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Bioequivalence study of eltrombopag 75 mg film-coated tablets under fasting conditions during the Covid-19 pandemic in healthy Caucasian male subjects

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Abstract

This study aims to determine the bioequivalence of the reference preparation and the test preparation containing eltrombopag when both were given during the COVID-19 pandemic while fasting. Participants in the research were healthy male Caucasian subjects. One film-coated tablet of the test preparation or one film tablet of the reference preparation, equivalent to 75 mg of eltrombopag, was given to the participants in a randomized order throughout each treatment session. At pre determined blood sampling points, blood samples were taken to determine the pharmacokinetics of eltrombopag. Eltrombopag concentrations in the samples were determined using an LC-MS/MS technique verified using ESI(–). The study results were used to calculate the rate (the maximum plasma concentration, or C_{max}) and extent (area under the concentration-time curve of plasma, or $AUC_{(0-72)}$ and $AUC_{(0-t)}$ of eltrombopag absorption from the test preparation and reference preparation. The 90% confidence intervals (CI) of the ln-transformed $AUC_{(0-72)}$, $AUC_{(0-t)}$, and C_{max} of eltrombopag met the bioequivalence requirements of 80.00–125.00%. Both trial preparations had a similar and very satisfactory safety profile.

Key points

- Bioequivalence of eltrombopag film-coated tablets
- Safety evaluation of eltrombopag film-coated tablets

Keywords Bioequivalence study, Eltrombopag, Pharmacokinetic, Bioavailability

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Introduction

Eltrombopag is a tiny molecule medication taken orally that is an agonist of the thrombopoietin (TPO) receptor. It binds to the human TPO receptor's transmembrane domain, initiating signaling pathways that support the differentiation and multiplication of progenitor cells in the bone marrow [1, 2].

When eltrombopag is given to healthy people at dosages ranging from 50 to 150 mg/day, there is a dose-proportional increase in exposure. The AUC Eltrombopag is about 1.7 times higher in patients with immune thrombocytopenic purpura (ITP). In chronic or persistent use, the AUC is about 2.8 times higher in patients with hepatitis C when compared with healthy subjects. At a dosage of 75 mg/day, the geometric mean accumulation ratio is 1.56 (90% CI 1.20, 1.63), which indicates that steady-state concentrations are usually attained after approximately one week of daily administration. Eltrombopag AUC is generally 3.2 times higher in patients with severe aplastic anemia who have not received definitive immunosuppressive therapy than in healthy subjects. It suggests that AUC in hepatitis C is more significant than in both healthy subjects and individuals with ITP. Moreover, eltrombopag oral suspension produces a plasma $AUC_{(0-\infty)}$ 22% greater than the tablet formulations [3].

The plasma levels of eltrombopag increase linearly with the dose, and it takes two and a half to five hours to reach their highest concentration when taken at 75 mg orally [3, 4]. A high-fat meal (876 calories, 52 g of fat, 71 g of carbs, 34 g of protein, and 427 milligrams of calcium) was shown to considerably lower plasma eltrombopag $AUC_{(0-\infty)}$, C_{max} and time to achieve C_{max} (t_{max}). The increased calcium content is primarily responsible for this decrease in $AUC_{(0-\infty)}$, C_{max} and t_{max}. On the other hand, irrespective of the meal's calorie content and lipid composition, a low-calcium meal did not significantly influence plasma eltrombopag level [5, 6].

A radiolabeled study found that the level of eltrombopag in blood cells is 50–79% compared to that in plasma. Based on in vitro investigations, eltrombopag binds to more than 99% of human plasma proteins [4]. Eltrombopag has an elimination half-life in plasma of 21–32 h in healthy subjects and 26–35 h in ITP patients. After absorption, eltrombopag is extensively metabolized via oxidation, cleavage, and conjugation with cysteine, glutathione, or glucuronic acid. Eltrombopag's oxidative metabolism is linked to CYP1A2 and CYP2C8, whereas UGT1A1 and UGT1A3 cause glucuronidation. These findings are based on in vitro investigations [7, 8]. Eltrombopag is mainly excreted in feces, where 59% of the dosage is eliminated, and 31% is eliminated in urine. The unaltered eltrombopag, which is undetectable in urine, is about 20% of the total dosage [7].

Any product's efficacy and safety must be shown for registration. The marketing authorization procedure for a novel generic product includes establishing the bioequivalence with a market standard by comparing relative bioavailability or showing therapeutic equivalence. The therapeutic equivalence procedure needs many more patients and a long time to show the similarity between the test and reference drugs. The bioequivalence trial based on bioavailability is the most sensible option [9, 10].

