

INVITED REVIEW

Bioequivalence of a biosimilar enoxaparin (Cloti-Xa™) and its innovator (Clexane®): A single-dose, randomized, double-blind, two-period, two-treatment, two-sequence, crossover, balanced study in healthy human subjects

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com**Abstract**

Currently, several biosimilars of low-molecular-weight heparins (LMWHs) with differing potencies are being developed and marketed globally. Thus, it is important that the potency of each biosimilar LMWH be compared with its innovator's molecule. The present study aimed to determine the bioequivalence of biosimilar (Cloti-Xa™) and innovator (Clexane®) formulations of enoxaparin sodium (40mg/0.4ml) in healthy human volunteers. It was conducted as a single-dose, randomized, double-blind, two-period, two-treatment, two-sequence, crossover, balanced, pharmacodynamic study (NCT05265676). The participants were sequentially and randomly administered subcutaneous injections of Cloti-Xa™ (test) and Clexane® (reference), separated by a one-week washout period. To assess the Anti-Xa & Anti-IIa activities, tissue factor pathway inhibitor (TFPI) release and activated partial thromboplastin time (aPTT), blood samples were obtained at various timepoints upto 24h after the drug administration. Bioequivalence was concluded if the two-sided 90% CI for the test to reference ratio of the population is within 80%–125% for each of the Ln-transformed values of A_{max} and $AUEC_t$ for Anti-Xa and Anti-IIa. TFPI and aPTT data were submitted as supportive evidence. The study sample consisted of twenty-four male participants. The 90% CIs of A_{max} and $AUEC_t$ for Anti-Xa activity were 105.50%–113.90% and 103.97%–112.08%, and for Anti-IIa activity were 106.56%–117.90% and 107.35%–124.86%, respectively. In addition, the 90% CI of the ratio of Anti-Xa/Anti-IIa activity falls within the acceptance criteria. TFPI and aPTT profiles were similar for both products. No serious adverse events were observed during the study. Conclusively, the results showed that Cloti-Xa™ and Clexane® are bioequivalent and well-tolerated.

KEYWORDS

anticoagulant, antithrombotic, bioequivalence, enoxaparin, heparin, low-molecular-weight-heparin, pharmacodynamic equivalence

Abbreviations: A_{max} , maximum activity; $AUEC_t$, area under the effect curve from time 0 to the last measured activity; aPTT, activated partial thromboplastin time; LMWH, low-molecular-weight heparin; BE, bioequivalence; TFPI, tissue factor pathway inhibitor.

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1 | INTRODUCTION

Enoxaparin is a widely used low-molecular-weight heparin (LMWH) obtained by alkaline β -eliminative cleavage of heparin benzyl ester derived from porcine intestinal mucosa.^{1,2} It is an antithrombotic drug commonly prescribed for the treatment and prevention of arterial and venous thromboembolism.³ In clinical settings, enoxaparin has consistently shown superior efficacy to treat deep vein thrombosis, pulmonary embolism and acute coronary syndrome, when compared to unfractionated heparin (UFH) and other LMWHs.^{2,4}

The mechanism of action of enoxaparin has been attributed to its ability to bind to antithrombin III, an inhibitor of coagulation factors Xa and IIa. Enoxaparin potentiates the action of anti-thrombin III and indirectly inhibits the conversion of prothrombin to thrombin, thus preventing clot formation.⁵ It preferentially inhibits the activity of factors Xa and IIa and has a higher ratio of anti-factor Xa to anti-factor IIa activity as compared to UFH. Therefore, the anticoagulant effect of enoxaparin is directly associated with its inhibitory effect on factor Xa activity.^{4,6} Furthermore, enoxaparin has certain other properties that make it the drug of choice in thromboembolic conditions; e.g., it has a weak interaction with platelets and causes the continuous release of tissue factor pathway inhibitor (TFPI) from endothelial cells.¹ Moreover, it is loosely bound to plasma proteins and has a long half-life with high bioavailability upon subcutaneous administration.^{1,4}

