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RESEARCH

A randomized, two-armed, double-blind, single-dose, cross-over, bioequivalence clinical trial to compare pharmacokinetic parameters and safety of recombinant human factor VIII with Fc fusion produced by AryoGen Pharmed Company versus Elocta® (reference product) in previously treated patients with severe haemophilia A

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Abstract

This clinical study evaluates the bioequivalence of recombinant factor VIII with Fc fusion protein (rFVIII-Fc) developed by AryoGen Pharmed Company compared to the reference product, Elocta® by Sobi Co., in severe haemophilia A patients. Fc-fused recombinant factor VIII represents a significant advancement in haemophilia A treatment, offering extended half-life and reduced infusion frequency, thus improving patients' adherence to treatment and quality of life. In a randomized, double-blind, single-dose crossover trial, 50 Iranian patients were assigned to treatment groups in a 1:1 ratio. Subjects received both the test and the reference product with a 7-day washout period between treatments. Pharmacokinetic assessments were conducted over five days post-administration to evaluate the primary outcome, the dose-normalized area under the curve (DNAUC). The results established bioequivalence between rFVIII-Fc (AryoGen Pharmed Company) and Elocta®, based on the DNAUC as the primary outcome, in which the ratio of test and reference products was calculated to be 108.56 (90% confidence interval 104.88 to 112.37), falling within the pre-defined equivalence margin of 80–125%. Secondary outcomes, including area under the curve (AUC_{inf}), maximum concentration (C_{max}), and half-life, further supported bioequivalence. Safety profiles were comparable, with adverse events mainly related to haemophilia A rather than the intervention. In conclusion, the rFVIII-Fc product is bioequivalent to Elocta® with a similar safety profile, offering an effective alternative for severe haemophilia A patients. This trial was registered in ClinicalTrials.gov (NCT06137092).

Keywords Factor VIII · Cross-over study · Haemophilia A · Biosimilar pharmaceuticals · Area under curve · Pharmacokinetics

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Introduction

Haemophilia A is a rare genetic disorder that leads to a deficiency in FVIII, causing disruptions in the blood coagulation pathway throughout an individual's lifetime [1]. There are currently an estimated 794,000 individuals worldwide who have haemophilia A, with roughly 270,000 of them experiencing a severe form of the disease [2]. Globally, out of every 10,000 people, one is born with haemophilia, and out of every 10 haemophilia patients, eight have haemophilia A. In Iran, up until 2020, there have been approximately 10,300 identified haemophilia patients, of whom 5,415 have been reported to have haemophilia A. The total consumption of FVIII in Iran for that year was reported to be 250,054,089 units [3].

Routine prophylactic treatment with FVIII is an established standard for managing severe haemophilia A [4]. This approach, involving regular administration of FVIII, has been effective in lowering the incidence of bleeding, preventing joint damage, and enhancing the quality of life for these patients [5]. However, the need for frequent intravenous administrations of traditional FVIII products poses a significant challenge, often affecting patient compliance due to the inconvenience [6].

To address this, various methods have been developed to prolong the half-life of FVIII in its recombinant form (rFVIII), aiming to decrease the necessity for frequent infusions [7]. One successful technique involves the fusion of the Fc portion of human immunoglobulin G (IgG) to the therapeutic protein. This method utilizes a natural biological process where the binding to the neonatal Fc receptor (FcRn), found in the endothelial cells of blood vessels, protects the IgG and Fc-fused proteins from being broken down in lysosomes, allowing them to be recycled back into the bloodstream [8, 9].

The recombinant FVIII Fc fusion protein (rFVIII-Fc), efmoroctocog alfa, which combines a single rFVIII molecule with the Fc domain of human IgG1, emerged as the first extended half-life FVIII product to receive approval in both the European Union (under the brand Elocta® by Sobi) and the United States (as Eloctate® by Sanofi) [10]. This product is used for both prophylaxis and treatment of bleeding episodes in haemophilia A patients across all age groups. The increased half-life of rFVIII-Fc in circulation has been validated [11, 12] and its long-term effectiveness and safety have been thoroughly demonstrated through various clinical trials [13–15] and real-world studies [16, 17].

