



INDIVIDUAL THERAPEUTIC MONITORING STRATEGY OF A FACTOR IX CONCENTRATE (OCTAFIX®) FOR PROPHYLAXIS IN PATIENTS WITH HAEMOPHILIA B, USING POPULATION MODELLING APPROACHES

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INTRODUCTION

Hemophilia B is a rare genetic disorder, characterised by patients’ missing or defective production of clotting factor IX (FIX), resulting in high risk of bleeding. Prophylaxis treatment is effective but demanding and expensive. FIX activity is reported as a percentage of FIX activity measured in healthy subjects.

Objectives

To analyse, using population modelling approaches, FIX activity profile after OCTAFIX® administration, in patients with severe (FIX < 1%) or moderate (FIX < 5%) haemophilia B.

To externally evaluate the predictability of individual parameters and comparison criteria under several sparse sampling designs, in order to propose individual therapeutic monitoring strategy.

PATIENTS AND METHODS

OCTAFIX®: a factor IX concentrate, administered to patients with severe or moderate hemophilia B. Several studies were conducted to evaluate its efficacy and safety:

- YNE-201 and YNE-202 studies in adults (completed in 1998),
- YNE-203 study in children (completed in 2005).

Population model development of Factor IX (FIX) kinetics in 47 adult and pediatric patients, after OCTAFIX single and multiple administrations, at doses ranging from 36 to 81 IU/kg (**Table 1**). FIX levels were determined by the modified Bethesda assay (limit of quantification:1%).

Table 1: Patients’ characteristics

Study	YNE-201	YNE-202	YNE-203	PekaFIX
Population	14	21*	24	14
Samples per patient	11	12	6	13
Weight * (kg)	80.2 [60-126]	72 [42-126]	16 [8.4-28]	71.5 [17-102.6]
Age * (years)	25 [18-81]	22 [12-71]	3.7 [0.8-7.4]	32.5 [4.2 – 56.4]

* 12 patients were included both in YNE-201 and YNE-202 studies

* reported as median [range min – max]

External evaluation of individual therapeutic monitoring strategies

Data from PeKaFIX study (**Table 1**) aiming at characterizing FIX kinetics after OCTAFIX administration, not considered for model development.

Several scenarios were considered and compared in PeKaFIX patients, based on the model developed on data from previous studies:

- 10 sampling schemes: rich sampling (13 samples per individual, considered as the reference); and sparse sampling (3-4 samples at various time points)
- Comparison criteria: Time-To-Reach XX% (5, 4 and 3%) and predicted FIX level at time T (48, 72, 96 and 120h). For each design, absolute change from reference was computed in each patient; and reported ad median [min-max] within the population.

Model development, parameter estimation and simulations were performed using Nonmem 7.3.

CONCLUSION

Using the proposed PK model, individual parameters for FIX kinetics can be predicted based on only few blood samples, **e.g. drawn at 0, 0.5 and 48 hours after OCTAFIX® administration** (Design 5, **Figure 3**).

The prophylactic dosing regimen can then be calculated (assuming dose-linearity) and adapted to each patient, depending on the threshold above which FIX level should be maintained (as a function of patient’s lifestyle) and its individual parameters. This approach will certainly help the management of an individualized prophylactic strategy.

RESULTS

FIX kinetic model:

Dose-normalized profiles show that FIX kinetics are different in adults and in children (**Figure 1**).

FIX kinetics was described by a 2-compartment disposition model and endogenous baseline. Interindividual variability was accounted for on clearance, central volume and baseline level. Allometric scaling (with estimated exponents) allowed simultaneous fit of pediatric data. Goodness-of-fit and parameter estimates are provided in **Figure 2** and in **Table 2**.