Nowadays, several biosimilars of LMWHs are available for clinical use in many countries, due to the expiration of patent rights of the innovator product.⁷ Although the biosimilar LMWHs usage results in considerable savings of healthcare expenditure, however, it is of utmost importance that these biosimilars should have similar activity and bioavailability to that of innovator molecule. Otherwise, the benefit/risk ratio of LMWHs and their biosimilars may vary and it would be difficult to ensure their equivalency.³ The term "biosimilar" refers to the biologic product which is developed to be highly similar to the innovator biologic product, where clinically both the products have similar safety and efficacy profiles.⁸ To compare the biosimilar version with the innovator product, conventional pharmacokinetic (PK) studies cannot be performed because of the difficulties in the physical detection of LMWH.⁹ The PK properties and bioavailability of LMWHs are routinely determined by pharmacodynamic (PD) surrogates such as Anti-Xa activity, Anti-IIa activity, and activated partial thromboplastin time (aPTT).^{1,6,9} The European Medicines Agency (EMA) recommends measuring Anti-Xa and Anti-IIa as the primary surrogate markers for the comparison of a biosimilar product to the innovator LMWH.^{1,10} Additionally, assessment of the ratio of Anti-Xa/Anti-IIa activity and the TFPI activity is recommended as the secondary parameters.¹⁰

Furthermore, the EMA also suggests that these PD parameters should be investigated in a randomized, single-dose, two-way crossover, preferably double-blind study using subcutaneous administration in healthy volunteers.^{8,10} Based on these guidelines, this study was designed and performed to determine the bioequivalence of the innovator (Clexane[®], Sanofi) with a biosimilar version (Cloti-Xa[™], Venus Remedies Limited) of Enoxaparin 40mg/0.4ml (4000 IU/0.4 ml) concentration, in healthy human volunteers.

2 | METHODS

2.1 | Study design and setting

This was a single-dose, randomized, double-blind, two-period, two-treatment, two-sequence, crossover, balanced study conducted at the Cliantha Research Limited, Ahmedabad, India, from February 2021 to March 2021. The study protocol was reviewed and approved by the IBIOME Independent Ethics Committee. Written informed consent was provided by all the subjects before executing any study-related procedure. This study was performed in compliance with the principles of the Declaration of Helsinki for Biomedical Research involving human subjects, the Guideline for Good Clinical Practice, United States Food and Drug Administration (US FDA) guidelines, EMA guidelines and the Indian Council of Medical Research (ICMR) guidelines. Study design and subjects' disposition is presented in Figure 1. This study was registered at ClinicalTrials.gov (<https://clinicaltrials.gov/show/NCT05265676>).

2.2 | Subjects

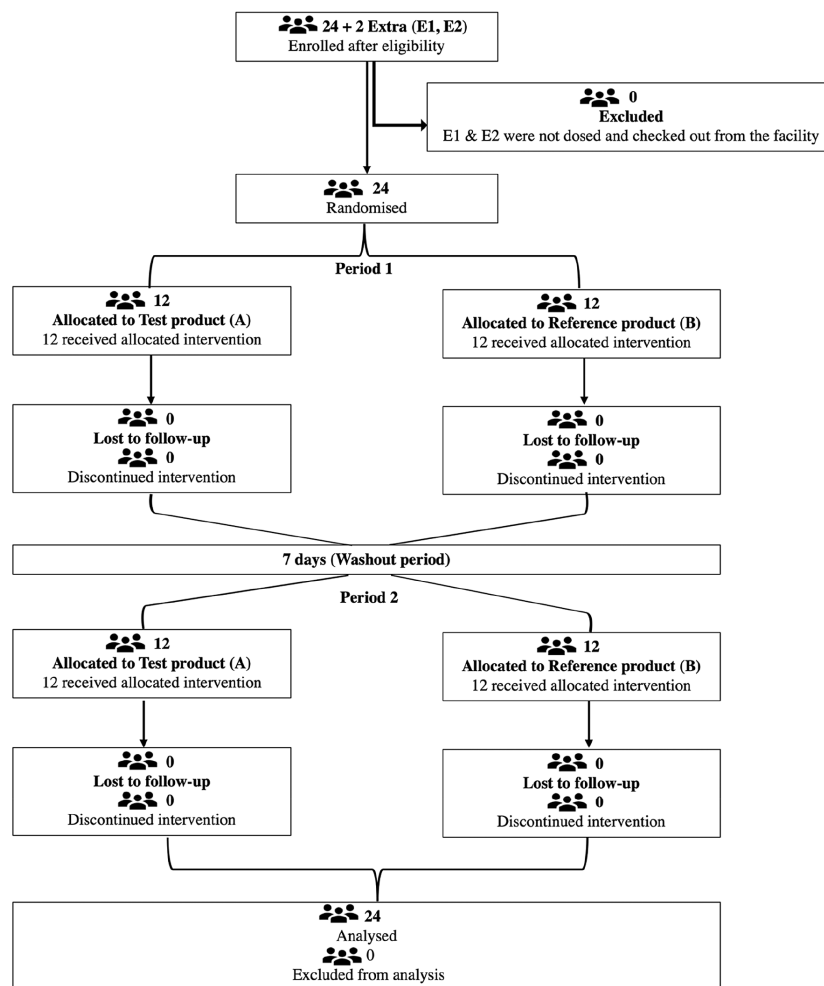
The study population consisted of healthy human male volunteers with age ranging between 18 and 45 years, weight of at least 50 kg, and BMI of 18.5 to 30.0 kg/m². Only subjects with no history of alcohol, smoking, or tobacco use (at least in the last 1 year) were enrolled. Subjects were only included in this study if they had no significant findings during screening (i.e., within 28 days prior to the administration of first dose), which included physical examination (clinical examinations), vital signs assessments, ECG examination, chest X-ray and safety-related clinical laboratory analysis (haematology, biochemistry, serology, coagulogram and urinalysis).