The present trial aims to investigate the bioequivalence between a test and a reference preparation, each containing eltrombopag, under fasting conditions during the COVID-19 pandemic. Revolade 75 mg Film Tablets, already registered and marketed for sale in Germany, are the reference medication used in this study. Fromer clinical trials have verified the safety and efficacy of this reference medication. Eltrombopag 75 mg Film-Coated Tablet, produced by İLKO Pharmaceuticals, Turkiye, has been used as the test drug.

Methods

The study was approved by an independent ethics committee-Ethics Committee for Bioavailability-Bioequivalence Trials of Erciyes University (date of approval: 15.06.2022; vote no: 2022/148) and the Turkish Medicines and Medical Devices Agency (TİTCK) of Turkish Ministry of Health, (date of approval: 01.07.2022, note no.: E-66175679-514.06.01-803603). Clinical trial number is not applicable.

The study was designed following the Turkish Pharmaceutical and Medical Preparations Law No. 1262, ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP), Turkish Regulations Regarding Clinical Trials of Drugs and Biologics and the Turkish Good Clinical Practice Guideline (13.11.2015) [11–13].

The purpose of the investigation was fully disclosed to each subject in a written document and oral presentation by the principal investigator or one of the co-investigators. Then, each participant voluntarily signed the Informed Consent Form.

Study design

This study was conducted in 48 healthy male individuals under fasting conditions. It was a single-dosage, mono-centric, randomized, open-label, two-period, crossover bioequivalence study. 68 Caucasian male subjects were screened between July 25, 2022, August 4, 2022, and August 15, 2022. After undergoing thorough physical examinations and clinical laboratory tests, 48 healthy male individuals were included in the research (Fig. 1).

