La profilassi personalizzata: dallo studio NuPreviq al nostro caso clinico

Alessandra Borchiellini

CRR Malattie Emorragiche e Trombotiche dell'Adulto
Dipartimento di Ematologia e Oncologia
Città della Salute e della Scienza
Torino

Optimal prophylactic treatment[1-3]

- Maintain a minimum level of FVIII:C of *at least 1 IU/dL (1%)*
- Convert severe to moderate disease
- Reduce the number of haemorrhages
- Prevent or delay arthropathy
- Protect from joint deterioration
- Improve quality of life

stava A, *et al. Haemophilia* 2013; 19: e1–47; 2. Richards M, *et al. Br J Haematol* 2010;149: 498–507; 3. Makris M. *Blood Transfus* 2012; 10: 165–8.

What are the variables?[1-3]

- **Patient**
  - Personal choices
  - PK
  - Activity levels
  - Co-morbidities
  - Venous access
  - Age
  - How much bleeding is acceptable?
- **Products**
  - Half life
  - PK
  - Manufacture
  - Costs
  - Volumes

1. Petrini P, *et al. Expert Rev Hematol* 2015;8: 237–46; 2. Valentino LA. *Haemophilia* 2014; 20: 607–15; 3.Oldenburg J. *Blood* 2015; 125: 2038–44.

Individually tailored prophylaxis

Strategies to optimise prophylactic treatment[1-3]

Clinical approach

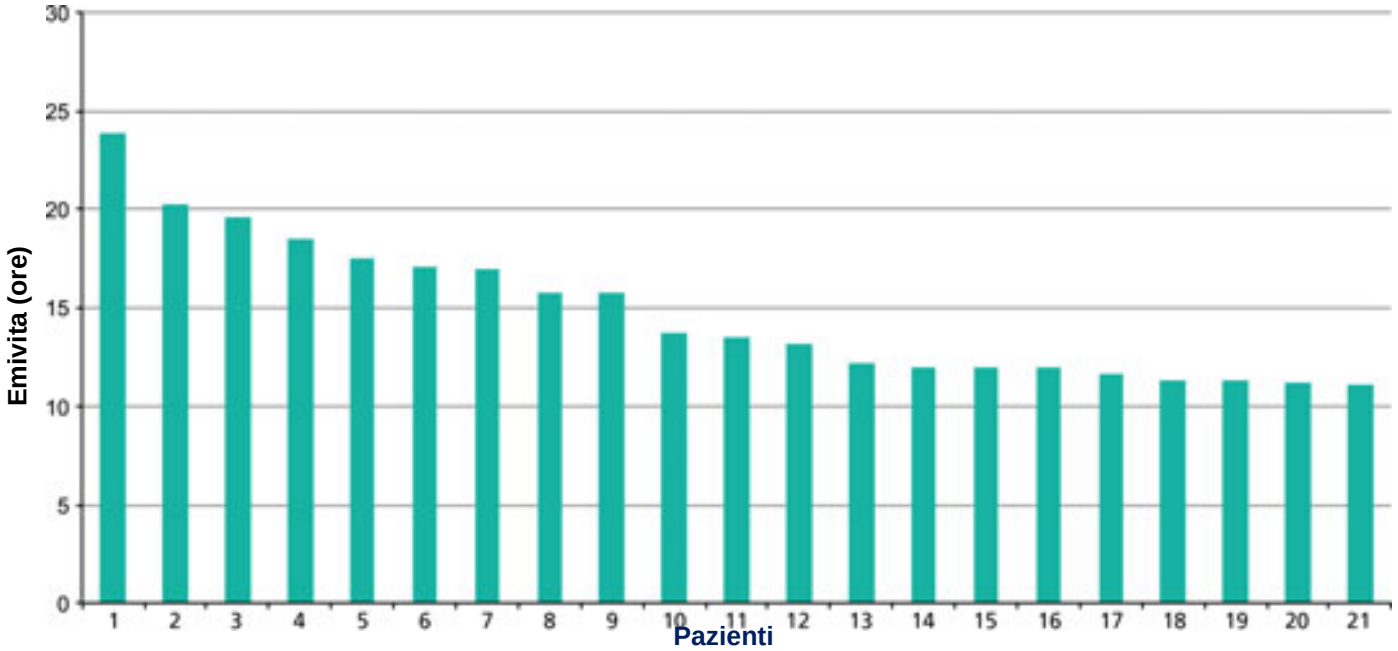
- Base dosing on observed bleeding pattern and clinical response to treatment
  - Adjust prophylaxis to daily activities of the patient
  - Adjust prophylaxis after spontaneous bleeds
  - Consider intensive prophylaxis in special situations
  - Consider peaks and troughs
- Clinical bleeding patterns may be significantly different in patients with similar coagulation factor activity