Volunteers with a history of systemic diseases/conditions such as diabetes, psychosis, asthma, ulcers (stomach, duodenal, and intestinal), piles and fissures, positive for anti-HIV antibody, syphilis or Hepatitis B and C, or conditions that may compromise the hemopoietic, gastrointestinal, renal, hepatic, cardiovascular, or any other system of the body, were not included. Individuals with a recent history of hormone replacement therapy, CYP enzyme inhibitors, depot injection or implant (30 days prior to the study), or those who received any other known investigational drug, or had drug dependence were excluded.

2.3 | Study drugs

This study was performed to compare and evaluate the PD profile of test and reference (innovator) products of enoxaparin in healthy human volunteers under fasting conditions. The test product (A) was Cloti-Xa[™] (enoxaparin sodium) prefilled syringe, manufactured by Venus Remedies Limited, India; and the reference product (B) was Clexane[®] (enoxaparin sodium) prefilled syringe, manufactured by CHINOIN Pharmaceutical and Chemical Works Pvt. Co. Ltd., a Sanofi Company, Hungary. Both the formulations had a concentration of 40mg/0.4ml (4000 IU/0.4ml).

FIGURE 1 Flow chart of study design and subject disposition.



The key comparative analysis data of Cloti-Xa™ and Clexane® are presented in Appendix A. Participants were randomly selected for one of the two sequences: either AB or BA. To ensure blinding, personnel who were not involved in any study-related activity were responsible for dispensing the investigational products.

2.4 | Blood sampling

On the dosing day of period 1, under fasting conditions (overnight, 8h), a single dose of either product A or B was administered subcutaneously into the abdominal wall of the subject. Injection sites were alternated in both periods (1 and 2) between left and right anterolaterally in a supine posture. The interval between the doses was 7 days (washout period). Blood samples for assessment of the PD parameters were collected at the following time points: pre-dose and 0.5, 1.0, 1.5, 2.0, 2.333, 2.667, 3.0, 3.333, 3.667, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0h post-dose in each study period.

2.5 | Pharmacodynamic (PD) assessment

The Anti-Xa and Anti-IIa activity was measured by the chromogenic method using commercial reagent kits—STA®-liquid Anti-Xa,

Diagnostica Stago and Actichrome® Heparin (Anti-IIa) kit, Biomedica Diagnostics, respectively. TFPI was assessed using Enzyme-Linked Immunosorbent Assay (ELISA) kit (Quantikine® Human TFPI ELISA kit) and aPTT was determined using clotting assay reagent kit—STA-C.K. Prest® 5-Diagnostica Stago.

Bioequivalence was assessed on the PD surrogate markers, i.e., Anti-Xa and Anti-IIa. Baseline-corrected TFPI and aPTT levels were assessed and considered as supportive evidence. The following PD parameters were calculated using non-compartmental analysis: the primary PD parameters included the maximum activity (A_{max}) and area under the effect curve from 0 to the last measured activity ($AUEC_t$); and the secondary parameters were AUEC from time 0 to infinity ($AUEC_i$), time of the maximum measured plasma concentration (T_{max}), first-order terminal elimination half-life (t_{half}), elimination rate constant (K_{el}). Both the primary and secondary PD parameters were calculated for Anti-Xa and Anti-IIa only.

Additionally, A_{max} , $AUEC_t$ & $AUEC_i$ were calculated for TFPI (baseline-corrected data), and A_{max} & $AUEC_t$ were calculated for the activity ratio of Anti-Xa/Anti-IIa and aPTT (baseline-corrected). PD parameters were calculated using the Phoenix® WinNonlin® professional software (version 8.1).