The primary aim of prophylactic therapy in haemophilia A is to prevent bleeding by ensuring that plasma levels of FVIII remain above a certain threshold. Studies have shown a direct correlation between the duration that FVIII levels stay below 0.01 IU/mL and the likelihood of bleeding occurrences [18]. Maintaining FVIII levels above this threshold is known to offer increased protection against joint bleeds. However, this threshold might not be universally adequate, and some patients may require higher levels for effective bleeding prevention [19].

The introduction of rFVIII-Fc has been a notable development, allowing patients with haemophilia A to maintain their FVIII levels above 0.01 IU/mL for longer periods.

The rFVIII-Fc produced by AryoGen Pharmed Company, referred to in this article as *rFVIII-Fc*, is a biosimilar product of the reference drug Elocta®. This study was conducted to evaluate the pharmacokinetic (PK) parameters and bioequivalence of the two products. Key PK parameters such as area under the curve (AUC) and maximum concentration (C_{max}) were measured to compare the two medications, thereby assessing their bioequivalence and supporting the potential use of rFVIII-Fc in clinical practice.

Methods

Study design

This study was a randomized, two-armed, double-blind, single-dose, cross-over, two-sequence, active-controlled, multi-center, bioequivalence clinical trial to compare PK parameters and safety of rFVIII-Fc versus Elocta®, in previously treated severe haemophilia A patients.

Intervention

In this cross-over study, each patient underwent two interventions. Participants were randomly assigned in a 1:1 ratio to receive either a single dose of 50 IU/kg rFVIII-Fc (Coageight) or 50 IU/kg Elocta®. This was followed by a transition to the alternate treatment, with a 7-day washout period between each dose. After each injection, blood samples were collected for PK assessments for five days. A final follow-up visit was conducted on the 28th day following the initial intervention.

Patients

Participants eligible for this study were male individuals aged 12 years or older, diagnosed with severe haemophilia A, characterized by endogenous FVIII levels below 1% (1 IU/dL). Eligibility criteria included a history of at least 150 exposure days to any FVIII product and adequate bone marrow and organ functions (platelets $\geq$ 80,000 cells/µL, haemoglobin $\geq$ 8 mg/dL, eGFR $\geq$ 30 mL/min, the liver transaminases $\leq$ 5×upper limit of normal range (ULN), serum bilirubin $\leq$ 1.5×ULN) as confirmed by laboratory tests. All

patients provided signed informed consents, either personally or through a legally authorized representative for those below the legal age of consent.

Key exclusion criteria included: The presence of inhibitors against FVIII (≥0.6 BU/mL) at screening visit or a history of inhibitor development to any FVIII products; a history of any coagulation disorders other than haemophilia A; being in an acute hemorrhagic state; infusion of any FVIII-containing products within 7 days prior to the first intervention; prior treatment with commercially available extended half-life FVIII products and planned elective surgery.

PK and immunogenicity assessment

Blood samples were collected at multiple time points: before, and at 0.25, 0.5, 1, 3, 6, 8, 24, 48, 72, 96, and 120 h following each intervention. The coagulant activity of rFVIII-Fc was determined using a chromogenic substrate assay (CSA). Additionally, the inhibitor formation was assessed at baseline, and then 7, 12, and 28 days after the first intervention, utilizing the Nijmegen-Bethesda assay. All these assays were performed in a centralized laboratory at Iranian Blood Transfusion Organization.

Outcomes

The primary outcome of the study was to assess dose-normalized area under the curve which is the calculated AUC from the start of the injection to the last blood draw, divided by the patient's administered dose ($DNAUC_{last}$).

Secondary outcomes included the AUC_{inf}, which is defined as the AUC calculated from the initiation of the treatment until an infinite time; C_{max}, as the highest concentration of rFVIII-Fc observed in the body; Incremental recovery (IR) as the ratio of the maximum concentration (IU/dl) to the administered dose (IU/kg), within an hour after the completion of the infusion; Half-life ($T_{½}$) as the duration required for the drug's concentration in the body to reduce to half of its initial value. Volume of distribution (V_d) denotes the volume in which the drug gets distributed after its entry into the body. Finally, clearance which was defined as the rate at which the drug is removed from the body.

Safety outcomes

Safety assessments included the incidence of adverse events (AEs). All AEs were classified based on the Medical Dictionary for Regulatory Activities (MedDRA Desktop Browser 4.0 Beta) terms using System Organ Class (SOC) and Preferred Term (PT). All the reported events were graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) [20]. Moreover, the seriousness of AEs was assessed according to ICH-E2B guidelines [21]. The causality relation was assessed based on the World Health Organization (WHO) criteria [22].