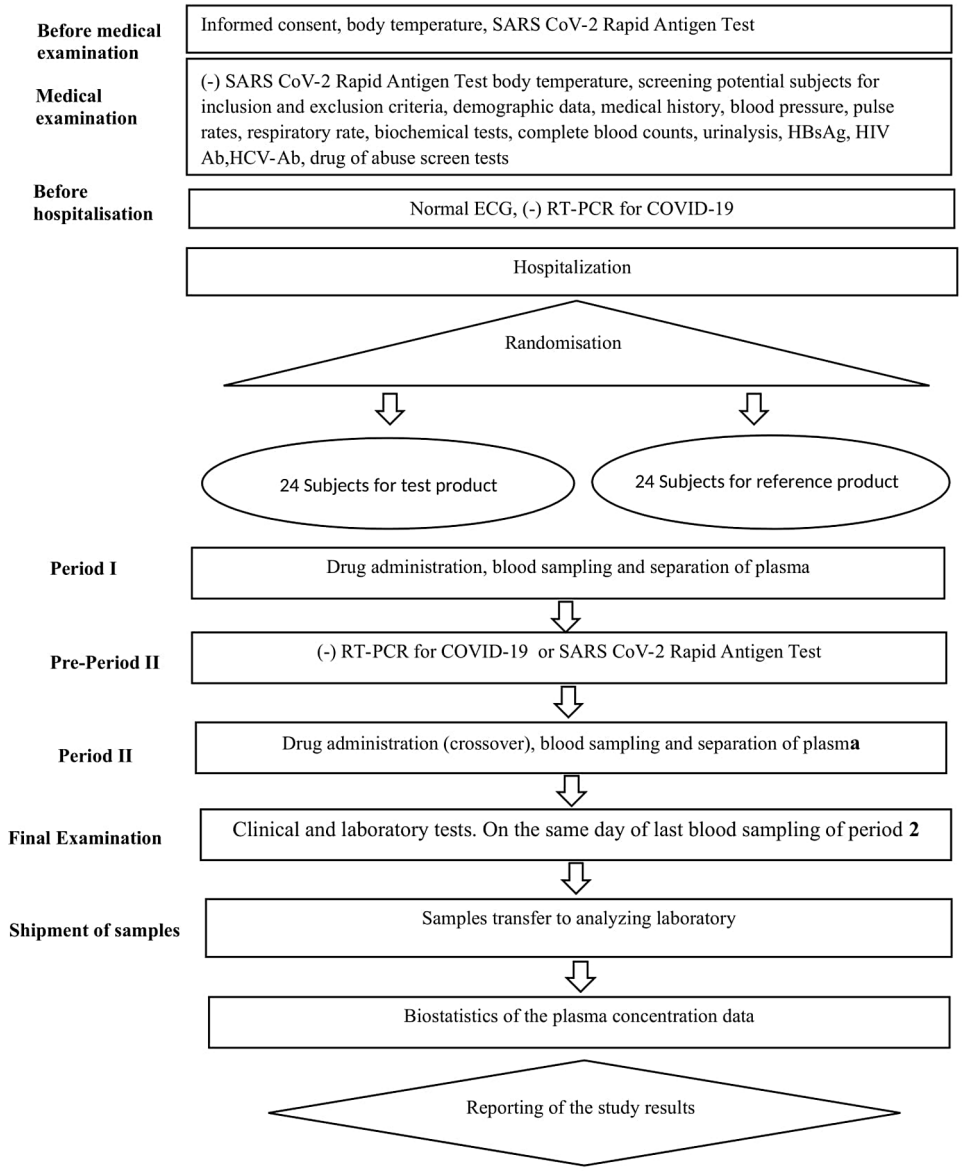

Fig. 1 Schematic study design

Precautions for COVID-19

Before the subjects were accepted to the clinical unit, their body temperature was measured, and a SARS-CoV-2 Rapid Antigen Test was performed. If the body temperature was within normal ranges and the rapid antigen test showed negative results, then the subjects were accepted to the clinical unit for screening. A combined throat/nasal swab was collected for an additional real-time Reverse Transcription Polymerase Chain Reaction (RT—PCR) COVID-19 test during screening. If this test also showed negative results and the subjects were considered suitable for the study, they were confined to the clinical unit. An additional COVID-19 real-time RT—PCR test or a SARS CoV-2 Rapid Antigen Test was also performed before the second period. Participants who had two negative COVID-19 test results were hospitalized in the clinical unit in the evening before drug administration.

Drug administration, study requirements and blood sampling

The subjects were hospitalized approximately 12 h before the medication was administered and discharged approximately 12 h after the administration. After being hospitalized, participants were given a snack in the evening with a total caloric value of approximately 600 kcal, which they were required to finish by 9:00 pm. The Investigational Products were administered the following morning, and the subjects were discharged approximately twelve hours later. The subjects were invited to the

clinical site for blood sampling at 24-, 36-, 48-, and 72 h post-administration. The test and reference preparations, each containing 75 mg of eltrombopag, were administered orally with 240 mL of water after at least ten hours of overnight fasting. A second medical professional performed mouth and hand checks to ensure that the drug was taken wholly and correctly. After the drug administration, subjects were instructed not to lie down for the next two hours, except in cases of orthostatic discomfort.

Overnight fasting continued after four hours post-dosing, with fluid intake restricted to tap water, allowing a maximum of 1.5 L on dosing days. Water was allowed one hour before and after the drug administration. A standard lunch (approximately 1200 kcal) was provided at the end of the fasting period, followed by a standard dinner (approximately 1200 kcal) 10 h post-dose. Smoking was prohibited during blood sampling periods. Alcohol consumption was restricted from two days before each dosing until after the final blood sampling of each period. Furthermore, from two days before the dosing until the last blood sample, meals and drinks that included caffeine or other methylxanthines (such as coffee, tea, cola, and chocolate) and fruit juices were prohibited. Consumption of grapefruit and orange products was not allowed from seven days before the first dosing until the final blood sampling.

Subjects were instructed to avoid prescribed systemic or topical medications for two weeks before the study and to stop taking over-the-counter (OTC) medications, including herbal products, one week before the survey. The use of systemic or topical drugs, including herbal products, was not allowed during the study. Additionally, participants were prohibited from using investigational medicines (i.e., medications that are not yet licensed) within the 60 days before the trial. Between periods I and II, a 14-day wash-out period was provided. Subjects were permitted to leave the clinical center after the final examination.

Blood sampling was done before the dosing and 30 min, 1 h, 1 h 30 min, 2 h, 2 h 20 min, 2 h 40 min, 3 h, 3 h 20 min, 3 h 40 min, 4 h, 4 h 30 min, 5 h, 5 h 30 min, 6 h, 7 h, 8 h, 12 h, 24 h, 36 h, 48 h, and 72 h after the dosing. Blood sampling (22 per period) was done with a short intravenous catheter. Every sample (7 milliliters) was placed into tubes containing K_2-EDTA as an anticoagulant. Following centrifugation at 3000 rpm, 4–7 °C, for 10 min, the separated plasma was given into two 3.5 ml transparent polypropylene tubes, each containing at least 1.5 ml of plasma, and kept at <–70 °C until it was transported to the analytical facility. After the trial was completed, one aliquot was sent to Analytisches Zentrum Biopharm GmbH, Berlin, Germany, via courier on dry ice (solid CO_2).

