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PHARMACOKINETIC PROFILE AND A BIOEQUIVALENCE STUDY OF APIXABAN TABLETS IN HEALTHY VOLUNTEERS

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ABSTRACT

Objective: *This study aims to demonstrate the bioequivalence (BE) and pharmacokinetic profiles of Apixaban film-coated tablet (Nobel İlaç), a Factor Xa inhibitor, with its reference product Eliquis 5 mg filmtabletten, manufactured by Bristol-Myers Squibb S.r.l., Italy, in healthy male volunteers under fasting conditions. Furthermore, the study design assesses the individual bioequivalence which ensures that a drug is interchangeable between its reference.*

Material and Method: *We have designed a single-dose, open-label, randomised, cross-over two-period study with a population of 32. The volunteers who have been applied to the study in Farmagen (clinical site) enrolled according to the protocol's criteria by the principal investigator. A validated method using liquid chromatography and tandem mass spectrometry was developed and approved to measure apixaban levels in human plasma. For bioequivalence, C_{max} and $AUC_{0\text{-}tlast}$ pharmacokinetic parameters were evaluated.*

Results: *The mean C_{max} were 110.474 ng/mL and 114.455 ng/mL; the mean $AUC_{0\text{-}tlast}$ were 1130.641 ng.hr/mL and 1138.439 ng.hr/mL for the test and reference products, subsequently. The comparative geometric mean ratios (90% CI) were 0.9054 - 1.0185 (C_{max}) and 0.9560 - 1.0142 ($AUC_{0\text{-}tlast}$). Also, both products were well tolerated, with no significant adverse events reported.*

Conclusion: *This study showed that both products are bioequivalent under fasting conditions since the key pharmacokinetic parameters of apixaban are found to be within the standard acceptability limits defined (80.00%-125.00%). A crucial study outcome is also the confirmation of individual interchangeability between the products. In conclusion, our BE study leads to an important contribution to pharmacotherapeutic options in anticoagulant therapy by providing a solid evidence base supporting our generic apixaban product with the reference product, Eliquis.*

Keywords: *Apixaban, bioequivalence, pharmacokinetics, venous thromboembolism, generic drugs.*

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SAĞLIKLI GÖNÜLLÜLERDE APİKSABAN TABLETLERİN FARMAKOKİNETİK PROFİLİ VE BİYOEŞDEĞERLİK ÇALIŞMASI

ÖZET

Amaç: Bu çalışma, bir Faktör Xa inhibitörü olan Apiksaban film kaplı tabletin (Nobel İlaç), referans ürünü Eliquis 5 mg filmtabletten, Bristol-Myers Squibb S.r.l., Italy tarafından üretilmiştir, açlık koşullarında sağlıklı erkek gönüllülerde biyoeşdeğerliğini (BE) ve farmakokinetik profillerini göstermeyi amaçlamaktadır. Ayrıca, çalışma tasarımı, jenerik ilacın referans ilaç ile aralarında değiştirilebilir olduğunu teyit eden bireysel biyoeşdeğerliği değerlendirmektedir.

Materyal ve Metot: Tek doz, açık etiketli, randomize, çapraz geçişli, iki periyotlu bir çalışma tasarlandı ve 32 kişilik bir popülasyon oluşturuldu. Farmagen'e (klinik merkez) başvuran gönüllüler, baş araştırmacı tarafından protokol kriterlerine göre dahil edilmiştir. İnsan plazmasındaki apiksaban seviyelerini ölçmek için sıvı kromatografisi ve ardışık kütle spektrometresi kullanılan bir yöntem geliştirilmiştir. Biyoeşdeğerlik için ise C_{maks} ve $AUC_{0\text{-}tlast}$ farmakokinetik parametreleri değerlendirilmiştir.