The adverse events of special interest (AESIs) included the development of inhibitor against rFVIII-Fc, serious thromboembolic events, hypersensitivity and injection site related reactions. Considering the study's design and half-life of the rFVIII-Fc, AEs were assessed only seven days after each intervention due to the elimination of both injected medications following the seventh day after the second intervention. Hence, reported AEs after the seventh day of the second intervention could not be attributed to either intervention.

Randomization and blinding

Patients meeting the eligibility criteria were randomly assigned to different groups using a permuted block randomization method. The randomization was performed using R-CRAN-version 4.0.3, using blocks of size 2 and 4. Randomization scheme was implemented whereby the patient, blinded to the intervention allocation, crosses over between the test and the reference drug.

Study size

A sample size of 40 patients was determined to demonstrate equivalence between the two treatment groups, using two one-sided Student's t-tests with a cross-over design, achieving 80% statistical power. The significance level is 5%, the true ratio of the $DNAUC_{last}$ means is assumed to be 1.00 and the coefficient of variation for the original, unlogged scale is considered to be 0.34. The bioequivalence margin is set at 0.80 to 1.25. Overall, considering a drop-out rate of 20%, the total required sample size is 50 patients.

Statistical methods

The primary PK parameter was calculated from the concentration-time data using standard non-compartmental methods. Statistical analysis consisted of using the t-student distribution to compute the confidence intervals (CIs) for comparing the natural log-transformed PK parameter ($DNAUC_{last}$) for the two groups. Log-transformed parameters were analyzed using repeated measure analysis of variance (rm ANOVA), including carryover effect. The concentration-time data was listed, tabulated and presented in graphical format by treatment. PK equivalence was declared if the 90% CI for the test-to-reference geometric mean ratio (GMR) lies within the 80–125% equivalence margin. Bioequivalence was demonstrated if the PK parameter meets the PK equivalence criteria.

Rm ANOVA analysis was used to analyze the secondary PK variables AUC_{inf}, C_{max}, IR, $T_{½}$, V_d, and clearance.

There was a summary statistic for each variable including the number of subjects, mean and standard deviation, frequency, and percentage. All patients who received at least one dose of the study medication, were included in the safety population. Safety analyses were conducted using descriptive statistics. All the statistical analyses were conducted using STATA version 14.0 and WinNonlin software version 6.4 with a significance level of 0.05 for all tests.

Ethics and quality control

The study was performed in accordance with good clinical practice guidelines and the declaration of Helsinki. Each participant signed a written informedconsent form before the initiation of the trial. The study supervised by Research Ethics Committee of Iran University of Medical Sciences (IR.IUMS.REC.1402.03). Moreover, this clinical trial was registered in ClinicalTrials.gov (NCT06137092).

Results

In this study, out of the 54 patients initially screened, 50 were randomized into treatment groups. They were assigned in a 1:1 ratio to receive either Elocta®/rFVIII-Fc or rFVIII-Fc/Elocta®. The study spanned from June 2023 to September 2023 across five centers. All participants underwent the first intervention as per their assigned treatment arm. However, during the transition phase, one patient did not receive the next intervention due to the need for an additional FVIII dose. Moreover, two patients were excluded from PK analysis due to using of tranexamic acid which can interfere with FVIII blood levels [23]. Another patient was also excluded from the analysis because of wrong allocated intervention. The details of patient allocation are illustrated in Fig. 1. Moreover, Table 1 shows the demographics of the participants.

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Primary results

The statistical analysis comparing the primary pharmacokinetic parameter between the two groups revealed a ratio of 108.56 (90% CI 104.88 to 112.37) which can prove the bioequivalence assumption based on the pre-assumed equivalence margin of 80–125%. Moreover, based on the 2×2 cross-over analysis of variance for the DNAUC neither the period effect nor the carryover effect was significant ($p=0.349$ and $p=0.152$, respectively). Statistical comparison of $DNAUC_{last}$ between the groups could be found in Table 2.

Secondary results

In Table 3, descriptive statistics related to the other PK parameters including IR, AUC_{inf}, C_{max}, $T_{½}$, V_d, and clearance are shown. The concentration-time graph of the two interventions is provided in Fig. 2.