For the baseline correction procedure of TFPI and aPTT data, pre-dose levels were subtracted from post-dose levels prior to the

calculation of the PD parameters. Any negative result was to be set to zero.

2.6 | Statistical analysis

The sample size for this study were estimated by assuming T/R ratio of 95.00%–105.26%; Intra-subject C.V (%) ~ 21%; Significance level of 5%; Power of 80% and Bioequivalence limits of 80.00%–125.00%. Based on these estimations, 20 subjects were sufficient to establish bioequivalence. However, considering the dropouts and withdrawals, 24 subjects were enrolled.

The bioequivalence of test and reference product was assessed by a statistical comparison of primary PD parameters (A_{\max} and $AUEC_t$) derived from the plasma concentration-time curves of Anti-Xa and Anti-IIa. The statistical analysis was performed using the SAS[®] statistical software (version: 9.4, SAS Institute Inc.). Descriptive statistics for all the applicable PD parameters were calculated. An analysis of variance was calculated using PROC GLM from SAS[®] for the difference due to the treatment, period, sequence, and subject within the sequence as a fixed effect on natural logarithms (Ln) transformed data of A_{\max} , $AUEC_t$, and $AUEC_i$ for Anti- Xa, Anti-IIa, TFPI (baseline-corrected), and aPTT (baseline-corrected). Treatment and period effects were tested using the mean square error, and sequence effect was tested using subject (sequence) as the error term at 5% level of significance. Two one-sided 90% CIs for geometric least square mean ratio, intra-subject variability, and power was also calculated for these PD parameters between the test and reference products.

The average bioequivalence of the products was concluded if two-sided 90% CI for the test to the reference ratio of the population means was within 80% and 125% interval for each of the Ln-transformed data, A_{\max} and $AUEC_t$ for Anti-Xa and Anti-IIa (primary objective). The data from TFPI and aPTT were submitted as supportive evidence.

2.7 | Safety and tolerability assessment

Safety measurements (vital signs measurements) were performed at the time of check-in, prior to dosing, at 2-, 6- and 10-h post dose and prior to check-out of each study period. In addition to these, physical examination (clinical examination) was also performed at the time

of check-in and prior to check-out of each study period. Laboratory tests (i.e. screening of subjects, except serology & urinalysis) were re-assessed at the end of the study. Local tolerability was performed by assessment of the injection site at the time of check-in of each period, at about 2-, 6- and 10-h post-dose and at the time of check out in each period. Subjects were advised to report the adverse events (AE) occur at any time during the study and were specifically asked for these by trained study personnel in a non-leading manner at the time of physical examination (clinical examinations), during vital signs recording and at about 16- and 24-h post-dose in each period. All AEs were recorded.

3 | RESULTS

A total of 24 male participants were enrolled in this study. All subjects completed the study. The mean age was 35 ± 6 years, and the mean BMI and weight were 22.5 ± 2.6 kg/m² and 61.6 ± 6.9 kg, respectively. Primary PD parameters of Anti-Xa and Anti-IIa were assessed for bioequivalence, and the test and reference products were compared statistically. The 90% CI values for Anti-Xa activity for PD parameters— A_{\max} and $AUEC_t$ were 105.50%–113.90% and 103.97%–112.08%, respectively. Similarly, the 90% CI values of Anti-IIa activity for A_{\max} and $AUEC_t$ were 106.56%–117.90% and 107.35%–124.86%, respectively. Values for both Anti-Xa and Anti-IIa activities were well within the bioequivalence interval of 80% and 125%. Data in Tables 1 and 2 indicate that both the test and reference products were bioequivalent under fasting conditions. Mean peak concentration-time curves for Anti-Xa and Anti-IIa are presented in Figure 2.

Data determining the activity ratio of Anti-Xa/Anti-IIa is presented in Table 3. 90% CI value of the activity ratio of Anti-Xa/Anti-IIa between test and reference treatments for A_{\max} and $AUEC_t$ were 95.05%–100.62% and 86.21%–100.75%, respectively. Values for activity ratio were within the acceptance criterion of 80% and 125%. The results of secondary PD parameters (T_{\max} , T_{half} , K_{el}) of Anti-Xa and Anti IIa activity for test and reference product is presented in Table 4.

Data for baseline-corrected TFPI and aPTT are presented in Table 5. CIs of TFPI (baseline-corrected) for A_{\max} (102.43%–116.05%) and $AUEC_t$ (109.29%–119.50%) fulfilled the acceptance criteria of 80%–125%. aPTT (baseline-corrected) for A_{\max} (106.36%–122.51%) fell within the acceptance criteria, but $AUEC_t$ (98.80%–129.14%) crossed the upper limit. Concentration-time curves for baseline-corrected TFPI and aPTT are presented in Figure 3.