Bulgular: Test ve referans ürünler için, sırasıyla, ortalama C_{maks} 110,474 ng/mL ve 114,455 ng/mL; ortalama $AUC_{0\text{-}tlast}$ 1130,641 ng.hr/mL ve 1138,439 ng.hr/mL olarak bulunmuştur. Karşılaştırmalı geometrik ortalama oranlar (%90 CI) 0,9054-1,0185 (C_{maks}) ve 0,9560-1,0142 ($AUC_{0\text{-}tlast}$) olmuştur. Ayrıca, her iki ürün de iyi tolere edilmiş ve ciddi bir advers olay bildirilmemiştir.

Sonuç: Apiksabanın temel farmakokinetik parametreleri tanımlanan standart kabul edilebilirlik sınırları (%80-%125) içinde bulunduğundan, her iki ürünün de açlık koşulları altında biyoeşdeğer olduğu keşfedilmiştir. Çalışmanın önemli bir sonucu da ürünler arasındaki bireysel değiştirilebilirliğin doğrulanmasıdır. Sonuç olarak, BE çalışmamız jenerik apixaban ürünümüzü referans ürün Eliquis ile karşılaştıran sağlam bir kanıt sunarak antikoagülan tedaviler yelpazesine önemli bir katkı sağlamaktadır.

Anahtar kelimeler: Apiksaban, biyoeşdeğerlik, farmakokinetik, venöz tromboembolizm, jenerik ilaçlar.

INTRODUCTION

Venous thromboembolism (VTE) is a cardiovascular condition which affects one out of every 1000 people. Both pulmonary embolism (PE) and deep vein thrombosis (DVT) are included in it. Blood clots are formed in a deep vein, habitually in the thigh, pelvis, or lower leg, causing painful leg swelling in DVT. PE, on the other hand, can cause severe pain in the chest, dyspnoea, and death in severe cases.[1,2] VTE can cause the same symptoms as well and has a significant impact on people's health. If left untreated or improperly treated, there is a substantial risk of relapse.[1,3,4]

Patients with idiopathic VTE have a reported recurrence risk of 25% to 30% five to ten years after their event.[5,6] On the contrary, a randomized controlled trial showed that there were 6.4% recurrences of venous thromboembolism in the three-months treatment group and 7.4% in the six-months treatment group; the two treatment regimens had a similar effect.[7] Also, another study found that anticoagulant therapy of proximal DVT reduces recurrence to about 4% at three months, while anticoagulant therapy of PE significantly reduces morbidities and mortality.[3] Anticoagulant treatment lowers the risk of stroke in patients with atrial fibrillation (AF). Depending on the risk of bleeding, immediate anticoagulation therapy is required for the treatment of VTE. Several novel direct oral anticoagulants have been offered to address this, including dabigatran (a direct thrombin inhibitor) and direct activated coagulation factor X (FXa) inhibitors such as apixaban and rivaroxaban.[1,3,4]

Apixaban is a novel oral anticoagulant that was approved by the EMA in 2011 and the FDA in 2012 to reduce the risk of stroke and blood clots in patients with non-valvular AF.[8,9] It was later approved to treat DVT and PE as well as prophylactic treatments after various orthopaedic surgeries. Apixaban is an orally administered, highly selective, reversible, and direct inhibitor of FXa, the first component in both the intrinsic and extrinsic coagulation pathways. It has strong and direct inhibitory effects without requiring antithrombin III. Apixaban inhibits free and clot-bound FXa, in addition to prothrombinase activity, preventing clot formation. It inhibits thrombin production and thrombi formation by binding to the active site of FXa (inhibition constant (Ki) 0.08 nmol L-1).[10,11]

Apixaban has linear pharmacokinetics, meaning that exposure is proportional to doses ranging from 2.5 to 10 mg. It is rapidly absorbed orally, mostly from the upper gastrointestinal system (GIS), and is unaffected by meals. Apixaban has a bioavailability (BA) of more than 50% (~66%).[10,11] It is a chemically unique neutral bicyclic pyrazole with a molecular weight of 459.5 g/mol. Apixaban has a moderate aqueous solubility of