Pharmacokinetic approach

- Number of infusions per week to maintain residual plasma FVIII level > 1%
- Is measuring the trough level enough?
- Dosing and frequency of infusions according to personal PK data
  - Population-based PK?
  - Individual PK of each patient?

1. Petrini P, *et al*. *Expert Rev Hematol* 2015;8: 237–46; 2. Valentino LA. *Haemophilia* 2014; 20: 607–15;
3. Oldenburg J. *Blood* 2015; 125: 2038–44; Ar MC, *et al*. *Eur J Haematol* 2015; 93(Suppl. 76): 16–20.

Dati di emivita (HL) di Nuwiq da GENA-01



- Lo studio di PK con *Nuwiq* (GENA-01) ha dimostrato differenze considerevoli tra i pazienti relativamente ai dati di emivita, compresi in un range tra 11,1 e 23,8 ore

- In base a queste differenze è stato avviato lo studio sulla profilassi, *NuPreviq,* per valutare la possibilità di estendere gli intervalli di somministrazione in pazienti adulti affetti da emofilia A

NuPreviq: Studio sulla profilassi personalizzata con Nuwiq

Studio NuPreviq: studio di fase 3b prospettico, in aperto, multicentrico	
Obiettivi dello studio	**1. Valutare efficacia e sicurezza della profilassi personalizzata con Nuwiq in base alla PK, in pazienti adulti con emofilia A grave precedentemente trattati** **2. Ottimizzare l'intervallo di somministrazione raggiungibile con dose non superiore a 60-80 IU/kg, in grado di mantenere una concentrazione minima (trough) di FVIII ≥ 0,01 IU/ml (≥ 1%)**
Fase dello studio	**IIIb**
Numero di centri	**20**
Numero di paesi in UE	**8**
Numero di PTP (>150 ED) con HA grave(<1% FVIII), ≥18 anni di età	**66**
Periodo di osservazione	**in media 8 mesi**
Coordinatore dello studio	**Andreas Tiede, Germania**

NuPreviq: Study design[1]

Initial PK evaluation	Duration: 72 hours Dose: 60 ± 5 IU/kg Blood sampling: Baseline, 0.5, 1, 3, 6, 9, 24, 30, 48, 72 h Analysis: Trough and peak level (FVIII:C)
Standard Prophylaxis Phase I *1–3 months*	Duration (months): Median: 2.8 Dose: 30–40 IU/kg Interval: Every other day or 3 times per week Analysis: Calculation for Phase II (n = 66)
Personalised Prophylaxis Phase II[2] *6 months*	Duration (months): Median: 6.1 Dose & Interval: Personalised based on PK analysis Analysis: Trough level (FVIII:C) at 2, 4 and 6 months

1. 68 patients were screened; last patient completed the study on January 16th, 2015.
2. Monthly compliance checks throughout study, plus trough level measurement after 2-months visit (n = 66), 4-months visit (n = 65), 6-months visit (n = 65).

NuPreviq study summary: prolonged haemostatic protection

Personalised prophylaxis[2–4]

3.5	**Median dosing interval** (days)
58%	Dosed **twice weekly or less**
2.7–4.2%	FVIII trough level over 6 months*
-21%	**Median** possible (actual) **prophylactic dose reduction per week** compared with routine prophylaxis
0	Median **number of bleeds per year**
73%	**Patients without bleeding**
0	Inhibitors
	Well tolerated

* For patients in whom the highest trough levels are desired, a standard prophylaxis regimen (> 2 weekly) or a higher personalised prophylaxis dose may be appropriate.

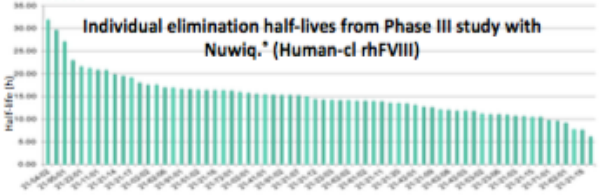
1. GENA 21 study results. Data on file. 2016; 2. Oldenburg J, *et al*. *Haematologica* 2015; 100: 149–56;
3. Valentino LA, *et al*. *Haemophilia* 2014; 20 (Suppl. 1): 1–9; 4. Kessler CM, *et al*. *Haemophilia* 2015; 21 (Suppl. 1): 1–12.