Figure 1: Dose-normalized FIX:C measured by one-stage clotting assay YNE-201 (blue), YNE-202 (red), YNE-203 (green)

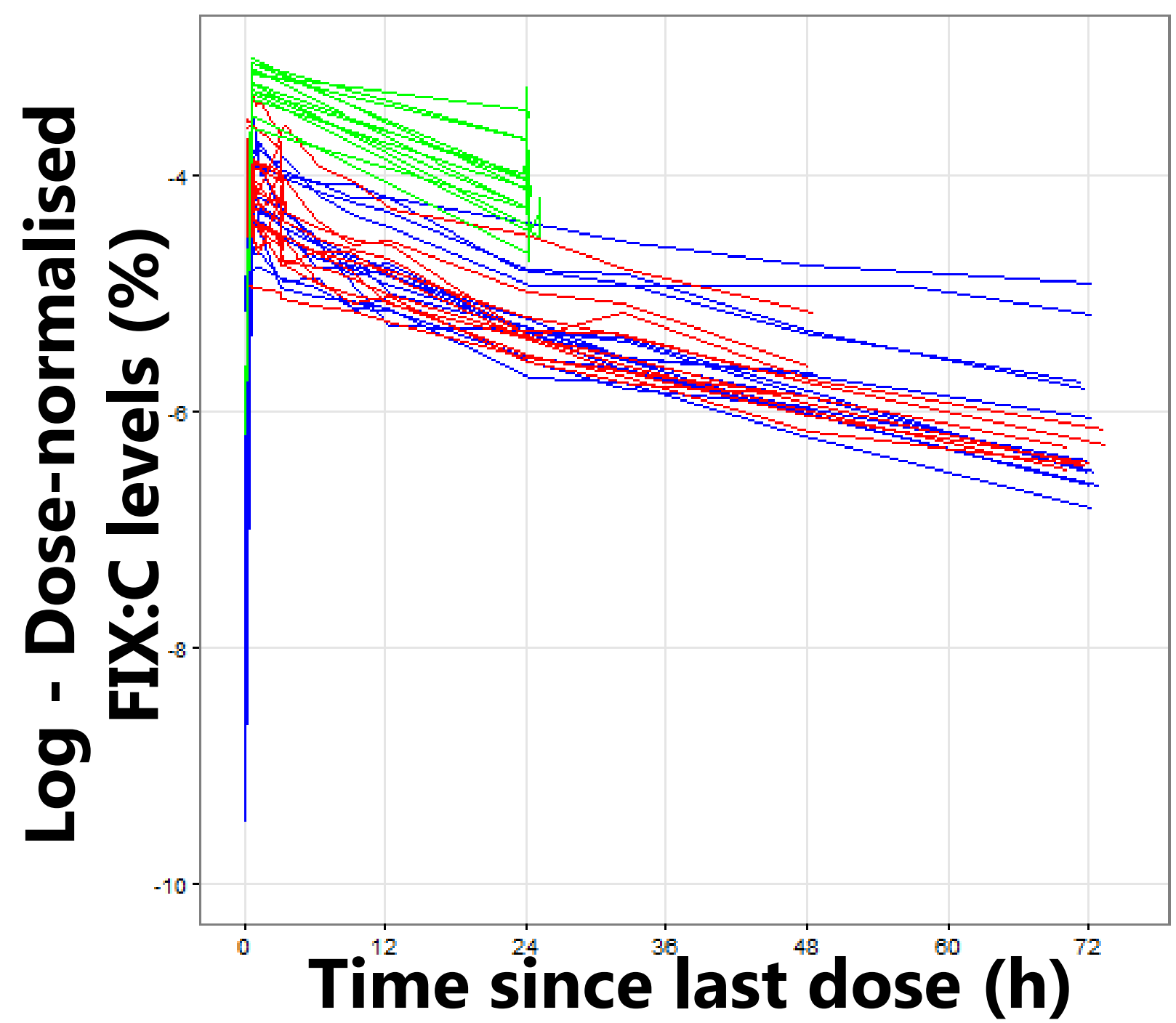


Figure 2: Observations versus Population/Individual predictions

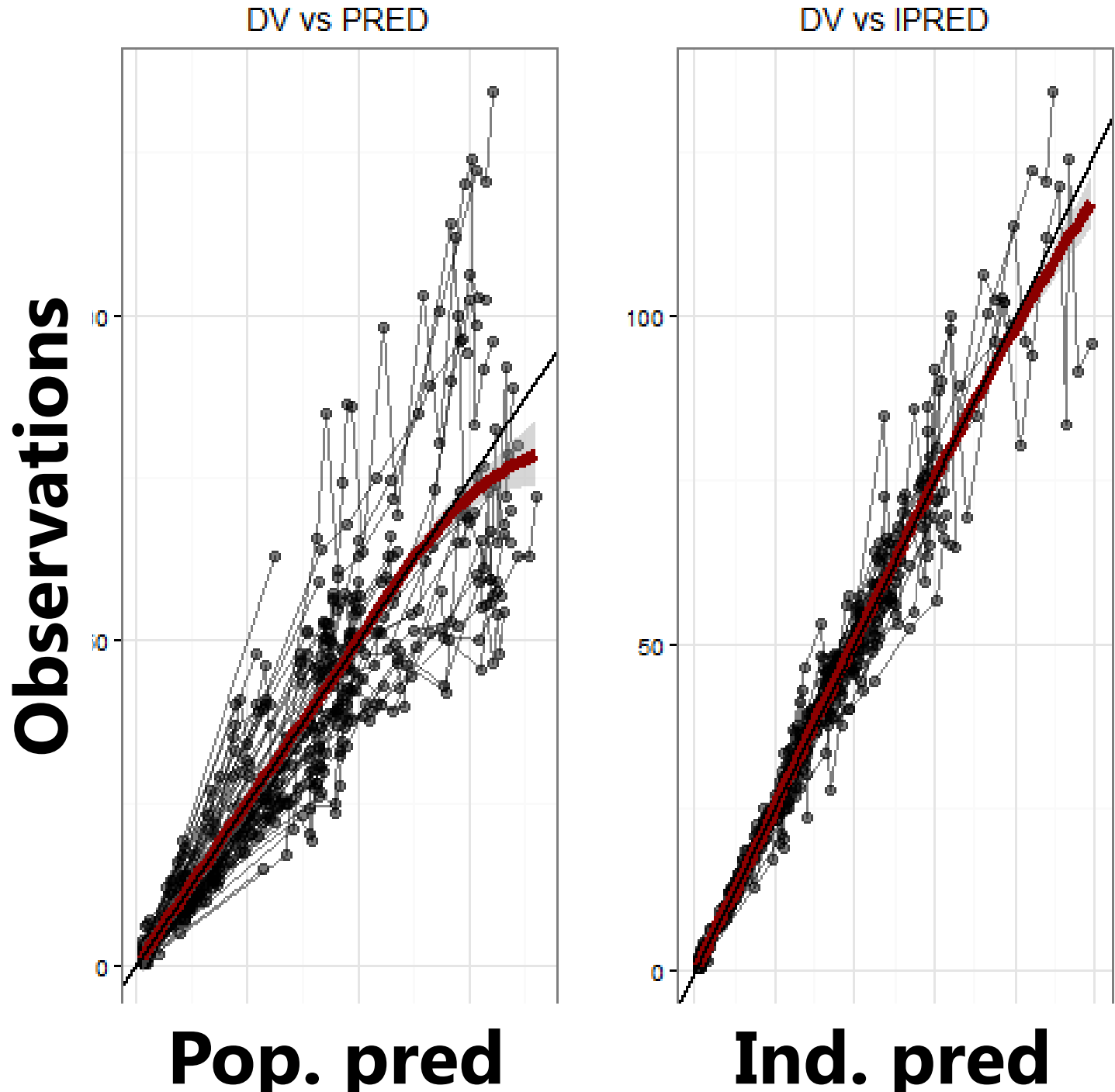


Table 2: FIX parameters for YNE-201 -202 and -203 studies

Parameter	Description	Value (RSE%)	IIV CV % (RSE %)
CL (L.h ⁻¹ . (70 kg) ^{AS.CL})	Clearance from central compartment	2.09 (8.4)	33.4 (20)
Vc (L. (70 kg) ^{AS.V})	Volume of central compartment	64.0 (4.7)	26.4 (18)
Q (L.h ⁻¹ . (70 kg) ^{AS.CL})	Intercompartmental clearance	1.73 (14)	-
Vp (L. (70 kg) ^{AS.V})	Volume of peripheral compartment	29.9 (14)	-
BSL (%)	Basal FIX level	1.09 (10)	34.7 (68)
Add. Res. Err. (%)	Additive residual error	0.633 (17)	-
Prop. Res. Err (-)	Proportional residual error	0.12 (11)	-
AS_CL (-)	Allometric exponent for clearances	0.706 (8.1)	-
AS_V (-)	Allometric exponent for volumes	0.852 (5.5)	-