40-50 g/mL and a Caco-2 permeability of 0.9×10–6 cm/s, which shows a rather incomplete absorption from the GIS.[10]

Apixaban has a quick onset, reaching a peak plasma concentration within 3-4 hours of oral administration.[12] The steady-state concentrations are achieved by day three. The volume of distribution (steady state) is roughly 21 litres with 87% of the substance bound to plasma proteins. The CYP3A4/5 enzyme mediates the primary metabolic pathway, with minor contributions from other CYP enzymes. Unaltered apixaban is the main drug-related component in circulation, while the primary metabolite is an O-dimethyl apixaban sulphate conjugate with no clinically significant activity.[10,13] In healthy individuals, the plasma half-life of apixaban is relatively 12 hours, and the overall clearance rate is 3.3 l/h. Most of the drug is excreted through faeces (both biliary and direct intestinal excretion), and around 27% is eliminated by the kidneys. Apixaban plasma concentrations over time, as measured through the area under the curve (AUC), are higher in individuals with renal impairment. Similarly, older patients had greater plasma concentrations compared to younger ones. Although the pharmacokinetics of apixaban does not appear to be significantly affected in patients with mild-to-moderate hepatic impairment, it is contraindicated in patients with serious hepatic dysfunction or coagulopathy. Although the risk of drug interactions is low, apixaban should be used with caution when combined with powerful CYP3A4 inhibitors or inducers.[10,12,13]

BA and bioequivalence (BE) have become critical in drug development because they play a significant role in ensuring the quality consistency of medicine, lowering the cost of reference drugs and facilitating the acceptance towards generic alternatives.[14,15] BE studies are critical in determining generic products' therapeutic equivalence to the reference drug. These studies employ statistically sound methods to determine whether the generic version has comparable BA and efficacy to the reference product. Various factors can influence the likelihood of demonstrating BE, including clinical study designs (such as fasting conditions, study power), the active pharmaceutical ingredient forms used, and sampling schemes etc. Multidisciplinary collaboration is required for an effective design that takes the right sample size and length of clinical study to overcome these obstacles.[14,15] These studies are crucial for the development of generic pharmaceuticals, especially for drugs that do not demonstrate high solubility such as apixaban.[10]

BE studies evaluate the therapeutic efficacy and safety of a drug by measuring pharmacokinetic (PK) and pharmacodynamic (PD) parameters after the administration of study drugs. The relevant outcome measures are PK parameters such as peak plasma concentration (C_{max}) and AUC, which describe the rate and extent of absorption of the substance. The ratio of each PK characteristic of the generic to the reference is statistically calculated. Also, systemic exposure measurements are considered to be linked to safety and efficacy outcomes as well, which might be reported as biomarkers, surrogate endpoints, or clinically beneficial endpoints.[15,16] As one of the study designs, individual BE ensures that a drug is interchangeable between its reference. It is assessed when the same participant receives both the test and reference products at different time point. It ensures that when a person moves from their current drug to an equivalent product, there will be no significant differences in efficacy and safety. The underlying assumption here is that the BA and intra-individual distribution of both products are equivalent.[17–20]

The importance of BE studies is growing due to the rapid rise of generic drugs' production and usage, which accounted for almost 50% of total consumption in Europe and the United States in 2007.[21] The generics industry is immense, with unbranded generics accounting for 80% of prescriptions in the United States in the fiscal year 2013. Oncology, in particular, is fertile for generics, with numerous medications set to expire patent in the near future.[22] Following the global trend in the pharmaceutical market, Türkiye's pharmaceutical industry has undergone tremendous expansion, with the market nearly tripling in value from 2008 to 2017. In Türkiye, generic pharmaceuticals have a larger market share and outsell reference drugs in terms of unit sales. According to numbers from the Pharmaceutical Manufacturers Association of Türkiye, the Turkish pharmaceutical market reached TL 30.9 billion in 2018, a significant growth from TL 13.4 billion in 2010.[23] Also, Kanavos et al. have shown that in the US, Canada and 5 European countries, the average difference between the original and generic price declines up to 80% in the 3 years after first admission and the average generic's price during this period is 55% of the reference. These data show that generics are generally more affordable and can increase patient access.[24] It should also be noted that twenty-five European countries support the use of generics with strong policies as of 2018.[25]

Objective of this study was to assess the BE of the newly developed Apixaban 5 mg Film Coated Tablet, with those of reference product, "Eliquis 5 mg filmtabletten" administrated in healthy male volunteers under fasting conditions.