Study drugs

The test product, Eltrombopag 75 mg Film Coated Tablets (T), batch no: 2213819001, expiry date: 04.2024, was produced under Good Manufacturing Practices (GMP) conditions by İLKO İlaç Sanayi ve Ticaret A.Ş., Turkiye. The innovative product, Revolade 75 mg Filmtabletten (Film Tablets) (R), batch no: BALJ7X, which was acquired from the German market, served as the reference preparation.

Bioanalytical method

Samples were analyzed for concentrations of eltrombopag with a validated LC-MS/MS method with ESI(–). Guidelines for Good Laboratory Practice (GLP) were used to perform the analytical procedures [14, 15]. The lower limit of quantification (LLOQ) for eltrombopag was set at 0.150 µg/mL for plasma samples. The mean relative deviations of quality control (QC) samples, reflecting inter-assay accuracy (bias %), were as follows: 4.7% for high-quality control (HQC), 2.7% for medium-quality control (MQC), –6.2% for low-medium-quality control (LMQC), and 4.8% for low-quality control (LQC). The corresponding mean values for inter-assay precision (CV %) were 3.2% for HQC, 3.7% for MQC, 3.4% for LMQC, and 4.1% for LQC. The method validation covered the relevant stability aspects, including long-term stability, wet extract stability, and long term stability. The storage duration of the samples prior to the bioanalysis, as well as the time between sample collection and freezing of the plasma, were both within the validated stability timeframes established during method validation. These factors were thoroughly assessed to ensure the integrity and reliability of the bioanalytical results.

Assessment of pharmacokinetics and statistics

Eltrombopag's $AUC_{(0–72)}$ and C_{max}, were estimated to be the primary target variables.

In addition to $AUC_{(0–\infty)}$, parameters such as t_{max}, $t½_{(\lambda z)}$, λ_z and $AUC_{\%–extrapol}$ were also examined as auxiliary variables. To better approximate a normal distribution, $AUC_{(0–72)}$, $AUC_{(0–\infty)}$, $AUC_{(0–t)}$, and C_{max} data were transformed logarithmically before analysis and then subjected to parametric testing using ANOVA. The 90% confidence interval for the test/reference ratio of geometric means was calculated by retransforming the log-transformed values. Bioequivalence was determined if the 90% CI fell within the 80.00–125.00% range for $AUC_{(0–72)}$ and C_{max}, as specified in the study protocol, and also for $AUC_{(0–t)}$, which was considered as an extrapolatory pharmacokinetic variable. t_{max} values were also statistically evaluated. Non-parametric analysis results (90% CI from two one-sided Wilcoxon tests) were used as supportive data and were not used for the primary bioequivalence assessment. Parameters of the individual

estimate of the terminal elimination rate constant (λ_z) and half-life ($t½_{(\lambda z)}$), along with $AUC_{\%-extrapol}$, were tabulated with their descriptive statistics. Differences in t_{max} were assessed through non-parametric analysis (90% CI from two one-sided Wilcoxon tests) using Phoenix WinNonlin V8.3.5.340.3. For calculating λ_z [h-1], the slopes of the log-linear concentration/time curves were based on the last four data points above the LLOQ. The parameters $AUC_{(0-72)}$, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{max}, λ_z, $t½_{(\lambda z)}$ and $AUC_{\%-extrapol}$ of eltrombopag were determined with the program Phoenix WinNonlin V8.3.5.340.

Safety assessment

All adverse events (AEs) were recorded in Case Report Forms (CRF) for each subject. These AEs included those reported spontaneously by the participants, identified during regular questioning (upon admission to the clinical unit before the 1st and 2nd periods, and at study times of 0 h (within 60 min before dosing), 1 h and 6 h, 12 h, 24 h, 36 h, 48 h and 72 h during both periods). Additionally, any AEs observed by the investigator were also recorded.

