Data Article

Pharmacokinetic characteristics of the triple inactivated plasma-derived Kedrion FIX concentrate: data from the KB037 clinical trial

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ABSTRACT

The pharmacokinetics data of phase I/II clinical trials (EudrACT Number: 2005-006186-14) of the new, triple inactivated plasma-derived Kedrion FIX concentrate was designed according to the recommendations of SSC-ISTH [1,2]: 11 post-infusion FIX/time points samples during the first 72 h. The PK data were also analysed by a modified, less dense, 9 FIX/time points, sample design. The outcomes of the safety and efficacy study and the pharmacokinetics’ results have been previously and partially described [3,4]. The single-dose PK at enrolment (PK I) and the end of the trial (PK II) were analyzed by WinNonlin 7.0 (Pharsight) and according to three different methods: Non-Compartment Analysis (NCA), One Compartment Method (OCM), and Two-Compartment Method (TCM).

The outcomes of PK parameters by TCM show that a higher number of FIX/time concentration points may not always give a better definition of the decay curve. On the other hand, the Terminal HL of NCA is deeply affected by the goodness of the last two-three points. The quite long Kedrion FIX HL may allow for a cost/effective tailoring of prophylaxis in haemophilia B patients.

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Specifications Table

| Subject                          | Hematology                                                                 |
|----------------------------------|-----------------------------------------------------------------------------|
| Specific subject area            | Pharmacokinetics of a new plasma-derived FIX concentrate                |
| Type of data                     | Tables, Graphs                                                             |
| How data were acquired           | Pharmacokinetic data, FIX:C/times, at enrolment and after six months of   |
|                                  | treatment, (on-demand five patients, prophylaxis nine patients) have       |
|                                  | been collected at the end of a regulatory, clinical trial of new Kedrion   |
|                                  | FIX concentrate (See Supplementary data)                                   |
| Instruments:                     | WinNonlin 7.0, Phoenix, Pharsight Corp, California, USA:                   |
|                                  | Non-compartment Analysis (NCA) and Two Compartment Model (TCM or 2CP model)|
| Data format                      | Raw data Analyzed: FIX:C IU/dL, Lambda_2 1/hrs, HL_Lambda_2 hrs, Cmax/Dose |
|                                  | IU/dL/IU/kg, AUC U^h/dL, AUMC U^h2/dL, V_d dl/kg, Cl dl/h/kg, MRT hrs,    |
|                                  | Alpha 1/hrs, Alpha_HL hrs, Beta_HL hrs, Vss dl/kg                        |
| Parameters for data collection   | Haemophilia B severe or moderately severe patients underwent a single     |
|                                  | dose Kedrion FIX PK after 3-4 days wash out. FIX assay has been            |
|                                  | centralized in a single Laboratory                                      |
| Description of data collection   | The data were collected using a Case Report Form, according to the        |
|                                  | protocol approved, see Eudract-Code 2005-006186-14                         |
| Data source location             | Institution: Kedrion Biopharma                                           |
|                                  | City/Town/Region: Barga (Lucca)                                           |
|                                  | Country: Italy                                                            |
|                                  | Latitude and longitude (and GPS coordinates, if possible) for collected    |
|                                  | samples/data: Not available                                               |
|                                  | Primary data sources: Clinical Study Report KB037, 21/12/2001             |
| Data accessibility               | The source data, individual single-dose PK I and II, are hosted with the   |
|                                  | article as supplementary data.                                            |
| Related research article         | Castaman G., Borchiellini A., Santagostino E., Radossi P., Aksu S., Yilmaz|
|                                  | M., Serban M., Uscatescu V., Truica C., Fasulo MR, Mancuso ME, Paladino   |
|                                  | E., Valpreda A., Guarnieri C., Macchia R., Scarpellini M., Mathew P., and  |
|                                  | Morfini M.                                                                 |
|                                  | Non-Compartment and Compartmental Pharmacokinetics, Efficacy, and         |
|                                  | Safety of Kedrion FIX concentrate Eur J Pharm Sci. 2020 Jul 23:105485.    |
|                                  | doi: 10.1016/j.ejps.2020.105485. Online ahead of print.PMID: 32712218   |