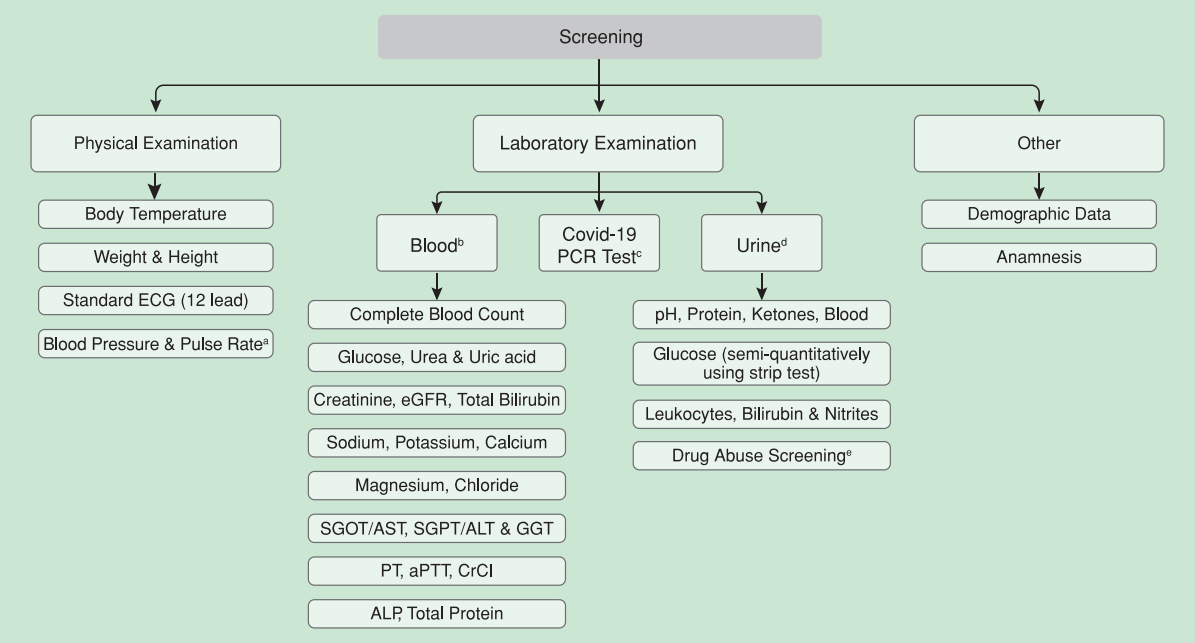

Figure 1. Screening parameters

a) Measured after five minutes of supine resting b) Blood was drawn under fasting conditions c) On the day of screening, two Covid-19 PCR tests were performed d) If any urine test result was positive, the sediment was also examined e) It's followed by an alcohol breath test

MATERIAL AND METHOD

Population

Healthy Caucasian male volunteers (aged between 18 and 45) who had a body mass index between 18.5 and 30.0 kg/m^2 and had no congenital anomalies or chronic diseases qualified as eligible participants. Volunteers who were deemed appropriate by the principal investigator (MD, Professor in Pharmacology) were invited from the volunteer pool of the clinical site (Gaziantep University, FARMAGEN GCP Centre) and screened on 01.07.2020.