Results

Demographic results

Forty-eight healthy male Caucasian subjects were enrolled in the study after a comprehensive screening (including first medical examination, blood and urine laboratory tests, ECG and others). Out of these, 46 subjects, aged (18–50 years) with a Body Mass Index (BMI) between 18.7 and 29.7 kg/m², finished the study as planned. Two subjects withdrew from the study: the first left after period I for personal reasons, and the second before period II due to a medical issue (a positive RT-PCR COVID-19 test).

Eltrombopag concentrations were investigated using plasma samples from the 46 participants who completed the research. The average (±standard deviation) demographic data for these 46 subjects were 33.3 (±9.4) years in age, 77.4 (±12.1) kg in weight, 174 (±7.4) cm in height, and a BMI of 25.6 (±3.2) kg/m² (Table 1).

Table 1 Summary of the subjects' demographic data

Summary demographic data	Age* [a]	Weight* [kg]	Height* [cm]	BMI*/** [kg/m²]
Mean	33.3	77.4	174	25.6
SD* **	9.4	12.1	7.4	3.2
CV [%]** **	28.1	15.6	4.2	12.5
Minimum	18	50.8	161	18.7
Maximum	50	99.0	192	29.7

*At the time of pre-study examination

**Body mass index should be in the range of 18.5–30 kg/m²

***Standard deviation

****Coefficient of variation

Pharmacokinetic results

As a result of the blind review of analytical data, the pharmacokinetic data set (n=46 subjects) represented all subjects who completed the study, all devoid of protocol violations, without violation of entry criteria and with all of the primary target variables available for measurement. There were noticeable similarities between the test and reference drugs when comparing pharmacokinetic data. Eltrombopag's $AUC_{(0-72)}$ and C_{max}, were first estimated using pharmacokinetic values based on the literature indicating a long half-life of 21–32 h. However, The study's findings showed that the half-lives of the reference and test items were around 18 h. As a result, $AUC_{(0-72)}$ could only be assessed for 16 subjects. Analysis of variance (ANOVA) and two one-sided t-tests were used to compute the 90%CI for the test/reference ratios of geometric means for the primary pharmacokinetic variables $AUC_{(0-72)}$, C_{max}, and the additional variable $AUC_{(0-t)}$, assuming a log-normal distribution of the data. This was done to assess the bioequivalence between the test and reference preparations.Eltrombopag characteristics showed no significant differences, such as $AUC_{(0-72)}$, $AUC_{(0-t)}$, and C_{max} (Table 2).

The comparative bioavailability of eltrombopag of the test drug, determined by comparing the geometric means of AUC (0–72), is 99.26%, AUC (0–t) is 111.03%, and Cmax is 111.79% (ratio, i.e., point estimator of 90% CI) (Table 3).

During analysis of variance of primary pharmacokinetic parameters $AUC_{(0-72\ h)}$, $AUC_{(0-t)}$ and C_{max}, no statistically significant period effects were observed.

For a more comprehensive evaluation, Fig. 2a and b present mean plasma concentration-time profiles for eltrombopag across different time points and treatments. These graphical representations confirm the same pharmacokinetic characteristics between the test and reference products. In conclusion, the data from both tables and figures support the claim of bioequivalence between the test and reference products.

Safety evaluation

Five out of the 48 subjects experienced seven adverse events during the study. Four adverse events occurred before dosing: three (3 x headaches) of them even before the first drug administration and one (1 x positive COVID-19 RT-PCR test) before the second drug administration (two weeks after the first treatment). So, these adverse events were evaluated to be "unlikely" drug-related. Two of the remaining treatment-emergent adverse events (2 x headaches) were mild, and one (1 x high blood glucose level) was of moderate intensity. Two headaches occurred in period II after the test preparation. High blood glucose was observed during the final examination. The last dose administered to this subject

Table 2 Results of pharmacokinetic testing (arithmetic mean ± SD.; *n* = 46) of eltrombopag

Treatment	*$AUC_{(0-72)}$ [µg/mL*h]	C_{max} [µg/mL]	$AUC_{(0-t)}$ [µg/mL*h]	t_{max} [h]	λz [1/h]	t½ (λz) [h]	AUC (0–∞) [µg/mL*h]	$AUC_{\%-extrapol}$ [%]
T: Eltrombopag								
75 mg Film Coated Tablets	107.898	8.49	83.149	2.95	0.046	18.27	90.683	7.73
batch no.: 2213819001	± 33.848	± 2.919	± 36.723	± 0.82	± 0.0237	± 7.4	± 42.18	± 3.35
R: Revolade								
75 mg Filmtabletten (Film Tablets)	110.488	7.534	75.512	3.33	0.05	17.14	82.982	8.55
batch no.: BALJ7X	± 26.191	± 2.517	± 34.810	± 0.9	± 0.0249	± 7.52	± 39.997	± 3.46