IIV: Inter-individual variability; CV: coefficient of variation
RSE: Relative Standard Error

Individual dose-optimisation strategy

All evaluated sampling schemes gave adequate individual predictions in terms of - predicted FIX profile (**Figure 3**),

- predicted FIX level at a given time (**Table 3**),
- time-to-reach a given FIX level (**Table 3**).

Better performance were obtained when sampling schemes included samples up to 48 hours over schemes up to 24 hours after administration.

Table 3: Comparison of predicted criteria in PeKaFIX population

	Design 2 3 samples	Design 3 3 samples	Design 4 4 samples	Design 5 3 samples	Design 6 3 samples	Design 7 3 samples	Design 8 3 samples	Design 9 3 samples	Design 10 3 samples
Sampling times:	0,1,24	0,1,48	0,1,6,24	0,0,5,24	0,0,5,48	0,3,24	0,6,24	0,24,48	0,24,96
FIX at time T:									
FIX _{48h} (%)	1.4 [-0.5;5.0]	0.6 [-0.8;1.4]	1.3 [0.0;5.3]	1.4 [-0.1;5.3]	0.7 [0.1;1.4]	1.4 [-0.5;4.8]	1.3 [0.0;5.2]	0.3 [-0.3;1.3]	0.5 [-0.5;1.0]
FIX _{72h} (%)	1.0 [-0.2;4.2]	0.5 [-0.3;0.9]	1.0 [0.1;4.4]	0.9 [-0.0;4.3]	0.5 [0.1;0.9]	1.0 [-0.2;4.1]	1.1 [0.1;4.4]	0.3 [-0.0;1.4]	0.4 [-0.2;0.8]
FIX _{96h} (%)	0.7 [-0.1;3.3]	0.4 [-0.0;0.7]	0.7 [0.1;3.5]	0.7 [-0.0;3.4]	0.3 [0.1;0.8]	0.8 [-0.1;3.3]	0.8 [0.1;3.5]	0.3 [0.0;1.3]	0.3 [-0.1;0.7]
FIX _{120h} (%)	0.5 [-0.2;5]	0.2 [0.1;0.6]	0.5 [0.0;2.6]	0.5 [-0.0;2.5]	0.2 [0.1;0.6]	0.5 [-0.0;2.5]	0.6 [0.1;2.7]	0.2 [-0.0;1.1]	0.3 [-0.0;0.6]
Time-to-reach XX%:									
TTR 5% (h)	8.5 [-2;28]	4.5 [1;9]	8.5 [1;29]	8.5 [-1;28]	4.5 [1;9]	9 [-2;28]	9.5 [1;30]	4.5 [0;13]	5 [-2;8]
TTR 4% (h)	8 [-1;23]	4.5 [1;9]	7 [1;25]	8 [0;23]	5 [1;10]	9 [-1;24]	8 [1;25]	5 [0;15]	6 [-1;9]
TTR 3% (h)	8.5 [-1;18]	4 [1;10]	7.5 [0;19]	8 [0;17]	4 [1;10]	9 [-1;19]	9 [2;21]	2 [-1;9]	7 [-1;8]

Absolute change from reference ($Crit_{Design} - Crit_{Ref}$) reported as median [min; max] across individuals
Reference defined as predictions from Design 1 (13 samples at 0,0.16,0.5,1,3,6,9,12,24,32,48,72,96 hours after injection)

Figure 3: Predicted FIX profile using sparse sample (Design 5, ID 4101)

Blue dots: sparse samples
Black dots: real observations
Green line: individual prediction
Red line: population prediction