Volunteers who were excluded from the study were those with a history or current presence of asthma, atopic constitution, or allergy to apixaban and the finished product's excipients. Additionally, volunteers with prothrombin time (PT) and activated partial thromboplastin time (aPTT) results above the upper limit, creatinine clearance (CrCl) value below 50 mL/min test and a positive Covid-19 PCR test results were not eligible as well. Additional exclusion criteria included the existence of any kind of porphyria, as well as cardiovascular, neurological, musculoskeletal, hepatic, gastrointestinal, renal, pulmonary, endocrinological, metabolic, or mental illnesses. Except for a single dose of analgesics that do not interact with the study product, volunteers were excluded if they had used any systemic or topical medication within two weeks (or six elimination half-lives of the study drug if it is longer) before the study began. Individuals with any disease that would impair the drug's absorption, distribution, metabolism, or excretion as well as those who had taken any vitamins or herbal supplements within 7 days of the first dose were also unable to participate.

These investigations were carried out in conformity with the Declaration of Helsinki, as well as any applicable international guidelines for Good Clinical Practice and Good Laboratory Practice, also, the pertinent laws and regulations of Türkiye where the trials were conducted[16,26–29] The study protocol had been thoroughly explained under the supervision of the principal investigator (PI) and all volunteers gave written informed consent prior to the screening.

The Clinical Study Protocol (dated 29.05.2020), the Informed Consent Form (dated 29.05.2020), and the Case Report Form (dated 29.05.2020) of the study had been approved by the Republic of Türkiye's Ministry of Health on 29.05.2020, Turkish Medicines & Medical Devices Agency on 09.06.2020, and The Bioavailability-Bioequivalence Research Ethics Committee of Erciyes University, Kayseri on 09.06.2020 (Decision No:2020/109).

Screening Period

The day before the isolation, the initial examination was conducted. The parameters in Figure 1 were part of the clinical screening. The auto-analyser was used to conduct each of the following clinical laboratory tests at a contractual and approved lab (GAMA Medical Laboratory - Gaziantep). Also, in Gaziantep, Türkiye, at the FARMAGEN,Covid-19 PCR tests were conducted.

Table 1. Specifications of both Investigational Medicinal Products (IMPs)	
Test Product	Apixaban 5 mg Film Coated Tablet
Marketing Authorization Holder / Manufacturer	Nobel İlaç Sanayii ve Ticaret A.Ş.-Türkiye
Reference Product	Eliquis 5 mg Filmtabletten
Manufacturer	Bristol-Myers Squibb S.r.l., Italy
Marketing Authorization Holder	Bristol Myers Squibb / Pfizer EEIG, Ireland
Marketing site	Bristol Myers Squibb GmbH Co. KGaA, Germany.

Table 2. Summary of the study's demographic statistics			
***n=31**	**Age**	**Weight (kg)**	**Height (cm)**
Mean	24.55	76.19	175.87
SD	7.77	12.51	6.75
Minimum	18	61	165
Maximum	42	120	201
Participant 27**	22	77	172

:** All participants were Caucasian male, *:** Drop-out participant, **SD:** standard deviation

Table 3. Pharmacokinetic Results for both Investigational Medicinal Products (IMPs)		
	Arithmetic Mean ± SD (n=31)	
Parameters (Units)	**Test (T)**	**Reference (R)**
C_{max} (ng/mL)	110.474±24.552	114.455±22.657
$AUC_{0\text{-tlast}}$ (ng.hr/mL)	1130.641±265.030	1138.439±225.126
$AUC_{0\text{-}\infty}$ (ng.hr/mL)	1148.898±269.568	1157.030±231.410
t_{max} (hr)	2.815±0.979	2.842±1.097
$t_{½}$ (hr)	9.479±3.406	9.440±4.757
λz (1/hr)	0.079±0.020	0.083±0.022
MRT (hr)	11.736±2.324	11.593±2.117

C_{max}: Maximum concentration
$AUC_{0\text{-tlast}}$: Area under the plasma concentration-time curve from zero to the last measurable concentration
$AUC_{0\text{-}\infty}$: Area under the plasma concentration-time curve from zero up to the infinity
t_{max}: Time to reach the maximal concentration
$t_{1/2}$: Terminal half-life
λz: Terminal rate constant
MRT: Mean residence time

