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ORIGINAL RESEARCH ARTICLE

An Open-Label Crossover Study of the Pharmacokinetics of the 60-mg Edoxaban Tablet Crushed and Administered Either by a Nasogastric Tube or in Apple Puree in Healthy Adults

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Abstract

Background Edoxaban is an orally active, direct factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in non-valvular atrial fibrillation and for the treatment of venous thromboembolism.

Objectives This study assessed the pharmacokinetics, safety, and tolerability of the edoxaban 60-mg tablet crushed and administered via a nasogastric tube in a water suspension or orally mixed in apple puree.

Methods This phase 1, open-label, crossover study randomized 30 healthy adults to receive three edoxaban treatment regimens (oral 60-mg edoxaban tablet, or 60-mg edoxaban tablet crushed and administered via a nasogastric tube or orally in apple puree) in one of six treatment sequences.

Results Total edoxaban exposure was similar between the intact and crushed tablet regimens (mean area under the plasma concentration–time curve from time zero to infinity: whole tablet, 2132 ng·h/mL; nasogastric tube, 2021 ng·h/mL; apple puree, 2076 ng·h/mL). Mean maximum plasma concentration, area under the plasma concentration–time curve from time zero to the time of the last measurable concentration, terminal half-life, and apparent total body clearance values were also similar. Time to maximum plasma concentration was significantly shorter for the nasogastric tube suspension and apple puree vs. the whole tablet [Hodges–Lehmann estimate of median difference (90% confidence interval): -0.75 $(-1.25, -0.28)$; $p = 0.0003$ and -0.62 $(-0.99, -0.26)$; $p = 0.0024$, respectively]. The maximum plasma concentration, area under the plasma concentration–time curve from time zero to infinity, and area under the plasma concentration–time curve from time zero to the time of the last measurable concentration were similar between treatment regimens; 90% confidence interval of the geometric least-squares means ratios were within the predefined 80–125% bioequivalence criterion. The safety and tolerability of edoxaban did not differ between treatment regimens.

Conclusion The results support the use of edoxaban tablets crushed and administered either via a nasogastric tube or orally mixed in apple puree in patients who are unable to swallow solid oral dose formulations.

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Key Points

Edoxaban is a direct oral anticoagulant that has been approved in North America, Europe, and Asia for the reduction of stroke risk in non-valvular atrial fibrillation and the treatment of venous thromboembolism.

Dysphagia (difficulty swallowing) is a major concern in the elderly population and may result in reduced patient adherence to medications. Therefore, solid oral formulations crushed and mixed into food or provided as a water suspension via a nasogastric tube are important alternative methods of administration.

This randomized single-dose crossover study supports the use of 60-mg edoxaban tablets crushed and administered either in apple puree and taken orally or as a water suspension via a nasogastric tube as alternative methods of edoxaban administration in healthy adults.

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1 Introduction

Edoxaban is an orally active, direct factor Xa inhibitor with linear and predictable pharmacokinetics approved in North America, Europe, and Asia for the reduction of stroke risk in non-valvular atrial fibrillation (NVAF) and the treatment of venous thromboembolism (VTE). The recommended edoxaban dose is 60 mg for patients with NVAF or VTE not meeting the dose reduction criteria, and 30 mg for patients meeting the dose reduction criteria (i.e., creatinine clearance 15–50 mL/min for NVAF, or creatinine clearance 15–50 mL/min, body weight ≤60 kg, or taking select concomitant P-glycoprotein inhibitors for VTE) [1]. The absolute bioavailability of oral edoxaban 60 mg in healthy subjects is 62% [2] and is not significantly affected by food [3]. Edoxaban is rapidly absorbed, primarily in the proximal small intestine in healthy subjects [4], with peak plasma concentrations occuring within 1–2 h after dosing [5]. The terminal elimination half-life of edoxaban in plasma following oral administration has a range of 10–14 h [1]. Edoxaban is eliminated through multiple pathways, including renal and biliary excretion and metabolism. Renal clearance accounts for approximately 50% of total clearance and metabolism and biliary secretion account for the remaining 50% [6].

