Pharmacokinetic (PK) profiles in boys with hemophilia A assessed using a population PK Program (myPKFiT™) and WinNonlin®

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INTRODUCTION

Trough factor (F)VIII levels in boys with severe hemophilia A receiving prophylaxis are primarily influenced by the individual's pharmacokinetic (PK) profile and the frequency of clotting factor replacement infusions.

Aims of this study are to:

1. Report an analysis of FVIII PK profiles using two PK programs
2. Explore practical reduced sampling time points suitable for use with the population PK (myPKFiT™) program

METHODS

- **Study Cohort** (Table 1):
  - 14 boys with severe hemophilia A
  - 72 hr washout
  - 50 IU/kg of a recombinant FVIII concentrate (Advate®, Baxalta US Inc.)

Table 1: Demographic characteristics

14 boys	Mean ± SD (range)
Age (yr)	10.9 ± 3.1 (6.5 - 17.9)
Weight (kg)	42.3 ± 20.6 (17.6 - 93.8)
Dose (IU/kg)	51.3 ± 5.5 (43.9 - 62.5)

- **FVIII activity levels**

Taken at the following time points:

- **pre-infusion** and **1**, **9**, **24** and **48 hrs post-infusion**

- **PK-parameters**

Clearance [**Cl**], volume of distribution at steady state [**Vss**], terminal half-life [$\mathbf{t_{1/2}}$] and **Time to 1%** FVIII level

Calculated using

- Phoenix® WinNonlin® 6.4, two-compartment model (Certara®)
- myPKFiT™ (web-based application, Baxalta US Inc.)

- **Statistical Analysis**

Evaluated by Intra-class correlations (ICC)*:

1. Two-compartment model on WinNonlin® **VS** myPKFiT™
2. 5 sampling points **VS** 2 or 3 sampling points on myPKFiT™

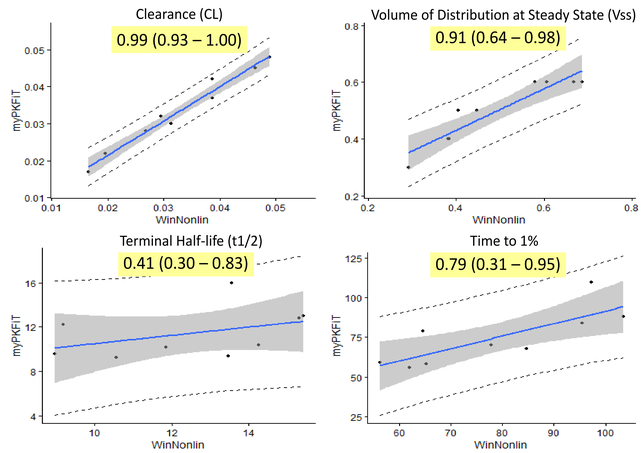
* Pair-wise deletion was used

RESULTS

Result 1

Agreement for Cl and Vss between myPKFiT™ and WinNonlin® was excellent, with strong agreement for time to 1% FVIII and fair agreement for $t_{1/2}$ (Fig.1).

Fig 1: Agreements between WinNonlin® VS myPKFiT™ . Shown are ICC and 95%CI for ICCs



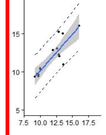
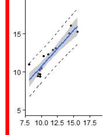
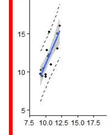
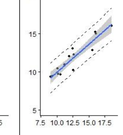
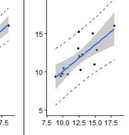
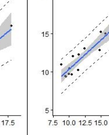
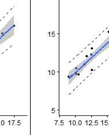
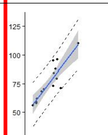
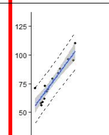
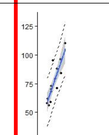
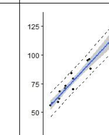
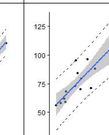
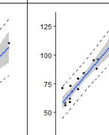
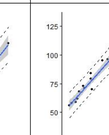
ICC Criteria [1] (classification of agreement)

>0.8 = almost perfect	0.4-0.6 = moderate
0.6-0.8 = substantial	0.2-0.4 = fair

Result 2

myPKFiT™ PK parameters derived from sampling time points at **1 hr and 9 hrs** and **1 hr and 24 hrs** had excellent agreements (ICC's of approx. 0.9) for $t_{1/2}$ and time to 1% compared to the 5-point sampling schedule and are practical in an outpatient setting (Table 2).

Table 2: Agreements 5 sampling points VS 2 or 3 sampling points on myPKFiT™

5 VS:	**1 & 9 hrs**	**1 & 24 hrs**	1 & 48 hrs	9 & 24 hrs	9 & 48 hrs	24 & 48 hrs	9 & 24 & 48 hrs
Required hospital visit (Days)	**1**	**1**	2	2	2	3	3
Terminal Half-life							
ICC (95%CI)	**0.86 (0.62-0.95)**	**0.92 (0.76-0.97)**	0.59 (0.09-0.84)	0.91 (0.75-0.97)	0.76 (0.41-0.93)	0.90 (0.74-0.97)	0.91 (0.75-0.97)
Time to 1%							
ICC (95%CI)	**0.88 (0.66-0.96)**	**0.92 (0.78-0.98)**	0.60 (0.12-0.85)	0.95 (0.84-0.98)	0.83 (0.56-0.94)	0.94 (0.81-0.98)	0.95 (0.85-0.98)

CONCLUSIONS

1) Key PK parameters (Cl and Vss) are essentially identical with the myPKFiT™ and WinNonlin® PK programs.
2) The sparse sampling evaluation with the myPKFiT™ program produced 2 combinations of 2-point PK samplings (1 & 9 hrs post-infusion and 1 & 24 hrs post-infusion) that show excellent agreement for $t_{1/2}$ and time to 1% FVIII which are clinically relevant and practical in an outpatient clinical setting.
3) The low level of agreement (ICC 0.6) for the 1 & 48 hrs. post-infusion 2- point PK sampling suggests that it would not be an optimal sampling schedule.

REFERENCES

[1]Fleiss and Cohen . The equivalence of weighted Kappa and the intraclass correlation coefficient as measures of reliability. Educ Psychol Meas 1973; 33:613 -619

ACKNOWLEDGEMENTS

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