Table 4. Statistical analysis for Apixaban								
Parameter	**Difference**	**DiffSE**	**TESTLSM**	**REFLSM**	**Ratio**	**90% CI**	**CV%**	**Power%**
$ln(C_{max})$	-0.0405	0.0346	4.6782	4.7187	0.9603	0.9054-1.0185	13.685	99.977
$ln(AUC_{0\text{-tlast}})$	-0.0154	0.0174	7.0024	7.0178	0.9847	0.9560-1.0142	6.851	100.000

$AUC_{0\text{-tlast}}$: Area under the plasma concentration-time curve from zero to the last measurable concentration
C_{max}: Maximum concentration

A licenced local laboratory performed all of these laboratory testing. Before the study began, the PI submitted the acceptable ranges and units of measurement for the laboratory parameters that would be established during the trial. In each case report form (CRF), the reference measurements of the specific laboratory tests were recorded. An authorised copy of the original laboratory results was also given to the PI.

Study Design

Intervention and Comparison

In this single-dose, open-label, randomised, cross-over two-period study, 32 healthy male participants were randomly assigned to 2 groups using the Random Allocation Software V.1.0.0.[30] Both products were administered in the relevant treatment sequence, and the study participants received both during the study. The demographics of the participants is submitted in the Table 1. 32 participants were randomised and included into the study. Following overnight fasting, 31 healthy male participants received one oral dosage of either Eliquis 5 mg Filmtabletten (Table 2) or Apixaban 5 mg Filmcoated Tablet (Nobel Lac) in accordance with each period's randomization. The test and reference products were administered with 240 mL water. There has been one drop-out. Participant No 27 left the study with his own decision in Period I and has not been replaced in accordance with the Clinical Study Protocol.

After the four-day washout period; the participants have been administered the other product in Period II that wasn't given to them in the Period I. Consequently, 31 of them went through with the clinical part of the study as planned.

The participants were fasted overnight (for at least ten-hours). The administrations had been carried out in the morning, around 8:00, and the precise time was documented on CRFs. Except when administering, participants were not permitted to consume any water from one hour prior to the administration until one hour following. The participants received the study product while sitting in bed, and over the following four hours, they did not lie down at any point. At four- and ten-hours following treatment, standard meals with 1200 kcal were served for lunch and supper, subsequently.

Sampling Points

A short intravenous catheter was used to collect blood samples (7 ml) at 0 (pre-dose) and 0.50, 1.00, 1.50, 2.00, 2.33, 2.66, 3.00, 3.33, 3.66, 4.00, 4.33, 4.66, 5.00, 6.00, 8.00, 10.00, 12.00, 24.00, 36.00, 48.00, 72.00 hours after dosing for both products for the fasting study. The blood samples were collected using K2EDTA, an anti-coagulating agent.

Blood sample tubes were inserted into tube holders and stored in freezing water. Each participant gave approximately 349 mL of blood in total for the study. About 28 mL of this was used for screening and post-study examinations. The tubes containing the blood

samples for PK analysis were promptly thawed at a temperature between 2 and 8 degrees Celsius and kept at that temperature for no longer than thirty minutes. The plasma from each sample was put into two 3 mL clear, polypropylene tubes for storage (at least 1.5 mL each tube) following 10 minutes of centrifugation (3.000 rpm, 4-6°C). The tubes were then placed in a freezer and kept at -70°C.

After concluding the clinical phase, the first half of plasma samples (master samples) in dry ice were sent to the Novagenix Bioanalytical Drug R&D Centre's (Ankara, Türkiye) Logistic Specialist (the responsible person), with a precaution label "Biological samples, keep frozen at -70°C".

As a precautionary measure, master and backup samples have been sent to Novagenix on different days. After receiving samples, the reception form was completed by the responsible person and the investigator was informed.