Safety results

A total of 49 AEs were reported in the first 14 days of the study. The majority of these AEs were related to the patients' underlying disease, haemophilia A. From these events, 31 occurred post rFVIII-Fc and 18 after Elocta® administration. Among these AEs, 11 out of 31 (35.48%) after rFVIII-Fc injection and five from 18 (27.78%) after Elocta® injection, had possible causality relation. Furthermore, four out of 31 (12.90%) and three from 18 (16.67%) AEs had probable/likely causality relation to rFVIII-Fc and Elocta® injection, respectively.

The incidence of the AEs with probable/likely or possible causal relation with the study interventions is demonstrated in Table 4.

According to the Table, 15 patients after receiving rFVIII-Fc and eight patients after receiving Elocta®, experienced at least one AE with probable/likely or possible causality assessment within seven days of each intervention. These events were graded as "1" or "2" in terms of severity.

Only one serious AE occurred during the study, in which a patient was hospitalized due to hemarthrosis five days after receiving the second intervention (rFVIII-Fc). This serious AE (SAE) was not related to any of the interventions and was attributed to the underlying condition of the patient.

Among all mentioned AESIs in the present study, only one case of inhibitor development against rFVIII-Fc was reported.

Immunogenicity

In the present study, only one positive immunogenicity sample was identified, which was related to day 28. The inhibitor titer was equivalent to 0.8 BU/ml. It is noteworthy that the inhibitor assessment conducted on day 12 yielded a negative result. Between days 12 and 28, the patient had received a FVIII product other than the study medications, to address a hematoma in their right arm. The treatment consisted of 1000 IU of plasma-derived FVIII administered on two separate days during this period. Following day 28, the patient underwent a retest, which yielded a negative result for the inhibitor.