Pharmacodynamic parameter	Geometric mean		90% CI	Outcome of BE result
	Test	Reference		
A_{\max} (IU/ml)	0.523	0.477	(105.50%–113.90%)	Bioequivalent
$AUEC_t$ (IU/ml)×h	4.526	4.193	(103.97%–112.08%)	Bioequivalent
$AUEC_i$ (IU/ml)×h	4.990	4.584	(104.72%–113.16%)	Not applicable

TABLE 1 Statistical analysis of pharmacodynamic variables for Anti-Xa activity

TABLE 2 Statistical analysis of pharmacodynamic variables for Anti-IIa activity

Pharmacodynamic parameter	Geometric mean			Outcome of BE result
	Test	Reference	90% CI	
A_{max} (IU/ml)	0.070	0.063	(106.56%–117.90%)	Bioequivalent
$AUEC_t$ (IU/ml)×h	0.399	0.345	(107.35%–124.86%)	Bioequivalent
$AUEC_i$ (IU/ml)×h	0.658	0.604	(92.08%–128.84%)	Not applicable

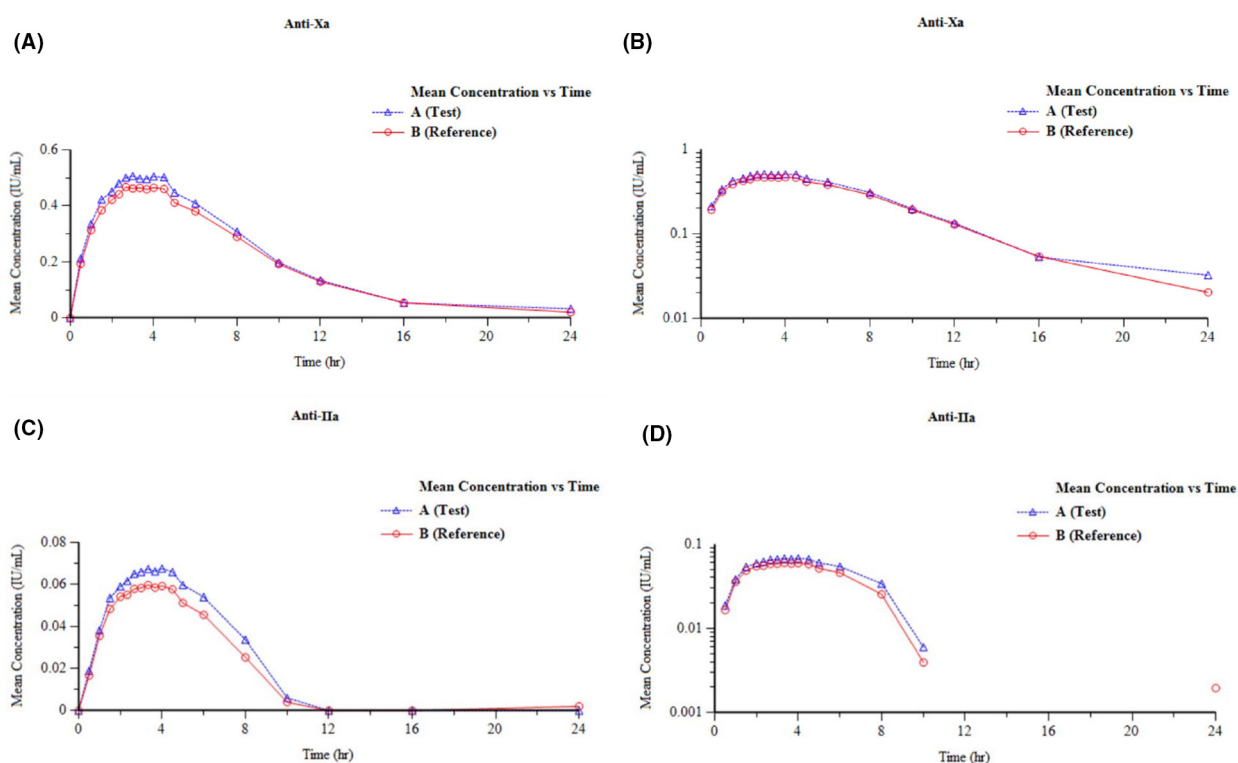


FIGURE 2 Linear and semi-logarithmic plots Anti-Xa and Anti-IIa activities. The line graphs represent linear and semi-logarithmic plots of mean concentrations vs. time for (A–B) Anti-Xa and (C–D) Anti-IIa.