NuPreviq: Long-term program of treatment personalization and support for patients and clinicians

Morfini M[1], Fagnani S[2], Borchiellini A[3], Milan M[4], Schinco PC[3], Zanon E[4], Gagliano F[5], Gamba G[5], Ambaglio C[5]

[1]Italian Association of Haemophilia Centres (AICE), Florence, Italy; [2]Kedrion Biopharma, Barga, Italy; [3]Dept. of Haematology/Oncology, Molinette University Hospital, Turin, Italy; [4]Haemophilia Center, Padua, Italy, [5]Haemophilia Center, Palermo, Italy.

INTRODUCTION



Nuwiq.® (human-cl rhFVIII, simoctocog alfa) is a new-generation rFVIII protein, without chemical modification or fusion with any other protein, which is produced in a human cell line [1].

Pharmacokinetic (PK) responses to FVIII infusion vary widely between patients due to factors such as age, weight, clinical phenotype and dose/dosing schedule [1]. Clinical studies with Nuwiq.® in adult patients with severe haemophilia A revealed differences between patients with half-lives ranging from 6.5 to 32.0 hrs [1]. These results suggested to tailor patients' treatment with a traditional, single-dose, individual PK study. Unfortunately, this approach is quite demanding due to the requirement of frequent blood samples and thus repeated health center (HC) visits. To alleviate this demanding requirement, a minimal set of blood samples, well-distributed throughout the post-infusion period, was defined. In addition, HC visits were only necessary to obtain the baseline sample, the dose infusion of Nuwiq® and the "1st hour" sample. Home health care was used to draw at least four post infusion samples.

METHODS

All patients underwent a 4 day wash-out. The PK design was as follows:

- Obtained at HC: Baseline sample, Nuwiq.® infusion and 1h blood sample
- Obtained at home (by nurse): 8±1h, 24±1h, 48±1h and 72±1h blood samples

The blood samples obtained at home were brought to the HC (T = 8 ± 2°C). Two aliquots (0.5 mL each) of platelet-poor plasma were obtained by centrifugation and stored (T = -20/-40°C). All frozen samples were sent to Central Laboratory LabCorp for analysis (FVIII assay). Demographic data and PK timings were sent to Accovion with the desired trough (1, 2, 3 or higher IU/mL). The PK data were analyzed with a 1 or 2 compartment (1CP or 2CP) model. The model giving a lower AIC (Akaike Information Criterion) was considered the best and was used to predict doses and intervals.

RESULTS

Results of the individualised FVIII PK analysis

Patient I.D.	Dose (IU/kg)	Best model	IVR (dL/kg)	$T_{1/2}$ (h)	V (mL/kg)
03-01-01	50.0	2CP	2.00	15.4	46.3
03-03-01	48.8	1CP	2.02	14.2	54.0
03-04-01	40.0	2CP	1.47	24.5	59.2
03-07-01	52.6	2CP	1.86	20.1	49.3

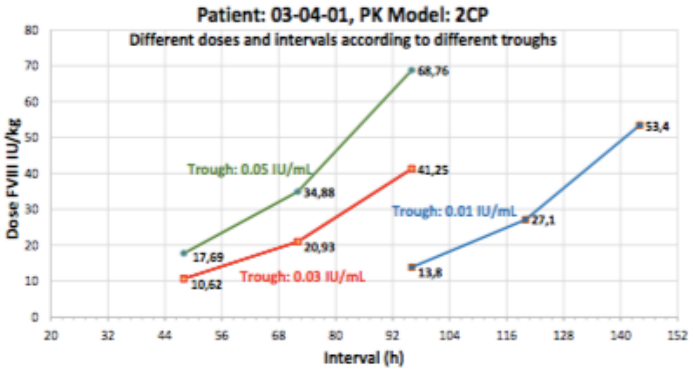
Simulated single dosing scheme, trough 1 IU/dL

