PHARMACOKINETIC PROPERTIES, SAFETY AND TOLERABILITY OF NEW B-DOMAIN DELETED RECOMBINANT FACTOR VIII (OCTOFACTOR) IN PATIENTS WITH SEVERE AND MODERATE HEMOPHILIA A

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Objectives:

The primary objectives were to
- Determine the pharmacokinetic parameters of Octofactor in patients with severe and moderate hemophilia A.
- Assess the safety and tolerability of different doses of Octofactor in patients with severe and moderate hemophilia A.

The secondary objectives were to
-Set the maximum tolerated dose of Octofactor in practically possible range of doses.
-Evaluate FVIII activity in the activated partial thromboplastin time (APTT) clotting assay after Octofactor infusions in doses 25 IU kg^{-1} and 50 IU kg^{-1}.

Methods:

The study was performed in 12 previously treated male patients from 24 to 57 years old. Patients were divided into 3 groups. In 1st group 3 patients received a single dose of 10 IU kg^{-1} of Octofactor. In the 2nd group 6 patients received a single dose of 25 IU kg^{-1}, and then after 4 days wash out period - a single dose of 50 IU kg^{-1}. In the 3rd group 3 patients received a single dose of 60 IU kg^{-1} of Octofactor (fig. 1).

One-stage clotting assay was used for evaluation of FVIII activity before and after infusions of Octofactor. Blood samples for plasma FVIII concentrations were collected by venipuncture at 5 min before injection, and at 15, 30 min, and 1, 3, 6, 12, 24, 48 and 72 h after injection. Pharmacokinetic parameters were calculated using plasma samples, which had been separated from citrated whole blood collections and frozen at -60ºC until assayed.

Figure 1. **Study design**

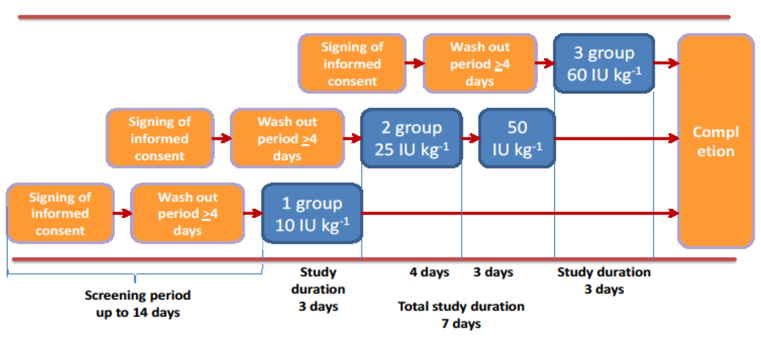
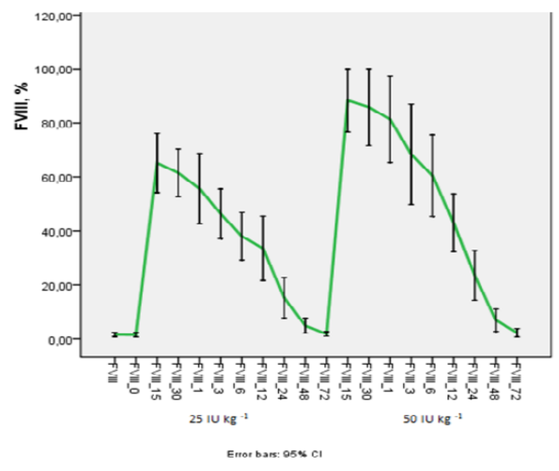


Figure 2. **Activity of FVIII**



Variable	Mean (*M*)	Standard Deviation (*SD*)
Kel (1 h^{-1})	0.059	0.0061
$T_{1/2}$ (h)	12.69	1.35
$AUC_{0-72\ h}$ (IU h dl^{-1})	1497.8	472.1
$AUC_{0-\infty}$ (IU h dl^{-1})	1517.8	496.87
$AUC_{0-\infty}$ (%)	1.01	1.21
MRT (h)	17.38	2.51
CL (dl h^{-1})	2.94	1.16
C_{max} (IU dl^{-1})	89.68	12.81
T_{max} (h)	0.33	0.13
K-value (IU dL^{-1} per IU kg^{-1})	1.79	0.26
IVR (%)	78.85	10.8

Results:

15 minutes after the infusion of Octofactor there was a significant increase in activity of FVIII, accompanied by its normalization. Activity of FVIII 48 hours after Octofactor infusion was about 5% of normal (fig. 2). The infusion of 50 IU/kg of Octofactor resulted in FVIII activity increase so that mean K-value was 1.79±0.26 IU dl^{-1} per IU kg^{-1} with a range of 1.5- 2.2 IU dl^{-1} per IU kg^{-1} and mean in vivo recovery (IVR) was 78.85 % ±10.8 with a range of 67.95 – 96.4 %. The mean elimination half-life ($T_{1/2}$) was 12.69±1.35 hours with a range of 10.66 – 14.44 hours. The mean values of area under the curve ($AUC_{0-72\ h}$), clearance (CL) were 1498±472 IU h dl^{-1} and 2.94±1.16 dl h^{-1} respectively. Other pharmacokinetic parameters are shown in the table. During the study APTT reduced to normal value after a dose of 25 IU kg^{-1} (37,6±2,1sec) and after a dose of 50 IU kg^{-1} (34,6±1,9 sec). The normal level of APTT was maintained for at least 6 hours after administration of Octofactor in dose of 25 IU kg^{-1}, and not less than 12 hours after a dose of 50 IU kg^{-1}. Octofactor was well tolerated in all studied doses. No clinically significant changes in vital signs were noted between pretreatment and posttreatment examinations. There were no treatment-related adverse events, thrombosis formation or FVIII inhibitor development after BDDrFVIII single dose of 10 IU kg^{-1}, 25 IU kg^{-1}, 50 IU kg^{-1}, and 60 IU kg^{-1} infusions.

Conclusions:

1. The results of the present phase I study demonstrate the safety and good tolerability of Octofactor in all studied doses. The maximum dose of Octofactor in the study was 60 IU kg^{-1} , but according to the results the not a maximum tolerated dose.
2. FVIII activity and APTT changes after infusion show pharmacological activity of Octofactor.
3. The pharmacokinetic parameters are comparable to the reported results from other related studies where one-stage clotting assay was used.

References:

1. Morfini M. et al. A multicenter pharmacokinetic study of the B-domain deleted recombinant factor VIII concentrate using different assays and standarts. Journal of Trombosis and Haemostasis. 2003; 1: 2283-2289.
2. Zorenko V. et al. Pharmacokinetics, safety, and tolerability of Octofactor in hemophilia A patients: Results of phase I clinical study. Pediatric Haematology/Oncology and Immunopathology. 2013;12(2):30-7. (In Russian).