Value of the Data

- The new Kedrion FIX concentrate was submitted to three different viral inactivation steps to improve the safety of a pdFIX product; thus, it is essential to evaluate its safety, efficacy, and pharmacokinetics.
- Physicians can use this information to better serve the needs of patients with FIX deficiency. Haemophilia B patients can achieve therapeutic levels of FIX from a safer and cheaper FIX concentrate.
- The accurate PK data according to TCM may be useful to tailor the dosing frequency of prophylaxis, according to individual clearance of the concentrate (personalized prophylaxis).
- The improvement of PK parameters observed in haemophilia B patients who undergo prophylaxis might convince them to switch from on-demand to prophylaxis, thus decreasing joint arthropathy, improving quality of life for the patient, and thus improving productivity for society.
- Compared to the new and expensive extended half-life rFIX concentrates, Kedrion FIX may be cost/effective.
Fig. 1a. Plots of FIX:C decay curve by means of NCA, according to 11 sample points, at enrollment (PK I)
Fig. 1b. Plots of FIX:C decay curve by means of NCA, according to 9 sample points, at enrollment (PK I)
Fig. 2a. Plots of FIX:C decay curve by means of NCA, according to 11 sample points, at the end of the trial (PK II)
Fig. 2b. Plots of FIX:C decay curve by means of NCA, according to 9 sample points, at the end of the trial (PK II)
Fig. 3a. Plots of FIX:C decay curve by means of 2CP model, according to 11 sample points, at enrollment (PK I)
Fig. 3b. Plots of FIX:C decay curve by means of 2CP model, according to 9 sample points, at enrollment (PK I)
Fig. 4a. Plots of FIX:C decay curve by means of 2CP model, according to 11 sample points, at the end of trial (PK II)
Fig. 4b. Plots of FIX:C decay curve by means of 2CP model, according to 9 sample points, at the end of trial (PK II)


Table 1a
Parameters of PK I and PK II by Non-Compartmental Analysis; as far as the Terminal HL (HL Lambda_Z), two outliers (patients 03 01 and 14 05, bold and in Italic) are present in the outcomes of PK II. Significant improvements of AUC, AUMC, CI, and MRT were observed at PK II

| N | ID  | Lambda_z | HL_Lambda_z | Cmax_D | AUC | Vd | CI | AUMC | MRT |
|---|-----|----------|-------------|--------|-----|----|----|------|-----|
|   |     | 1/Hours  | Hours       | IU/dl/| U^2/h/dl | dl/kg | h/kg | U^2/h^2/dl | Hours |
| 1 | 01  | 0.0191   | 36.21       | 1.07  | 1625 | 1.2917 | 0.0247 | 39989 | 24.62 |
| 1 | 01  | 0.0170   | 40.83       | 1.19  | 1386 | 1.3464 | 0.0229 | 34091 | 24.60 |
| 1 | 02  | 0.0194   | 35.78       | 1.30  | 1716 | 1.1562 | 0.0224 | 42385 | 24.70 |
| 1 | 03  | 0.0312   | 22.20       | 1.54  | 2082 | 0.6727 | 0.0210 | 46807 | 22.48 |
| 1 | 04  | 0.0193   | 35.98       | 1.54  | 2296 | 0.8378 | 0.0161 | 59408 | 25.88 |
| 1 | 09  | 0.0249   | 27.79       | 1.57  | 2275 | 0.7168 | 0.0179 | 57751 | 25.38 |
| 1 | 12  | 0.0256   | 27.03       | 2.20  | 2925 | 0.5373 | 0.0138 | 71187 | 24.33 |
| 1 | 12  | 0.0134   | 51.69       | 1.03  | 1697 | 1.5247 | 0.0204 | 44400 | 26.16 |
| 1 | 14  | 0.0232   | 29.91       | 1.22  | 1758 | 1.0074 | 0.0233 | 42524 | 24.20 |
| 1 | 14  | 0.0124   | 55.73       | 1.01  | 1222 | 2.0985 | 0.0261 | 29644 | 24.27 |
| 1 | 14  | 0.0138   | 56.15       | 1.09  | 1466 | 1.9417 | 0.0268 | 33383 | 22.77 |
| 1 | 14  | 0.0141   | 48.13       | 1.40  | 1755 | 1.5035 | 0.0212 | 39157 | 22.32 |
| 1 | 14  | 0.0250   | 27.72       | 1.22  | 1801 | 0.8923 | 0.0223 | 45350 | 25.18 |
| 1 | 15  | 0.0239   | 28.98       | 0.76  | 706  | 2.7376 | 0.0655 | 16897 | 23.92 |
| 14 Mean | 0.0202 | 37.08 | 1.29 | 1765 | 1.3046 | 0.0246 | 43070 | 24.34 |
| Median | 0.0193 | 35.88 | 1.22 | 1735 | 1.2239 | 0.0224 | 42459 | 24.47 |
| 1 | 1 S.D. | 0.0057 | 10.77 | 0.35 | 531 | 0.6209 | 0.0123 | 13472 | 1.18 |
| Min | 0.0124 | 22.20 | 0.76 | 706 | 0.5373 | 0.0138 | 16897 | 22.22 |
| Max | 0.0312 | 53.73 | 2.20 | 2925 | 2.7376 | 0.0655 | 71187 | 26.16 |