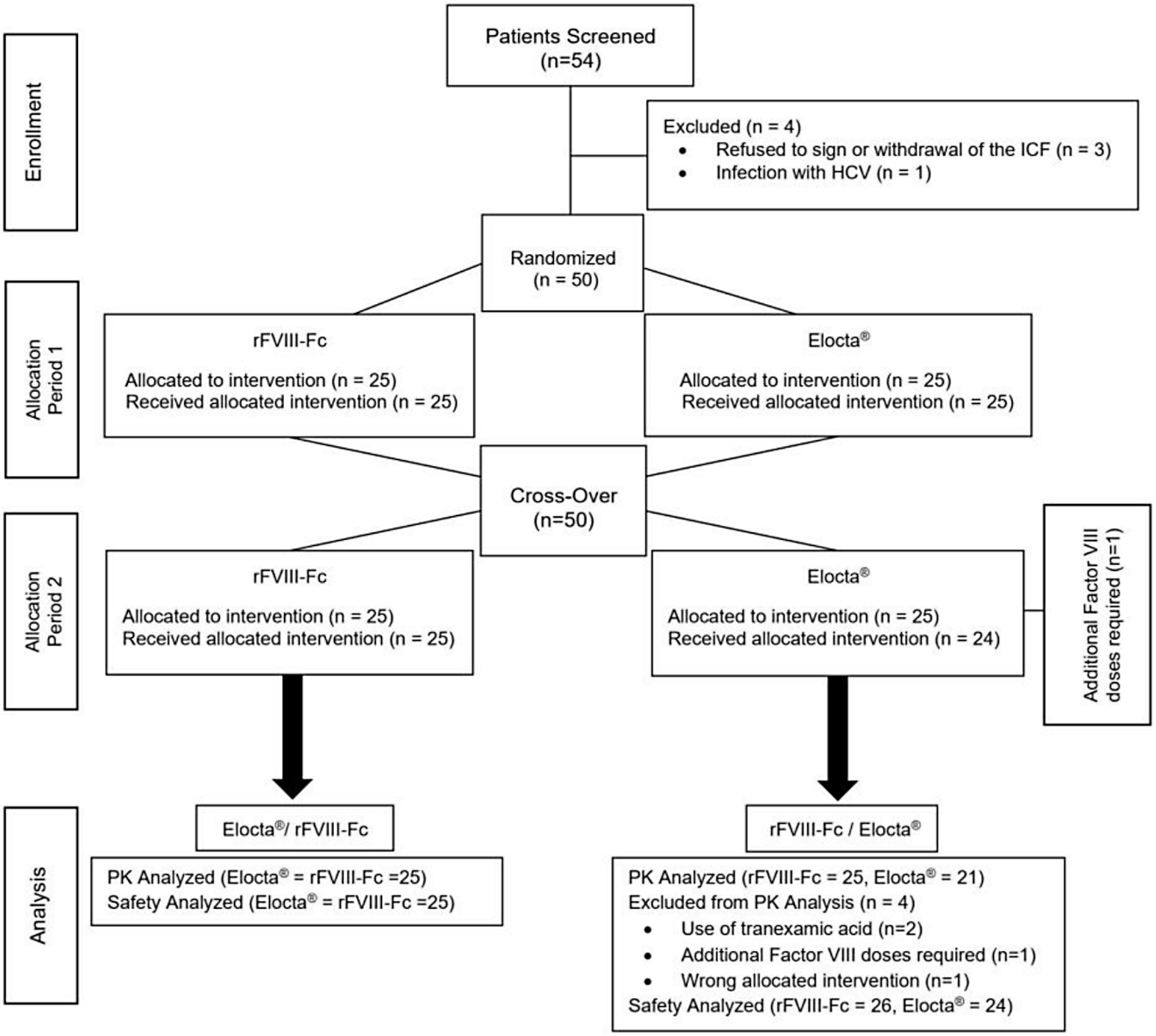

Fig. 1 Patients' disposition; Abbreviations: HCV, hepatitis C virus; ICF, informed consent form; PK, pharmacokinetics; rFVIII-Fc, recombinant factor VIII with Fc fusion protein produced by AryoGen Pharmed Company

Table 1 Demographic characteristics of the patients

Characteristic ($N=50$)	Median (IQR)	Mean (SD)
Age (years)	24.5 (18)	27.74 (11.43)
BMI (kg/m^2)	22.25 (6.70)	22.56 (4.78)

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation

Table 2 Statistical comparison of $DNAUC_{last}$ between groups

Primary outcome	Reference	Test	Ratio	Lower 90% CI	Upper 90% CI
DNAUC	Elocta®	rFVIII-Fc	108.56	104.88	112.37

Abbreviations: CI, confidence interval; $DNAUC_{last}$, dose-normalized area under the curve; rFVIII-Fc, recombinant factor VIII with Fc fusion protein produced by AryoGen Pharmed Company

Discussion

This study showed that the rFVIII-Fc product manufactured by AryoGen Pharmed Co., commercially known as Coageight, is bioequivalent to the reference product, Elocta®. This is because the DNAUC ratio of the two products, as well as the upper and lower limits of the 90% CI, fell within the pre-determined equivalence margin of 80–125%.

Regarding the secondary outcomes of the study, no meaningful differences were observed between the PK parameters including AUC_{Inf}, clearance, V_d, half-life, C_{max}, and IR. Therefore, it can be said that, both products perform similarly and are comparable in this regard.

Table 3 Descriptive statistics related to secondary outcomes

Group	Parameters	DNAUC	C_{max}	AUC_{inf}	V_d	Cl	Half-life	IR
rFVIII-Fc (*N*=50)	Mean	62.956	189.22	3209.585	0.543	0.018	20.67	3.752
	Median	60.49	183.5	3137.65	0.39	0.02	17.83	3.64
	Range	86.74	131	4567.45	2.76	0.02	60.74	2.63
	Geometric Mean	59.428	185.292	3024.699	0.452	0.017	18.947	3.673
	CV% Geometric Mean	35.45	20.96	35.88	53.75	35.87	40	21.14
Elocta® (*N*=46)	Mean	57.932	171.739	2950.072	0.641	0.019	22.06	3.409
	Median	55.37	168	2801.61	0.45	0.02	19.4	3.24
	Range	87.99	168	4655.98	2.73	0.03	59.1	3.44
	Geometric Mean	54.814	166.719	2784.453	0.527	0.018	20.348	3.306
	CV% Geometric Mean	34.98	25.23	35.63	57.94	35.54	38.21	25.68