The test and reference products were well-tolerated by the study subjects. During the post study laboratory assessment, clinically significant abnormalities were found for two subjects and the same was documented as an adverse event (AE). The AEs were mild in severity. One was a decrease in the platelet count, possibly related to the test product (A), and the other AE was an increase in the C-reactive protein levels which was considered unlikely related to the reference product (B). Overall, there were no serious AEs reported throughout the study period.

4 | DISCUSSION

Biosimilars are not true generics because they are not identical to the innovator product; rather, they are deemed clinically and biologically similar to it. They are used for the same indication and at the same dose as the innovator product.¹¹ The current study describes the use of a biosimilar LMWH enoxaparin that is prepared at the same dose and for the same indications as the innovator (reference) product.

Generally, LMWHs differ in their PK and PD properties, which could be possibly due to the depolymerization processes or the manufacturing methods that result in its structural variability.¹² Therefore, producing biosimilar LMWH is a challenging task and its market authorization requires adequate evidence that it meets the same standards of quality, efficacy, and safety as of its innovator.¹³ To determine bioequivalence, we conducted this study to compare the biological activity of “Cloti-Xa™”, an enoxaparin sodium-pre-filled syringe of 40 mg/0.4 ml (4000 IU/0.4 ml) with that of the innovator product “Clexane®”.

Certain regulations have been laid down by the US FDA and EMA for determining the bioequivalence between a biosimilar LMWH and the reference product.^{10,14} According to the FDA, the test enoxaparin product should demonstrate bioequivalence using the same active ingredient, dose, route of administration, and strength as of its reference product.^{12,14} EMA suggests the comparison of pharmacodynamic properties – Anti-Xa, Anti-IIa activity, ratio of Anti-Xa and Anti-IIa activity and TFPI between the test and reference LMWH. Furthermore, they also recommend that these PD properties should be investigated in a randomized, single dose, two way

Pharmacodynamic parameter	Geometric mean		Ratio of geometric mean (%)	90% CI
	Test	Reference		
A_{max} ((IU/ml)/(IU/ml))	7.461	7.629	97.80	(95.05%–100.62%)
$AUEC_t$ (IU/ml)×(h)/(IU/ml)×(h)	11.345	12.174	93.19	(86.21%–100.75%)

TABLE 3 Statistical analysis of pharmacodynamic variables for the ratio of Anti-Xa/Anti-IIa activity

TABLE 4 Comparison of secondary pharmacodynamic variables of Anti-Xa and Anti-IIa

	T_{max} (h)		T_{half} (h)		K_{el} (1/h)	
	Test	Reference	Test	Reference	Test	Reference
Anti-Xa	3.759±0.699	3.590±0.652	4.746±1.629	4.246±1.208	0.163±0.056	0.177±0.051
Anti IIa	3.427±0.703	3.354±0.714	4.944±3.585	5.486±4.229	0.196±0.105	0.193±0.111

Data presented as mean±SD.

TABLE 5 Statistical analysis of baseline-corrected, tissue factor pathway inhibitor (TFPI) and activated partial thromboplastin time (aPTT)

Pharmacodynamic parameter	Geometric mean			
	Test	Reference	90% CI	
TFPI (baseline-corrected)	A_{max} (pg/ml)	41,414.401	37,984.017	(102.43%–116.05%)
	$AUEC_t$ (pg/ml)×h	216,794.215	189,705.294	(109.29%–119.50%)
	$AUEC_i$ (pg/ml)×h	233,105.704	198,460.954	(110.14%–125.26%)
aPTT (baseline-corrected)	A_{max} (s)×h	6.050	5.300	(106.36%–122.51%)
	$AUEC_t$ (s)×h	43.443	38.461	(98.80%–129.14%)

cross over, double blind study involving healthy volunteers following subcutaneous administration.¹⁰ Based on these guidelines, the present clinical study was conducted accordingly.^{10,14} No changes or amendments were made during the execution phase in the Ethics Committee approved study protocol.