End of the study

| N | ID  | Lambda_z | HL_Lambda_z | Cmax_D | AUC | Vd | CI | AUMC | MRT |
|---|-----|----------|-------------|--------|-----|----|----|------|-----|
|   |     | 1/Hours  | Hours       | IU/dl/| U^2/h/dl | dl/kg | h/kg | U^2/h^2/dl | Hours |
| 1 | 01  | 0.0236   | 29.42       | 1.19  | 1826 | 0.9800 | 0.0231 | 45565 | 24.95 |
| 1 | 01  | 0.0134   | 51.69       | 1.14  | 1586 | 1.3284 | 0.0178 | 42590 | 26.86 |
| 1 | 02  | 0.0162   | 42.70       | 1.26  | 1742 | 1.3063 | 0.0212 | 43846 | 24.96 |
| 1 | 03  | 0.1655   | 4.19        | 1.78  | 2552 | 0.1182 | 0.0196 | 55461 | 21.73 |
| 1 | 04  | 0.0210   | 32.98       | 1.44  | 2098 | 0.8745 | 0.0184 | 52282 | 24.90 |
| 1 | 09  | 0.0221   | 31.41       | 1.70  | 2922 | 0.6341 | 0.0140 | 76497 | 26.18 |
| 1 | 12  | 0.0184   | 37.63       | 1.86  | 3092 | 0.6961 | 0.0128 | 79465 | 25.70 |
| 1 | 12  | 0.0211   | 32.79       | 0.91  | 1299 | 1.4636 | 0.0309 | 33729 | 25.96 |
| 1 | 14  | 0.0359   | 19.31       | 1.28  | 2055 | 0.6014 | 0.0216 | 51279 | 24.96 |
| 1 | 14  | 0.0181   | 38.38       | 1.32  | 1716 | 1.1614 | 0.0210 | 41122 | 23.96 |
| 1 | 14  | 0.0259   | 26.72       | 1.24  | 1958 | 0.8362 | 0.0217 | 47885 | 24.46 |
| 1 | 14  | 0.0252   | 27.56       | 1.34  | 1979 | 0.7963 | 0.0200 | 49563 | 25.04 |
| 1 | 14  | 0.0022   | 321.84      | 1.28  | 2097 | 1.9595 | 0.0042 | 61379 | 29.27 |
| 14 Mean | 0.0160 | 43.19 | 0.55 | 950 | 2.5193 | 0.0404 | 25992 | 27.35 |
| Median | 0.0303 | 52.84 | 1.31 | 1991 | 1.0911 | 0.0205 | 50446 | 25.45 |
| 1 | S.D. | 0.0211 | 32.89 | 1.28 | 1968 | 0.9273 | 0.0205 | 48724 | 25.00 |
| Min | 0.0022 | 4.19 | 0.55 | 950 | 0.1182 | 0.0042 | 25992 | 21.73 |
| Max | 0.1655 | 321.84 | 1.86 | 3092 | 2.5193 | 0.0404 | 79465 | 29.27 |

Wilcoxon signed-rank test

| Z  | P   | 0.360 | 0.450 | 0.660 | 0.013 | 0.097 | 0.036 | 0.013 | 0.026 |

1. Data Description

The raw data of Kedrion FIX concentrate PK performed in 14 haemophilia B patients [on demand (n = 5) or continuous prophylaxis (n = 9)], at enrolment in the clinical trial and after six months of treatment, are reported in the supplementary data file (Kedrion FIX PK I data.xls)
Table 1b
– Parameters of PK I and PK II by Non-Compartmental Analysis according to 9 post-infusion FIX/time points; a significant improvement of AUC, AUMC, Cl, and MRT was observed at PK II