Abbreviations: AUC_{inf}, area under the curve *infinite*; CI, confidence interval; Cl, clearance; C_{max}, maximum concentration; CV, coefficient of variation; $DNAUC_{last}$, dose-normalized area under the curve; IR, incremental recovery; rFVIII-Fc, recombinant factor VIII with Fc fusion protein produced by AryoGen Pharmed Company; V_d, volume of distribution

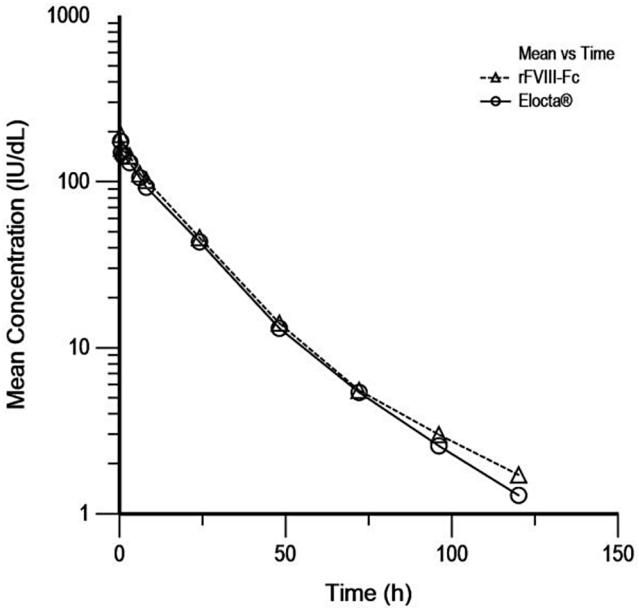

Fig. 2 Kinetic profiles of recombinant factor VIII with Fc fusion protein produced by AryoGen Pharmed Company (rFVIII-Fc) and Elocta®

Table 4 Incidence of adverse events (AEs)

Preferred Term[a]	rFVIII-Fc (%) [*N*=51]	Elocta® (%) [*N*=49]
Dizziness	3 (5.88)	0 (0)
Aggression	2 (3.92)	0 (0)
Headache	2 (3.92)	1 (2.04)
Abdominal pain	1 (1.96)	1 (2.04)
Dyspnoea	1 (1.96)	0 (0)
Nausea	1 (1.96)	0 (0)
Back pain	1 (1.96)	0 (0)
Rash	1 (1.96)	1 (2.04)
Hypertension	1 (1.96)	1 (2.04)
Somnolence	1 (1.96)	0 (0)
Skin discolouration	1 (1.96)	1 (2.04)
Rash maculo-papular	0 (0)	1 (2.04)
Malaise	0 (0)	1 (2.04)
Myalgia	0 (0)	1 (2.04)

[a] Reported adverse events in this Table have probable or possible causality relationship with the intervention

Abbreviations: rFVIII-Fc, recombinant factor VIII with Fc fusion protein produced by AryoGen Pharmed Company

It is important to note that the observed IR values were higher than those reported in previous studies for both groups. This enhancement may be attributed to the pharmacogenetic characteristics of the Iranian population or the stability of patient conditions at the time of measurement. Notably, similar elevated values have been documented in a limited number of other reports [24].

The half-life of the rFVIII-Fc product, as documented in individuals aged 12 years or older, ranges from 16.4 to 19.7 h, which is notably longer than that of the conventional FVIII product [25]. This could lead to an increased duration of effect, which is considered an advantage over the regular FVIII product. In this study, the geometric mean half-lives of both products were similar and approximately within this range, which is completely consistent with the mentioned parameters.

The results derived from the concentration-time graph for both groups also demonstrate the similarity in PK behavior between rFVIII-Fc and Elocta®. The cross-over study design, by considering each patient as their own control, effectively controls for internal confounding factors such as blood group, levels of von Willebrand factor, age, and other factors. This high inter-individual variability of response to FVIII in patients with haemophilia makes the results of this study highly reliable [26].

Based on the assessment of the medications in terms of $DNAUC_{last}$, this study demonstrates that the rFVIII-Fc product manufactured by AryoGen Pharmed Co., commercially known as Coageight, is bioequivalent to the reference product.

Findings of the study demonstrate that there is no difference between rFVIII-Fc and Elocta® in terms of safety. The majority of the reported events were bleedings which were associated with the underlying disease of the patients. Most of the reported

AEs with a possible or probable/likely causal relationship to the study interventions were grade 1 or 2 in terms of severity. Reported AEs were mainly categorized in the nervous system disorders, as observed in the study examining the effectiveness and safety of the FVIII product under the brand GreenGene F™ in Korean patients with haemophilia A [27].