The double-blind design of this study has several advantages. It reduces the risk of bias during dosage, data collection, and safety evaluation. In each phase, a washout period of 7 days between study drug administration is sufficient to prevent any carryover effect. The two-way cross over study design minimizes the risk of confounding factors as both the interventions (test product A and reference product B) are carried out on the same participants.¹⁵ The 80% to 125% CI is appropriate as it is a widely accepted interval for concluding bioequivalence.^{1,9,14,15,16}

Enoxaparin binds to antithrombin and preferentially inhibits the activity of factors Xa & IIa. Owing to this property of enoxaparin, these PD markers are considered appropriate surrogates for assessing bioequivalence.^{4,6} In the current study, statistical analysis of the primary PD parameters of Anti-Xa and Anti-IIa

activities for the test and reference products revealed bioequivalence, with CIs well within the acceptance criterion of 80% to 125% (Table 1 and 2). Mean plasma T_{max} , T_{half} and K_{el} for Anti-Xa and Anti-IIa of both the products compared well (Table 4). Following the administration of the test and reference product, the mean peak of Anti-Xa and Anti-IIa activities was detected between 3 and 4 h, respectively. Thereafter, a rapid decrease in the activities was observed, followed by a gradual decline. The mean curves of Anti-Xa and Anti-IIa activities for both products were similar (Figure 2).

Enoxaparin has a high ratio of Anti-Xa to Anti-IIa. Therefore, its anticoagulant effect is directly correlated with its inhibitory effect on factor Xa activity.^{4,6} In the present study, the activity ratio of Anti-Xa/Anti-IIa between test and reference treatments for A_{max} and $AUEC_t$ were also within the acceptance limits (Table 3).

Moreover, this bioequivalent study was strongly backed by the statistical evaluation of the PD variables of TFPI and aPTT. TFPI is expressed by endothelial cells and reflects the biological activity of the vascular endothelium.^{1,9,17} LMWHs release TFPI into the

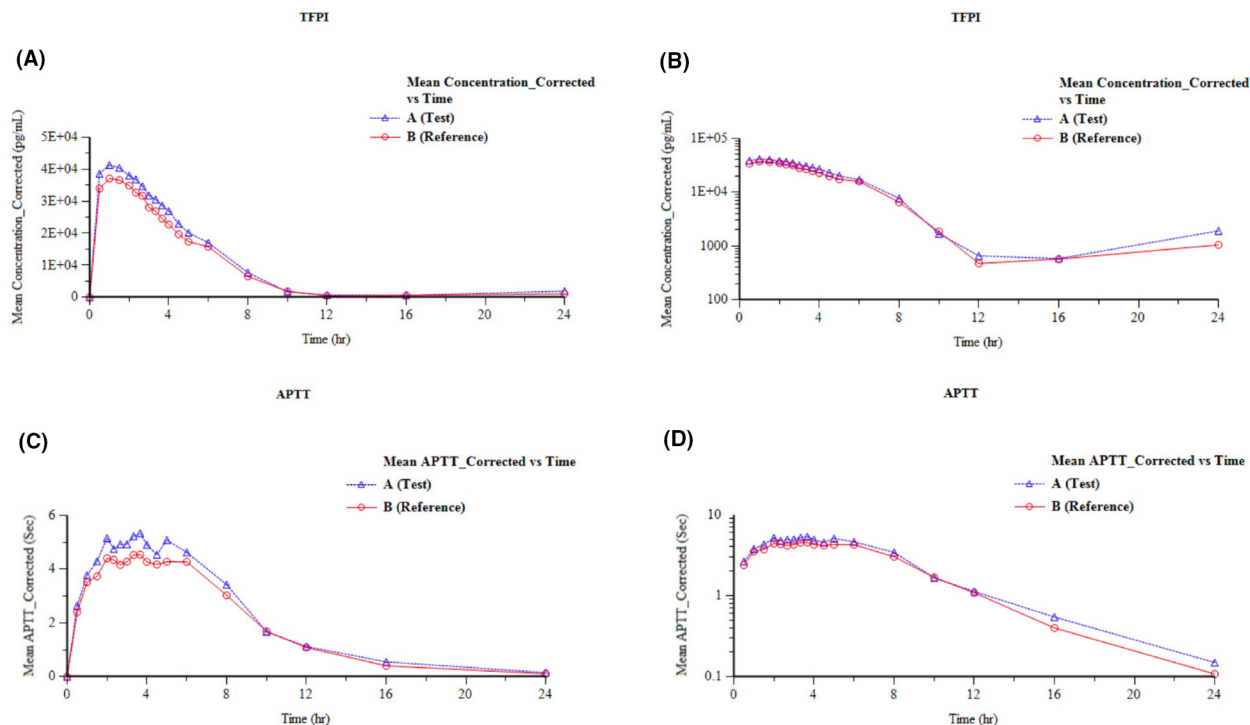


FIGURE 3 Linear and semi-logarithmic plots of TFPI and aPTT. The line graphs represent linear and semi-logarithmic plots of mean concentrations vs. time for baseline corrected (A–B) TFPI and (C–D) aPTT.