| Enrollment | Lambda_z | H.L_Lambda_z | Cmax_D | AUC | Vd | Cl | AUMC | MRT |
|------------|----------|--------------|--------|-----|----|----|------|-----|
| Hours | 1/Hours | Hours | IU/dL/IU/kg | h/dL | h/dL/kg | h/dL/kg | h^2/dL | Hours |
| 1 | 01 01 | 0.0248 | 27.90 | 1.07 | 1632 | 1.0432 | 0.0259 | 39710 | 24.33 |
| 2 | 01 02 | 0.0230 | 30.09 | 1.19 | 1409 | 1.0515 | 0.0242 | 34568 | 24.53 |
| 3 | 02 01 | 0.0191 | 36.31 | 1.30 | 1721 | 1.1668 | 0.0223 | 42265 | 24.56 |
| 4 | 03 01 | 0.0302 | 22.93 | 1.54 | 2100 | 0.7043 | 0.0213 | 46185 | 21.99 |
| 5 | 04 01 | 0.0191 | 36.31 | 1.54 | 2312 | 0.8392 | 0.0160 | 59599 | 25.78 |
| 6 | 09 02 | 0.0229 | 30.28 | 1.57 | 2183 | 0.8934 | 0.0204 | 50864 | 23.30 |
| 7 | 12 01 | 0.0256 | 27.06 | 2.20 | 2876 | 0.5456 | 0.0140 | 68524 | 23.83 |
| 8 | 12 02 | 0.0204 | 33.91 | 1.03 | 1708 | 1.1213 | 0.0229 | 44040 | 25.79 |
| 9 | 14 01 | 0.0231 | 29.98 | 1.22 | 1768 | 1.0044 | 0.0232 | 42406 | 23.98 |
| 10 | 14 02 | 0.0188 | 36.94 | 1.01 | 1195 | 1.6462 | 0.0309 | 28097 | 23.51 |
| 11 | 14 03 | 0.0297 | 23.31 | 1.09 | 1446 | 0.8020 | 0.0316 | 32293 | 22.33 |
| 12 | 14 04 | 0.0305 | 22.69 | 1.40 | 1725 | 0.8519 | 0.0260 | 36470 | 21.14 |
| 13 | 14 05 | 0.0237 | 29.20 | 1.22 | 1724 | 1.0222 | 0.0243 | 40791 | 23.67 |
| 14 | 15 01 | 0.0252 | 27.55 | 0.76 | 716 | 2.5930 | 0.0652 | 17045 | 23.79 |
| 15 | Mean | 0.0240 | 29.60 | 1.29 | 1751 | 1.1104 | 0.0263 | 41633 | 23.75 |

Non-Compartmental Analysis
(9 post-infusion points)

End of the study

| Wilcoxon signed-rank test | p | 0.129 | 0.158 | 0.659 | 0.019 | 0.864 | 0.022 | 0.013 | 0.028 |

Data.xls).
Figs. 1a/1b and 2a/2b show the plots according to the two, 11 or 9, Fix/time sample point designs of PK I and PK II, using NCA. The different Terminal HlLs are shown as the result of the selection of the last best fitting points. Tables 1a and 1b report in detail the parameters of PK I and PK II achieved by NCA, according to a 11 or 9 sample points design. Figs. 3a/3b and 4a/4b show the data obtained using TCM again according to
Table 2a
Outcomes of TCM at PK I and II, according to a post-infusion FIX/time 11 points. Two patients at PK I and five at PK II showed extremely high and unbelievable parameters due to the very flat disposition of the last part of the decay curve

Two Compartment Model (11 points)

