotting factor preparations with a prolonged plasma half-life; the concept of ‘exposure days’ requires additional consideration, since one infusion may result in several days of ‘exposure’.

The immunology of product neoantigenicity
Optimal design of pre-authorization clinical trials is hampered by an incomplete understanding of the precise nature of interactions between a FVIII product and the recipient’s immune system. Our limited knowledge derives in part from incomplete characterization of the PTP’s immune status relative to pre-trial therapeutic product exposure. Immunological ignorance is not routinely distinguished from active tolerance. Consequently, when a PTP develops an inhibitor during a new product trial, an immunological break in pre-existing tolerance cannot be distinguished from product-associated neo-immunogenicity. Systematic harmonized collection of clinical and biological data from subjects entering pre- and post-authorization studies will be required to scientifically address these questions (Supplemental Table 6).

Role of post-authorization studies
The regulatory intent of new product post-marketing surveillance is to expand the limited pre-authorization dataset on product safety and hemostatic efficacy (including PK) in adults and children through well-designed prospective post-authorization trials and observational studies. The FVIII/IX Subcommittee will establish a separate project group dedicated to establishing the requirements for international harmonized post-authorization studies using existing national and international database infrastructure and consensus standardized minimum datasets. Strategic data collection could also lead to greater understanding of immunogenicity.

Product authorization in children
While specific data are usually needed to ensure the safety and efficacy of therapeutics in children, this requirement may not be necessary for all drugs and biologics. The long history of safety of use of clotting factor concentrates in children based on initial data for adults would support this approach for these products. Therefore, after carefully evaluating adult PTP-generated data with a specific biologic or class
of therapeutics, it may be reasonable to adopt a worldwide harmonized approach to market authorization on the basis of adult PTP-generated safety and efficacy data, supplemented with PK data from a limited number of PTP children. The creation of appropriate models for structured post-marketing surveillance of product safety and efficacy in both adults and children is a critical aspect of this consideration. Precedence in this approach strongly suggests that safety can be maintained while minimizing an otherwise 2-3 year delay in access to these products for all hemophilia patients.

CONCLUSIONS

In conclusion, the CTPG believes that innovative and evidence-based approaches to pre- and post-authorization studies in PTPs could increase the feasibility of studying multiple new products in rare disease population without compromising assessment of product safety and efficacy, and lead to greater understanding of the underlying immunology of inhibitor development.

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REFERENCES


### Table. Sample sizes for phase 1 and 2

#### Phase 1

<table>
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<th>Cumulative incidence ruled out*</th>
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<th>3</th>
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<tr>
<td>4</td>
<td>91</td>
<td>137</td>
<td>178</td>
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#### Phase 2

<table>
<thead>
<tr>
<th>Incidence rate (per 100 person-years)</th>
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<th>2</th>
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<tr>
<td>2</td>
<td>185 [16%]**</td>
<td>279 [23%]</td>
<td>362 [30%]</td>
</tr>
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<td>3</td>
<td>123 [29%]</td>
<td>186 [45%]</td>
<td>241 [57%]</td>
</tr>
<tr>
<td>4</td>
<td>93 [40%]</td>
<td>140 [59%]</td>
<td>181 [73%]</td>
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<td>5</td>
<td>74 [48%]</td>
<td>112 [69%]</td>
<td>145 [82%]</td>
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<td>6</td>
<td>62 [54%]</td>
<td>93 [76%]</td>
<td>121 [88%]</td>
</tr>
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<td>7</td>
<td>53 [59%]</td>
<td>80 [81%]</td>
<td>104 [91%]</td>
</tr>
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<td>8</td>
<td>47 [63%]</td>
<td>70 [84%]</td>
<td>91 [94%]</td>
</tr>
</tbody>
</table>

* One-sided $\alpha = .025$; exact binomial model used according to current regulatory consensus.

** Power assuming a true 1% inhibitor incidence