Patient: 03-01-01			
Interval (h)	Dose (IU/kg)	C_{max} (IU/mL)	C_0 (IU/mL)
24	15.2	0.31	0.33
48	44.7	0.91	0.96
60	75.6	1.55	1.65
Patient: 03-03-01			
Interval	Dose (IU/kg)	C_{max} (IU/mL)	C_0 (IU/mL)
60	10.2	0.21	0.19
72	18.3	0.37	0.34
96	59.2	1.21	1.10
Patient: 03-07-01			
Interval	Dose (IU/kg)	C_{max} (IU/mL)	C_0 (IU/mL)
84	14.1	0.27	0.29
96	21.3	0.41	0.43
120	48.7	0.94	0.99

Accovion provided the program's national coordinator (M.Morfini) with PK outcomes and different doses per injection and treatment intervals according to trough requirements. Only those combinations of interval and dose resulting in an extrapolated C_{max} at t = 0 (C0) <2.0 IU/mL, and an estimated dose between 10.0 and 80.0 IU/kg, were considered valid and suggested to treaters. Given the large inter-patient variability in FVIII PK parameters, an approach based on patient's individual PK parameters (NuPreviq) would be expected to be more accurate than an approach based on average PK parameters of a wider population of patients.

Simulated single dosing scheme for patient 03-04-01

Trough: 0.01 IU/mL			
Interval (h)	Dose (IU/kg)	C_{max} (IU/mL)	C_0 (IU/mL)
96	13.8	0.22	0.23
120	27.1	0.44	0.46
144	53.4	0.87	0.90
Trough: 0.03 IU/mL			
48	10.6	0.17	0.18
72	20.9	0.34	0.35
96	41.3	0.67	0.70
Trough: 0.05 IU/mL			
48	17.7	0.29	0.30
72	34.9	0.57	0.59
96	68.8	1.12	1.16



CONCLUSIONS

The NuPreviq program provides the physician with valuable and objective treatment recommendations, that may lead to better prevention of bleeding, less injections and potentially less FVIII consumption individualize prophylaxis with Nuwiq®.

Reference:

1. Kessler C. et al - Spotlight on the human factor: building a foundation for the future of hemophilia A management. *Haemophilia 2015; 21 (Suppl. 1):1-12*

Servizio NuPreviq*: un servizio a lungo termine di personalizzazione della terapia, dedicato ai pazienti e ai medici