bloodstream from the vascular endothelium; TFPI suppresses the procoagulant tissue factor activity that contributes to the therapeutic efficacy of heparins.^{9,17} Therefore, TFPI was assessed as a supportive PD marker in this study. According to some biologics comparison studies, bioequivalence assessment is substantially supported by statistical evaluation of TFPI and aPTT.^{7,9} The results of a similar randomized trial showed that 90% CI for the maximum concentration of TFPI ranged from 90% to 113% and the claim of similarity was further accompanied by an aPTT profile that showed indistinguishable prolongation after the administration of the test and reference products.⁹ These findings were in accordance with our study, wherein the mean peak curves of TFPI and aPTT were similar to the reference product (Figure 3). Further, aPTT for both the products showed similar prolongation at all the time points (Figure 4).

Finally, considering all of the safety parameters, no serious AEs and significant AEs occurred over the course of the study. Overall, both the products were well tolerated as a single dosage administered under fasting condition.

There are a few limitations in the present bioequivalence study. First, the study was carried out only in healthy volunteers and therefore the coagulation activity of the products might vary in patients in the clinical settings. Secondly, the sample size was small with the single-dose design thus, future studies are required to extrapolate these results in general population. Lastly, several clinical trials were carried out previously using different dose strengths of enoxaparin compounds i.e., 40, 60, 80, and 100 mg for bioequivalence studies.^{1,6}

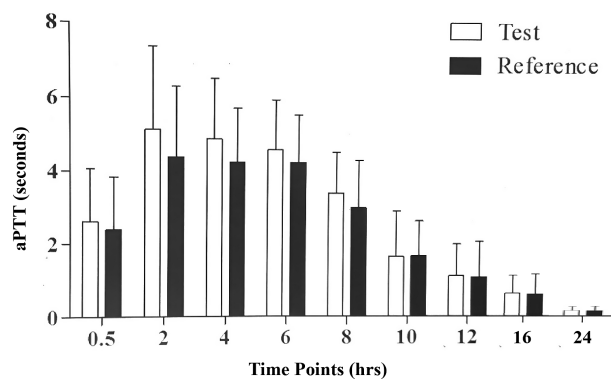


FIGURE 4 Comparison of activated partial thromboplastin time (baseline-corrected) at various time points for test and reference drug. Bar-graph representing the aPTT values of the test and reference drugs at 0.5, 2, 4, 6, 8, 10, 12, 16 and 24 h.

We used 40 mg/0.4 ml of enoxaparin in the present study as this dose has been found effective irrespective of the human body weight, however, at this dose, fewer timepoints for terminal samples could be evaluated. While they were enough to establish bioequivalence, it is recommended that higher doses are used in future bioequivalence studies.

In conclusion, the result of this clinical study showed bioequivalence of the test product (Cloti-Xa™) to that of the reference product (Clexane®) after a single dose subcutaneous injection in the healthy volunteers. Both products were well-tolerated, and both pharmaceutical products had similar overall safety and acceptability.

AUTHORS' CONTRIBUTIONS

Research design: S. Saxena, M. Chaudhary, S. Chaudhary and A. Aggarwal.

Contributed to the writing of the manuscript: S. Saxena, S. Chaudhary and A. Aggarwal.

ACKNOWLEDGMENTS

We are grateful to Cliantha Research Limited, India for conducting the experimental part and performing the data analysis; and Adduct Healthcare, India for the writing assistance.

FUNDING INFORMATION

The study was funded by Venus Remedies Limited, India.

CONFLICT OF INTEREST

Sumit Saxena, Manu Chaudhary, Saransh Chaudhary and Anmol Aggarwal are employees of Venus Remedies Limited and Manu Chaudhary owns stock and is the board member of Venus Remedies Limited. Venus Medicine Research Centre is the R&D Unit of Venus Remedies Limited.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Saxena S, Chaudhary M, Chaudhary S, Aggarwal A. Bioequivalence of a biosimilar enoxaparin (Cloti-Xa[™]) and its innovator (Clexane[®]): A single-dose, randomized, double-blind, two-period, two-treatment, two-sequence, crossover, balanced study in healthy human subjects. *Pharmacol Res Perspect*. 2022;10:e00979. doi:[10.1002/prp2.979](https://doi.org/10.1002/prp2.979)