

### NAME OF PROJECT

Subcommittee: **FVIII/FIX/RBD SSC: definition of ITI response with EHL FVIII products Working Group**

Date: **May 28, 2017**

- **Person responsible (Chair / Principal Investigator):** Maria Elisa Mancuso, MD, PhD (Milan, Italy)
- **Working Group:** Julie Curtin (Sydney, Australia), Amy Dunn (Columbus, Ohio, US), Dan Hart (London, UK), Gili Kenet (Tel Hashomer, Israel), Margaret Ozelo (Campinas, Brazil)
- **Design:** Survey, Literature Review, Evolving Clinical Experience, PK Model Data, Expert Opinion
- **Aim/Objective/Rationale (Needs assessment / Reason):**

#### **AIM:**

To focus on and define the response to ITI treatment in patients with hemophilia A treated with extended half-life (EHL) factor VIII (FVIII) concentrates

#### **OBJECTIVES:**

- 1) To define what is ITI treatment with EHL FVIII products.
- 2) To determine the PK parameters useful to define tolerance achieved with EHL products.
- 3) To review available literature on PK properties of different EHL FVIII products, on experimental proof of concept on their utility for ITI and on preliminary clinical experience in patients.
- 4) To discuss how the different PK profile may impact on tolerance achievement.
- 5) To discuss and define response to ITI using clinical and a laboratory endpoints (success, partial success, failure).

#### **RATIONALE:**

ITI treatment can be successfully performed with different FVIII products. Usually the same product used at time of inhibitor development is used in patients with newly diagnosed inhibitors. Limited data have been accumulated so far to evaluate the use of EHL FVIII concentrates for ITI treatment.

The modified and enhanced PK profile of EHL FVIII products and the biochemical mechanisms underlying their recycling in the bloodstream may favor ITI achievement with less prolonged exposure.

Moreover, a role for neonatal FcR in tolerance has been suggested.

Due to the modified PK properties of EHL products, response to ITI treatment may need to be redefined and tailored.

#### **Methodology:**

- 1) Develop and distribute a survey to hemophilia centers regarding current use of EHL FVIII products to induce immune tolerance in patients with inhibitors: which regimen, doses, which parameters are considered to define tolerance achievement.
- 2) Perform literature review on EHL products and immune tolerance (from preclinical studies to available guidelines)
- 3) Obtain clinical and PK data from treating physicians and/or pharmaceutical-sponsored clinical trials.
- 4) Obtain PK data on EHL FVIII from available PK models, published manuscripts and abstracts.
- 5) Determine recommendations based on data, analyses, expert opinion
- 6) Write manuscript, circulate for review by group, submit to JTH as SSC report

- **Expected timeline:**

- Project stage/set up: **May 2017**
- Launch: **July 2017 (ISTH Congress – Berlin)**
- Duration: **6 months ~ December 2017**
- Finalization/analysis: **4 months ~ April 2018**
- Reporting: **July 2018 (SSC Congress – Dublin)**

- **Expected outcomes** (ie. publications):

- **Publication type** (SSC Communication, Guidance document or original article):  
Guidance document from SSC WG and/or original article,

- **Description of project set/up and management, needed infrastructure and resources** (summary):

The purpose of this project is to develop guidance on how to define tolerance achievement in patients who receive ITI treatment with EHL FVIII products; and to evaluate which clinical and laboratory parameters are useful at this aim. This will be done by considering the PK properties of EHL products, preliminary preclinical and clinical data, accumulating new cases from field practice and/or from sponsored clinical trials and relying on expert opinion. The goal will be to provide highest level evidence to assess response to ITI with EHL FVIII concentrates.