Step 1

HTC

Discuss the benefits of personalized prophylaxis

Step 2

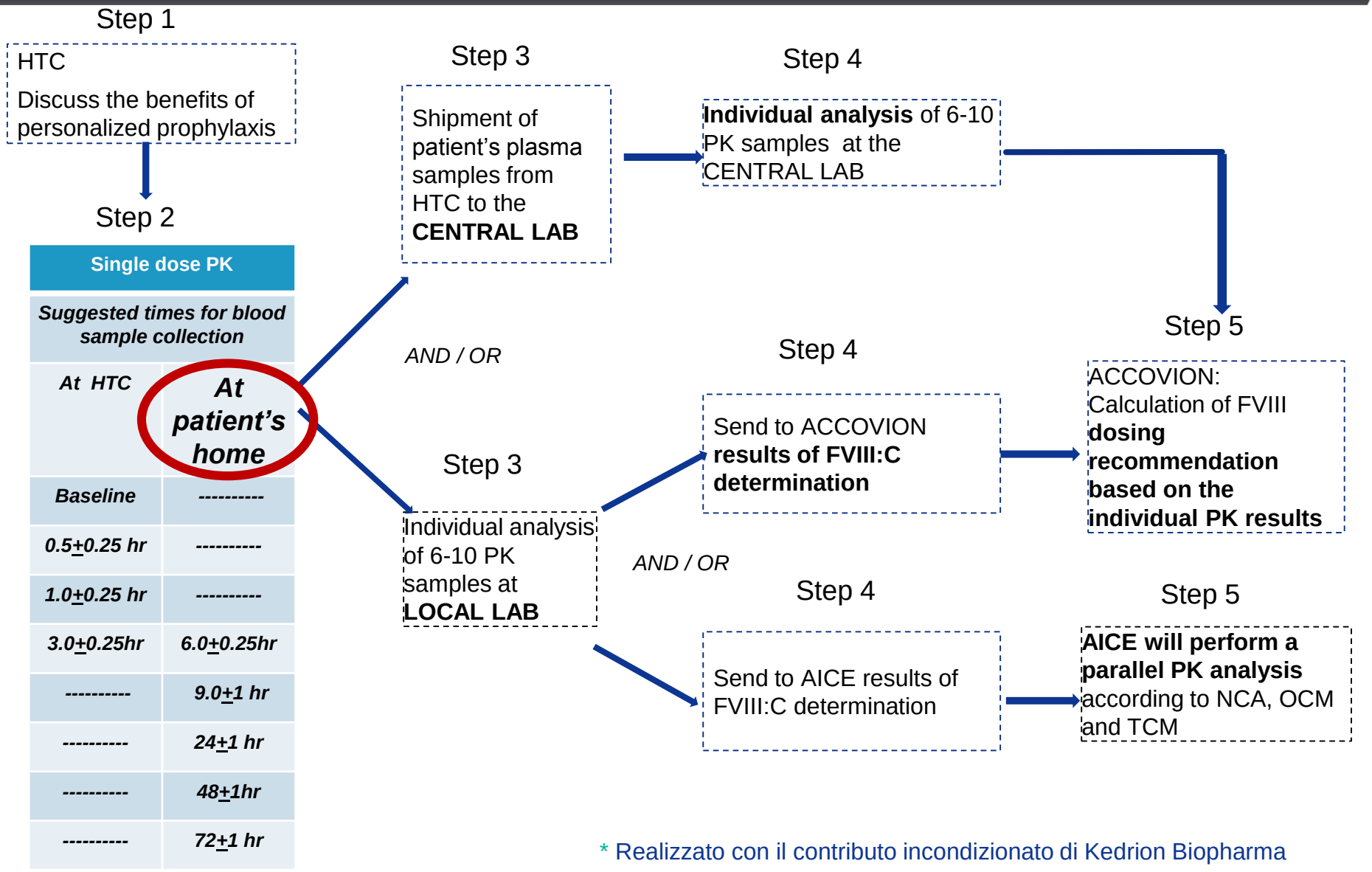
Single dose PK	
Suggested times for blood sample collection	
At HTC	***At patient's home***
Baseline	***----------***
0.5±0.25 hr	***----------***
1.0±0.25 hr	***----------***
3.0±0.25hr	***6.0±0.25hr***
----------	***9.0±1 hr***
----------	***24±1 hr***
----------	***48±1hr***
----------	***72±1 hr***

Il **Servizio NuPreviq*** **attivo e gratuito** su **tutto il territorio nazionale** prevede le seguenti attività:

- ✓ **Prelievi ematici al domicilio** del Paziente attraverso una rete di infermieri
- ✓ **Centrifugazione e preparazione** del campione ematico
- ✓ **Consegna** del campione ematico **a temperatura controllata** al Laboratorio del Centro Emofilia e/o al Laboratorio Centrale in Belgio
- ✓ Analisi **attività FVIII**
- ✓ Analisi **farmacocinetica** e successiva elaborazione di uno **schema di dosaggio** in base **al profilo farmacocinetico individuale e alle esigenze selezionate dal clinico**

* Realizzato con il contributo incondizionato di Kedrion Biopharma

NuPreviq Service*: un servizio a lungo termine di personalizzazione della terapia, dedicato ai pazienti e ai medici



* Realizzato con il contributo incondizionato di Kedrion Biopharma

CASO CLINICO

Età	***48 aa***
Peso	***60 Kg***
Emofilia A	***grave con inibitori ad alto titolo eradicati***
Regime	***profilassi 3.000 UI x 3/settimana***
HJHS	***60***
ABR	***2-3***
Trough level	**0.08 IU/dl**