| At enrolment | End of the study |
|--------------|------------------|
| **N** | **ID** | **Alpha_HL** | **AUC** | **Beta_HL** | **CL** | **K10_HL** | **MRT** | **Vss** | **N** | **ID** | **Alpha_HL** | **AUC** | **Beta_HL** | **CL** | **K10_HL** | **MRT** | **Vss** |
| 1 | 01 01 | 1.58 | 1892 | 26.77 | 0.0271 | 23.42 | 38.29 | 1.0379 | 1 | 00 01 | 0.84 | 2148 | 27.25 | 0.0239 | 23.73 | 39.13 | 0.9342 |
| 1 | 01 02 | 7.89 | 1857 | 43.27 | 0.0231 | 25.30 | 54.35 | 1.2544 | 1 | 00 02 | 5.64 | 2205 | 42.15 | 0.0194 | 31.19 | 57.95 | 1.1262 |
| 1 | 02 01 | 6.09 | 2191 | 36.64 | 0.0228 | 23.98 | 48.22 | 1.1004 | 1 | 00 03 | 3.33 | 2127 | 30.97 | 0.0235 | 22.82 | 42.96 | 1.0097 |
| 1 | 03 01 | 16.90 | >5000 | >200 | 0.0090 | 50.29 | >200 | 4.2810 | 1 | 00 01 | 0.71 | 2398 | 25.79 | 0.0203 | 23.07 | 37.09 | 0.7544 |
| 1 | 04 01 | 4.99 | 2977 | 35.86 | 0.0164 | 27.34 | 49.49 | 0.8110 | 1 | 00 02 | 10.76 | >10000 | >200 | 0.0001 | >200 | >200 | 3.2759 |
| 1 | 09 02 | 10.76 | >10000 | >200 | 0.0001 | >200 | >200 | >200 | 3.2759 | 1 | 12 01 | 2.24 | 3432 | 27.65 | 0.0139 | 22.18 | 39.09 | 0.5447 |
| 1 | 12 02 | 3.53 | 2153 | 33.53 | 0.0239 | 28.07 | 47.39 | 1.1326 | 1 | 12 02 | 12.13 | 2362 | 62.09 | 0.0212 | 23.36 | 60.55 | 1.2821 |
| 1 | 14 01 | 6.88 | 2123 | 31.46 | 0.0235 | 23.91 | 42.25 | 0.9951 | 1 | 14 01 | 8.13 | 1830 | 60.02 | 0.0260 | 26.44 | 71.70 | 1.8661 |
| 1 | 14 02 | 4.45 | 1629 | 24.44 | 0.0327 | 19.67 | 33.71 | 1.1035 | 1 | 14 04 | 12.13 | 2362 | 62.09 | 0.0212 | 23.36 | 60.55 | 1.2821 |
| 1 | 14 05 | 12.25 | 2843 | 70.90 | 0.0176 | 32.64 | 81.56 | 1.4346 | 1 | 14 05 | 12.25 | 2843 | 70.90 | 0.0176 | 32.64 | 81.56 | 1.4346 |
| 1 | 15 01 | 0.36 | 797 | 24.64 | 0.0697 | 10.56 | 34.86 | 2.4283 | 13 | * | Outliers |

ID = 03 01: An error occurred during curve stripping. Initial estimates cannot be determined for this model.

the two different, 11 or 9, sample point designs of PK I and PK II. Alpha and Beta HL of each PK are also added to each plot. Tables 2a and 2b report in detail the parameters of PK I and PK II achieved by TCM, according to a 11 or 9 sample points design. The source data, the assays of FIX:C (IU/dL), the bodyweight of the patient, the infused dose of Kedron FIX (IU/kg), and the post-infusion sample times are reported in the files provided as Supplementary data. The data are reported according to the format required by WinNonlin.

2. Experimental Design, Materials and Methods

Fourteen severe or moderately severe haemophilia B patients from eight Comprehensive Haemophilia Centres (4 in Italy, 3 in Romania, and 1 in Turkey) were enrolled in a new clinical trial plasma-derived FIX concentrate [KB037 trial]. The poor-platelet citrated plasmas have been collected before and after 0.25, 0.5, 1, 3, 9, 24, 32, 48, 50, and 72 of the test dose of Kedron FIX (11 points), according to a dense sample times design (SSE_ISTH). Fresh frozen plas-
mas have been frozen, stored at -40°C and shipped in dry ice to the Reference Laboratory of the Haemophilia Centre of Florence, within 30 days from the end of PK I or PKII, respectively. The FIX:C assay has been done by the One Stage clotting assay. For more details, see the previously published report [1]. The PK data have been analysed by Non-Compartment Analysis (NCA), One and Two Compartment Method (OCM and TCM). We consider only NCA and TCM results, being
the diagnostic tests for best fitting in favour of TCM [2]. A simplified sample design was also used to analyze the PK data, only 9 points, eliminating the 30 and 50 h FIX/time values.

Ethics Statement

The clinical trial was approved by Central Authorities of each country and local Ethics Committees. All haemophilia B patients signed a detailed and specific form for informed consent.

Declaration of Competing Interest

MM received a fee from Kedrion Biopharma for Compartmental analysis of the PKs and acted as a paid consultant to Kedrion SpA. CG, MS, RM, and PM are employees of Kedrion Spa.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dib.2020.106164.

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