A single case of SAE related to patient's underlying disease was reported in the study. None of the study interventions were deemed as a contributing factor for this particular event.

Regarding the immunogenicity results, one patient tested positive on day 28 of the study for rFVIII-Fc inhibitor. It is worth mentioning that this patient received the FVIII product twice between day 12 and day 28 of the study. However, the positive result recorded for this patient was inconclusive and couldn't be linked to either of the received injections during the study. According to the criteria of the World Federation of Haemophilia, an inhibitor level below 5 BU/ml is classified as a low titer, which is generally transient and disappears within six months [26, 27]. Therefore, these inhibitors do not have any clinical significance. Moreover, the inhibitor test was performed again for this patient, yielding a negative result for the inhibitor level.

Overall, based on the results obtained from this study, both rFVIII-Fc and Elocta® were well tolerated and are considered comparable in terms of safety.

rFVIII-Fc is recognized as a beneficial replacement therapy in haemophilia A patients, advancing the current treatment horizons, by addressing clinical challenges and quality of life for individuals dealing with this condition. It reduces infusion frequency due to the extended half-life, consequently enhances adherence while alleviating treatment burden [28]. Beyond reducing bleeding frequency and preventing joint damage, rFVIII-Fc contributes to improved joint and bone health, supported by its anti-inflammatory properties and potential to inhibit osteoclast formation, which mitigates bone resorption [29]. Considering its reduced immunogenicity and real-world efficacy, it is an excellent choice for treating severe haemophilia A [28, 29]. The biosimilar rFVIII-Fc was previously unavailable in Iran; however, by establishing this product as bioequivalent to the reference product, this limitation has been addressed, enabling patients to access its numerous benefits.

Conclusion

Based on the PK results, rFVIII-Fc is considered equivalent to Elocta®, the reference product. Moreover, the biosimilar product exhibits comparable safety results to the originator drug, thus making it a safe alternative for the management of haemophilia A patients.

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Author contributions A.E. conducted the study according to the accepted protocol and drafted the manuscript. S.A., Z.B., M.G., M.B., A.B., K.K., P.E., G.T., and A.S. participated in the study design and coordination, as well as revising the manuscript. M.A. supervised the laboratory procedures of the clinical trial. H.K. was Head of Medical Department of Orchid Pharmed Company and supervised the clinical trial conduction, helped to draft the manuscript, and performed the statistical analysis.

Funding This study was funded by AryoGen Pharmed Company.

Data availability All data produced in the present study are available upon reasonable request from the authors.

Declarations

Ethical approval Ethics approvals for this study has been achieved from Research Ethics Committee of Iran University of Medical Sciences by the following case number: IR.IUMS.REC.1402.03.

Patient consent The study was performed in accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. Each participant signed a written informed consent form before the initiation of the trial.

Clinical trial registration This clinical trial has been registered in ClinicalTrials.gov (NCT06137092).

Competing interests Aziz Eghbali received educational/research grants and travel supports to attend scientific meetings from Cinnagen (in addition to lecture honorarium), Baxter, and CSL. Peyman Eshghi has received: educational/research grants from Cinnagen (in addition to lecture honorarium), Biotest, Baxter, Novonordisk, and Pfizer. Moreover, he received travel supports to attend scientific meetings from all of the above and CSL. Samin Alavi has received research grant from Cinnagen and travel support from Baxter to attend a scientific meeting. Zahra Badiei has received educational/research grants and lecture honorarium from Cinnagen. Moreover, she received travel supports to attend scientific meetings from Baxter, Novo Nordisk, CSL, and Cinnagen. Mohammadreza Bordbar has received lecture honorarium and travel support to attend scientific programs from Novartis and Aryogen Pharmed Company. Hamidreza Kafi is head of the Medical Department of Orchid Pharmed Company, which is in collaboration with AryoGen Pharmed Company with respect to conducting clinical trials. Moreover, Araz Sabzvari is a member of the CinnaGen Medical Biotechnology Research Center, which collaborates with universities and researchers all over the world with regards to research and development of medications and health issues. Other contributors declared no related conflict of interest to this study.

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