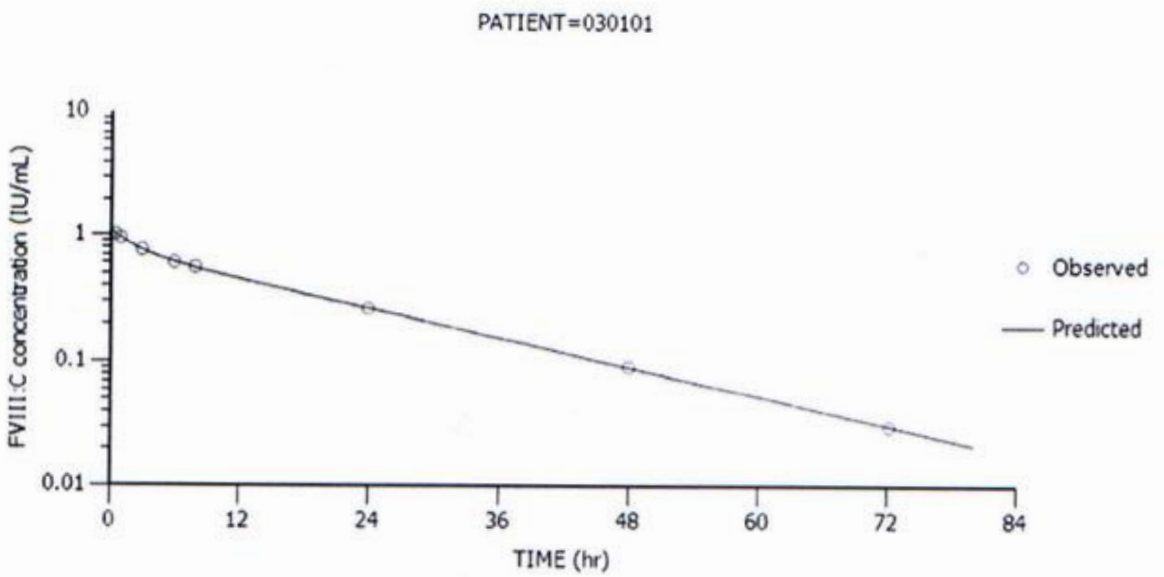
Caso clinico : PK

Time in relation to injection	Date	Time of blood withdrawal (hh/mm)	FVIII:C (IU/ml)
Before Nuwiq® infusion	19OCT2015	9:15	0.012
30 min (±5 min) post	19OCT2015	9:45	1.014
1 hour (±5 min) post	19OCT2015	10:15	0.947
3 hours (±15 min) post	19OCT2015	12:15	0.765
6 hours (±30 min) post	19OCT2015	15:15	0.609
9 hours (±1h) post	19OCT2015	17:15	0.557
24 hours (±2h) post	20OCT2015	9:15	0.262
30 hours (±2h) post			
48 hours (±2h) post	21OCT2015	9:15	0.091
72 hours (±2h) post	22OCT2015	9:30	0.03

Caso clinico : PK 1

Patient ID: 030101
Results of individualised analysis of FVIII pharmacokinetics (PK)

Graph 1: FVIII:C vs. Time



Observed: measured value, Predicted: value based on PK modeling

Fitting model for FVIII elimination:	2CP
Elimination half-life:	15.44 hrs
In-Vivo-Recovery:	2.00 (% per IU/kg)

PK dose options

Table 1: Simulated dosing schemes

									simulated dosing schemes					simulated dosing schemes accounting for accumulation in multiple dosing			
PK model	Weight (kg)	Nominal dose (IU/kg)	Cmax (IU/mL)	t1/2 (hr)	V (mL/kg)	C0 (IU/mL)	IVR (% per IU/kg)	target trough level (IU/mL)	Tau (hr)	est. dose (IU/kg)	est. Cmax (IU/mL)	est. C0 (IU/mL)	C0<2 and est.dose between 10 and 80	est. dose (IU/kg)	est. Cmax (IU/mL)	est. C0 (IU/mL)	C0<2 and est.dose between 10 and 80
2CP	60.0	50.0	1.014	15.44	46.3	1.079	2.00	0.08	24	15.2	0.31	0.33	*	10.0	0.20	0.22	*
									36	26.1	0.53	0.56	*	20.9	0.42	0.45	*
									42	[illegible]	0.69	[illegible]	*	[illegible]	0.59	0.62	*
									48	44.7	0.91	0.96	*	39.5	0.80	0.85	*
									56	64.0	1.30	1.38	*	58.8	1.19	1.27	*
									60	76.6	1.55	1.65	*	71.4	1.45	1.54	*
									72	131.2	2.66	2.83		126.0	2.56	2.72	

2.500 UI x 3/sett

FU ad 1 anno di profilassi personalizzata

- ✓ ABR = 0
- ✓ Ottima compliance

..e i COSTI?

- ✓ **Riduzione del consumo FVIII da 468.000 UI a 390.000 UI/anno**
- ✓ **Riduzione del costo della profilassi da 318.240 € a 253.500 €**
- ✓ **Riduzione del costo della profilassi del 20%**

GRAZIE