*n = 16 subjects included for $AUC_{(0-72)}$ evaluation

AUC: Area under the curve

C_{max}: The Maximum plasma concentration

t_{max}: Time to achieve C_{max}

λz: Individual estimate of the terminal elimination rate constant

t½: Half life

Table 3 Statistical results of eltrombopag (test vs. reference); *n* = 46

Primary pharmacokinetic parameters			Intrasubject variability
*$AUC_{(0-72)}$	85.58–115.12%	(ratio: 99.26%)	22.34%
*$AUC_{(0-t)}$	98.76–124.82%	(ratio: 111.03%)	34.38%
*C_{max}	100.69–124.11%	(ratio: 111.79%)	30.53%
Secondary pharmacokinetic parameters			**Intrasubject variability**
*$AUC_{(0-\infty)}$	98.35–123.13%	(ratio: 110.04%)	32.90%
**t_{max}	0.00–0.67 h	(median of difference reference-test: 0.34[h])	

*Two one-sided t-tests; ANOVA

**Non-parametric analysis

h: hour

AUC: Area under the curve

C_{max}: The Maximum plasma concentration

t_{max}: Time to achieve C_{max}

was the test preparation. The subject did not return to the clinical facility for the repeat tests. Both headaches were evaluated to be "possible" drug-related, whereas the high blood glucose level was assessed to be "unlikely" drug-related. Headaches seen pre-administration and one of the headaches seen during period II were treated with 500 mg paracetamol. All treatment-emergent adverse events recovered without sequelae, except for the high blood glucose level, for which the outcome is unknown as the subject refused to return to the clinical unit for the repeat measurement.

No severe adverse events were recorded. Table 4 summarizes the observed treatment-emergent adverse events.

Discussion

Bioavailability is the term used to describe the rate and extent of absorption and availability of the therapeutic moiety or active component in a pharmaceutical

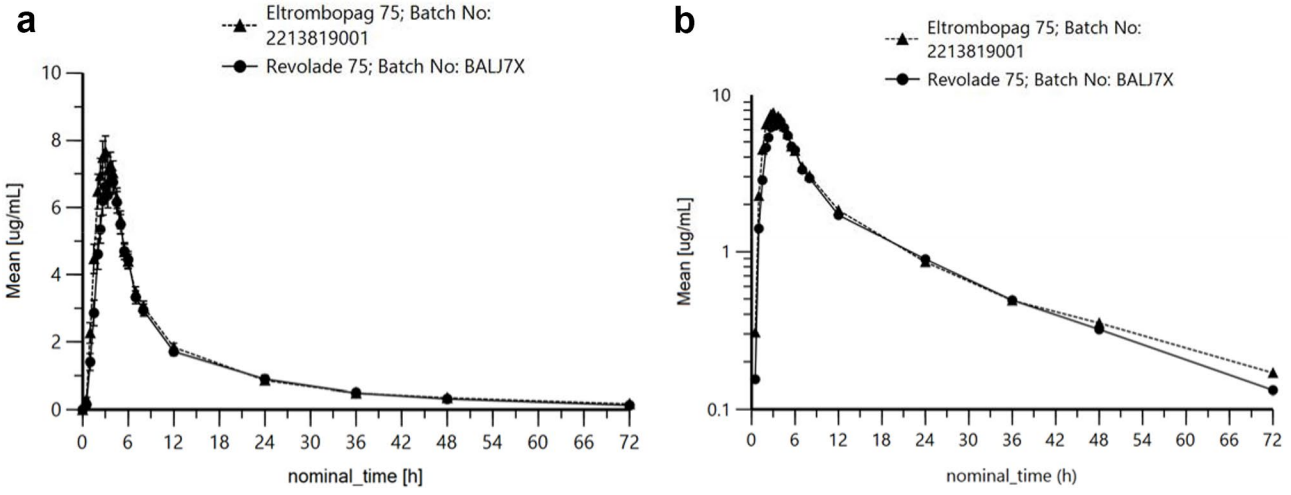

Fig. 2 **a** Eltrombopag mean plasma concentration/time profiles—linear (± SEM) plot (*n* = 46). **b** Eltrombopag mean plasma concentration/time profiles semilogarithmic plot (*n* = 46)