Outcome

Bioanalysis

At Novagenix, a technique was created and approved for the quantitative detection of apixaban in human plasma utilising validated liquid chromatography coupled to tandem mass spectrometry. 200 µL of human plasma was used to create the liquid-liquid extraction samples for the analysis. For apixaban, the technique was validated in a range of 0.5-300 ng/mL. According to FDA and EMA guidelines and other mentioned sources, the accuracy and precision of this approach were determined to be within the acceptable range.[31–35]

The clinical research organisation (CRO) did not know the allocation of the test and reference products until the analytical part of the study had been completed. The CRO personnel were able to identify the products as 'Product A' and 'Product B' which were allocated by the investigator site. Following the completion of the analytical part, the code was broken by a commission formed by the CRO's executives, as well as their assistants. After the code was broken, no reanalysis or data exclusion was performed.

Statistical Analysis

Phoenix® WinNonlin® (v8.1, Certara USA, Inc., Princeton, NJ) and the Analysis of Variance (ANOVA) test were used to conduct the statistical assay. The key PK elements (C_{max} and $AUC_{0\text{-tlast}}$) of apixaban were used to assess comparative BA using 90% Confidence Intervals

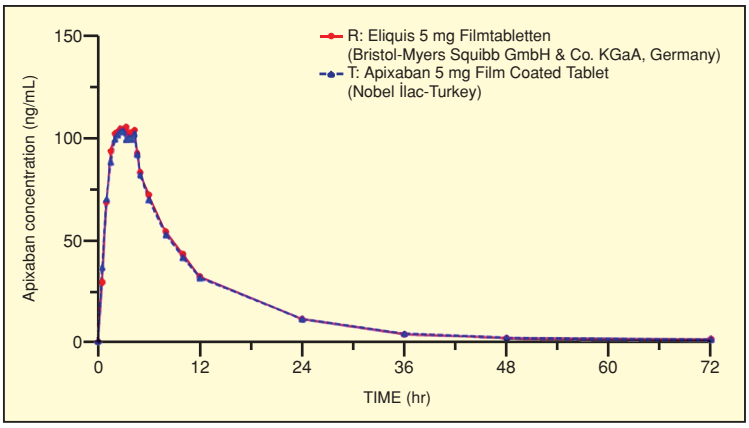

Figure 2. Both Apixaban Products' Average Plasma Concentrations

(CIs) for geometric mean ratios of both products. These products are considered to be bioequivalent if these key parameters are within the range of 80.00%-125.00%, as defined by the Turkish Medicines and Medical Devices Agency, the Republic of Türkiye Ministry of Health, and relevant international guidelines.

RESULTS

Participant 27 withdrew from the study in Period I at his own request and was not replaced nor included in the analyses, in accordance with the Clinical Study Protocol. In the end, 31 participants successfully went through with the clinical part of the study, and their samples were analysed. The demographics of the participants is submitted in the Table 2.

Figure 2, Table 3, and Table 4 show the average plasma concentrations over time profiles as well as the PK and statistical parameters of both products. The mean±SD C_{max} were 110.474±24.552 ng/mL and 114.455±22.657 ng/mL for test and reference products, respectively. The mean±SD $AUC_{0\text{-tlast}}$ were 1130.641±265.030 ng.hr/mL and 1138.439±225.126 ng.hr/mL for the test and reference products, subsequently.

All of the samples' concentrations in period 2 at $t_{0.00}$ were zero, <LLOQ, or less than 5% of C_{max}, showing that there was no carry-over effect.

The intra-individual variabilities of C_{max} and $AUC_{0\text{-tlast}}$ have been found as 13.685% and 6.851% and the power has been found as 99.977% and 100.00% respectively.

It has been discovered that both apixaban products are bioequivalent under fasting conditions since the 90% CI of the comparative geometric mean ratios for C_{max} (0.9054 - 1.0185) and $AUC_{0\text{-tlast}}$ (0.9560 - 1.0142) of apixaban are found to be within the standard acceptability limits defined in the Clinical Study Protocol as 80.00%-125.00%.