Table 4 Number, type and qualification of adverse events observed

Relationship with the drug	Adverse event (*n*)	Adverse events by treatment at onset of AE		
		Treatment T	Treatment *R*	Predose
Possible	Headache (2)	2	0	0
Unlikely	Headache (3)	0	0	3
Unlikely	High blood glucose (1)	1	0	0
Unlikely	Positive COVID-19 real-time PCR test (1)	0	0	1

n: Number

AE: Adverse events

T: Test

R: Reference

at the site of treatment action. The Guideline on the Investigation of Bioequivalence Committee for Medicinal Products for Human Use states that two medicinal products are bioequivalent if their bioavailabilities (rate and extent) after administration of the same molar dose are similar to such degree that their effects concerning both efficacy and safety will be essentially the same [13]. This condition is met if the AUC-ratio and C_{max}-ratio's 90% confidence intervals fall between 80.00% and 125.00%. According to the above guidance, $AUC_{(0-72)}$ may be used instead of $AUC_{(0-t)}$ for comparing exposure duration since the absorption phase for immediate-release formulations is completed in 72 h. Therefore, regardless of the drug's half-life, a sample duration greater than 72 h is not required for any immediate-release formulation. When doing research with a 72-hour sample interval and measurable concentration at 72 h, reporting $AUC_{(0-\infty)}$ and residual area is unnecessary; reporting $AUC_{(0-72)}$ suffices [16]. As eltrombopag was given in the literature data as a long half-life drug (21–32 h), $AUC_{(0-72)}$ was chosen as the primary pharmacokinetic parameter besides C_{max}. $AUC_{(0-t)}$ was initially foreseen as an exploratory variable.[3] However, the long half-life given in the literature for eltrombopag was not confirmed by the study results, where the half-lives of both test and reference drugs were calculated to be about 18 h. Consequently, $AUC_{(0-72)}$ could only be evaluated for 16 subjects. Therefore, besides $AUC_{(0-72)}$ and C_{max}, $AUC_{(0-t)}$ was also treated as a primary target variable. According to the current study, the extent and rate of eltrombopag absorption from test and reference preparation are comparable. The 90% CI for the Test/Reference ratio of ln-transformed $AUC_{(0-72)}$, $AUC_{(0-t)}$, and C_{max} of eltrombopag satisfies the 80.00 −125.00% bioequivalence requirements.

The bioequivalence acceptance range includes the 90% CI of the ln-transformed data for eltrombopag's secondary pharmacokinetic target variable $AUC_{(0-\infty)}$. Both study preparations have a very acceptable safety profile. There was no clinically significant variation in the therapies' safety and tolerability.

Conclusion

The clinical research area, except for COVID-19 research, was significantly interrupted, especially in the early period of the pandemic. In our GCP clinical facility, we started the clinical trial procedure by considering the risk of COVID-19 infection in our staff and subjects. The rationale for this action was to use a method that includes pre-study isolation of subjects and frequent checks for COVID-19 infection in our staff and subjects. While working with hotel isolation in the early days of the pandemic, we continued to work with measures such as the SARS Co-V-2 Rapid Antigen Test, RT- PCR tests, checking body temperature, and use of face masks. The significant contributions of this study are both indicating that clinical study can be done in periods of pandemics and showing that two eltrombopag products are bioequivalent.

Abbreviations

AUC	Area under the concentration time curve of plasma
C_{max}	Maximum plasma concentration
t_{max}	Time to achieve Cmax
t1/2	Half life
CI	Confidence intervals
CRF	Case report form
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
HPLC	High-performance Liquid Chromatography
LLOQ	Lower limit of quantification
QC	Quality control
HQC	High-quality control
MQC	Medium-quality control
LMQC	Low-medium-quality control
LQC	Low-quality control
LC-MS/MS	Liquid Chromatography Mass Spectrometer
TITCK	Turkiye Ilac ve Tıbbi Cihaz Kurumu

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Author contributions

All authors contributed to the concept and design of the study. O.P. and B.B. took decisions in the name of the sponsor. S.K. prepared study documentation and carried out the necessary application and submissions for the study. A.I. carried out the clinical part as the principal investigator, Z.S. and M.M. as co-investigator. M.R., performed Bioanalysis in plasma. W.M. performed the Pharmacokinetic analysis, statistics and reporting parts. A.I. and S.K. contributed to writing the manuscript. All authors approved the final version of the manuscript.

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Data availability

The data are not publicly available due to compromise the privacy of study participants and due to the fact that trade secret. The data that are publicly available are shared in the article.

Declarations

Ethics approval and consent to participate
The study was approved by an independent ethics committee-Ethics Committee for Bioavailability-Bioequivalence Trials of Erciyes University (date of approval: 15.06.2022; vote no: 2022/148) and the Turkish Medicines and Medical Devices Agency (TİTCK) of Turkish Ministry of Health, (date of approval: 01.07.2022, note no.: E-66175679-514.06.01-803603). The purpose of the investigation was fully disclosed to each subject in a written document and oral presentation by the principal investigator or one of the co-investigators. Then, each participant voluntarily signed the informed consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Oliva EN, Riva M, Niscola P, Santini V, Breccia M, Giai V, Poloni A. Eltrombopag for low-risk myelodysplastic syndromes with thrombocytopenia: ınterim results of a phase II, randomized, placebo-controlled clinical trial (EQOL-MDS). J Clin Oncol. 2023;41(28):4486–96.
2. Revolade International non-proprietary name: eltrombopag/eltrombopag olamine 17 December 2015 EMA/CHMP/38474/2016. https://www.ema.europa.eu/en/documents/variation-report/revolade-h-c-1110-ii-0023-epar-assessment-report-variation_en.pdf. Accessed 25 July 2024.
3. PROMACTA-eltrombopag olamine tablet, film coated highlights of prescribing information. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7714a0ed-34bb-46e6-a0a5-b363908b22c2%26version=21. Accessed 25 July 2024.
4. Stasi R, Evangelista ML, Amadori S. Novel thrombopoietic agents: a review of their use in idiopathic thrombocytopenic purpura. Drugs. 2008;68(7):901–12.
5. PROMACTA® (eltrombopag) tablets, for oral use highlights of prescribing information. https://www.novartis.com/us-en/sites/novartis_us/files/promacta.pdf. Accessed 25 July 2024.
6. Williams DD, Peng B, Bailey CK, Wire MB, Deng Y, Park JW, Collins DA, Kapsi SG, Jenkins JM. Effects of food and antacids on the pharmacokinetics of eltrombopag in healthy adult subjects: two single-dose, open-label, randomized-sequence, crossover studies. Clin Ther. 2009;31(4):764–76.
7. Alvaiz Generic Name: eltrombopag tablets. https://www.rxlist.com/alvaiz-drug.htm. Accessed 25 July 2024.
8. Burness CB, Gillian MK, Garnock-Jones KP. Eltrombopag: a review in Paediatric Chronic Immune Thrombocytopenia. Drugs. 2016;76:869–78.
9. Sözer G, Inal A, Sezer Z, Martin W, Ottmann E, Reinsch M, Koru SA. Bioequivalence study of capsules versus film tablets containing rivaroxaban in healthy Caucasian subjects under fasting and fed conditions. Clin Pharmacologyin Drug Dev. 2024;13(3):281–7.
10. Inal A, Sezer Z, Uluözlü B, Oflas M, Reinsch M, Martin W, Mazicioglu MM, Koru SA. Bioequivalence study of low dose drospirenone/ethinyl estradiol 3 mg/0.03 mg film tablets under fasting conditions in Turkish healthy female subjects. Pharmacol Res Perspect. 2024;12(4):e1253.
11. Pharmaceutical and medical preparations law; No: 1262. Publication date in the official gazette: 26th May, 1928 Issue No. 898. https://titck.gov.tr/storage/legislation/meFOxeFD.pdf
12. GCP regulations. Turkish pharmaceuticals and medical devices agency, 13 Nov 2015. https://titck.gov.tr/storage/Archive/2020/legislation/KADKLVZ01IKU13.11.2015Rev08_13ac0133-274b-44dc-98cd-33998758cc72.pdf.
13. Guideline on the investigation of bioequivalence Committee for Medicinal Products for Human Use (CHMP) CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, London, 20 Jan 2010. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf. Accessed 25 July 2024.
14. Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009. 21 July 2011. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-bioanalytical-methodvalidation_en.pdf. Accessed 25 July 2024.
15. Guidance for Industry Bioanalytical Method Validation U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM). May 2018. https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf. Accessed 28 July 2024.
16. Grabowski T, Marczak M, Jaroszewski JJ, Whitmire M. Comparison of bioequivalence study regulatory requirements for human and veterinary drugs. Regul Toxicol Pharmacol. 2012;64:233–42.

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