Safety Evaluations

During the study period, participants were treated under hospitalisation conditions and hospitalised at the Clinical Facility from the evening of Day 0 normally until the last blood sample was taken in the 2nd Period. They also completed the post-study and final exams under standard trial conditions during the profiling days. In each study period, adverse events were observed (screening/isolation days, day 0, at the time of pre-dose, and 1.00, 4.00, 12.00, 24.00, 36.00, 48.00, and 72.00 hours after the dosage).

Throughout the clinical part, the investigator or one of the co-investigators was present to provide medical care for the participants. On the day before the first dose, the participants arrived at the clinic from isolation at 18:30 and stayed there for 188 hours. Throughout the research period, body temperature was measured once a day in the morning. On the day of the final sampling in the 2nd period, all participants had a post-study, final exam, and laboratory testing.

The study had 31 fully completed participants and one drop-out participant (Participant No 27). Theoretically, they had apixaban in their systemic circulation for 96 hours [six fold of t½] in each period (a total of 192 hours for two periods).

Neither death nor serious adverse event occurred during the study. There have been four cases of non-serious adverse events. For the Test product, Participant 11 had abundant leukocytes in urine examination (in the final examination) and Participant 28 had headaches (in Period 2). For the Reference product, Participant 02 had a high ALT value (in the final examination), and Participant 15 had a headache (in Period 2).

Participants 11 and 02 had been called for a control examination on 13.07.2020, 15.07.2020, and 17.07.2020; but they didn't come. 500 mg of Paracetamol was given to Participants 28 and 15 and they fully recovered. It is also important to note that no positive cases were observed according to Covid-19 PCR test results during the study.

DISCUSSION

BE studies are an important part of generic R&D. Generic drug development can have significant positive impacts on the local economy. First and foremost, a growing local generic industry improves employment and infrastructure in areas such as research and development, manufacturing, and distribution. As far as that goes, a robust generic pharmaceutical industry can contribute to a country's economy by reducing healthcare expenses.[36,37] These savings can then be allocated to other areas of need in the healthcare industry or the economy as a whole.

Additionally, having strong generic suppliers and adjuvant policies can ensure that patients have consistent access to essential medications, thereby reducing the risk of drug shortages.[38,39] This is particularly important when the reference company doesn't license and supply the product to our country after the patent expires.

The purpose of this study was to determine the BE of the test product, Apixaban 5 mg Film Coated Tablet (Nobel İlaç), and the reference product, Eliquis 5 mg Filmtabletten. In other words, to see if both products induced equivalent PK responses when provided orally in a single dosage under fasting conditions.

Blinding the CRO for analytical analysis reduced bias and increased the validity of the results. They were unable to proceed with the statistical analysis until the code was broken under the supervision of a joint commission.

The occurrence of adverse events did not vary significantly between the two Investigational Medicinal Products (IMPs). Furthermore, both products were well tolerated, with no significant adverse events reported.

CONCLUSIONS

According to the guidelines provided by the Turkish Medicines and Medical Devices Agency and European Medicines Agency on the Investigation of BE, it is concluded that the test product is bioequivalent to the corresponding reference product.

A crucial element of this study's conclusion is the confirmation of individual interchangeability between the Apixaban 5 mg Film Coated Tablet (Nobel İlaç) and the Eliquis 5 mg Filmtabletten. This signifies that physicians can expect an identical efficacy and safety profile from the test product as that of the reference product. Therefore, when a patient transitions from their current medication, Eliquis, to our bioequivalent product, no significant difference in therapeutic outcomes have been expected.

In conclusion, our BE study leads to an important contribution to pharmacotherapeutic options in anticoagulant therapy by providing a solid evidence base supporting of our generic Apixaban product with the reference product, Eliquis. This not only provides a cost-effective alternative, but it also promotes greater patient access to critical anticoagulant therapies.

*The authors declare that there are no conflicts of interest.

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