Elderly or terminally ill patients with dysphagia often have difficulty swallowing solid oral medications [7]. Dysphagia is a major concern in the elderly population [8] and may result in reduced patient adherence to medications [9, 10]. Therefore, solid oral formulations crushed and mixed into food or provided as a water suspension via a nasogastric (NG) tube are important alternative methods of administration [11]. However, these manipulations may alter the bioavailability of a drug. Consequently, assessments of alternative methods of administration, with respect to bioavailability and pharmacokinetic (PK) properties, are necessary. The primary objective of this study was to assess the PK, safety, and tolerability profiles of the edoxaban 60-mg tablet in healthy adults when crushed and administered either via a NG tube or mixed with apple puree and ingested.

2 Methods

2.1 Study Design

This was a phase 1, single-clinical unit, open-label, randomized, single-dose, three-period, three-treatment crossover study of single-dose edoxaban conducted in USA from 26 April to 13 May, 2016. The primary objective of this study was to evaluate the bioavailability of edoxaban 60-mg tablets crushed and delivered either as a suspension via a NG tube or as a mixture with apple puree and ingested relative to edoxaban whole tablets in healthy adults. The secondary objectives were to assess the safety and tolerability of edoxaban tablets crushed and delivered either via a NG tube as a suspension or mixed with apple puree and ingested, and to assess the PK properties of the most abundant active metabolite of edoxaban, M-4, for all treatments. A single 60-mg dose of edoxaban represents the highest dose approved for its indications (i.e., NVAF and VTE) [1], and was, therefore, selected for use in this study. Prior to the initiation of the clinical study, in vitro studies were conducted and demonstrated the lack of adsorption of drug in suspension by the NG tube in the concentrations used in this study. In addition, edoxaban suspension was stable for 4 h in aqeous media, as well as in apple puree (data on file).

At screening and at check-in (day −1), participants were admitted to the clinical facility (Worldwide Clinical Trials, San Antonio, TX, USA) and were evaluated for inclusion/exclusion criteria, underwent a physical examination, provided blood and urine samples for clinical laboratory testing, and had vital signs checked. All participants remained in the clinical unit through the duration of the study (18 days). On day 1, eligible volunteers were randomized to receive three treatments (A: single oral 60-mg edoxaban tablet with water; B: single 60-mg edoxaban crushed tablet via a NG tube; C: single 60-mg edoxaban crushed tablet mixed in apple puree; Table 1) in one of six treatment sequences (i.e., ABC, ACB, BAC, BCA, CAB, or CBA). All treatments were administered in the morning following an overnight fast of 10 h. Treatments were administered on day 1 (treatment period 1), day 8 (treatment period 2), and day 15 (treatment period 3). Each treatment period was separated by a washout period of 7 days.

The NG tube used in this study was composed of polyvinyl chloride, and the lumen size was 12 French and was 48 inches in length (CR Bard, St. Louis, MO, USA). The study complied with local regulations, the Declaration of Helsinki, and the International Conference on Harmonisation Guidelines on Good Clinical Practice. All subjects provided written informed consent before participation.

2.2 Study Population

Healthy participants, determined by medical history, physical examinations, vital signs, 12-lead electrocardiograms, and clinical laboratory tests, were eligible to enroll if they were between 18 and 60 years of age, with a body mass index of 18–30 kg/m^2 at screening. Women of childbearing potential had to have a negative serum pregnancy test before each dose of study drug. Women of non-childbearing potential had to be surgically sterile or

Table 1 Study treatments

Treatment A (reference)	Single oral dose of a 60-mg round tablet of edoxaban with 240 mL of water
Treatment B	Single oral dose of a 60-mg tablet of edoxaban was crushed and mixed with 75 mL of water followed by 3×55-mL water rinses of a mortar and pestle, and administered via a NG tube as a suspension. Care was taken to assure that no visible residue was left on the mortar and pestle. Prior to drug administration, the position of the NG tube was confirmed with an X-ray, and 20 mL of water was injected into the tube to pre-wet and prime the lumen. Insertion of the NG tube was performed within 30–60 min of administration of the study drug and remained in place for at least 5 min after the last water rinse. After the study drug suspension had been administered, the NG tube was flushed with 15–30 mL of water
Treatment C	Single dose of a 60-mg tablet of edoxaban was crushed and mixed with 40 g of apple puree (Gerber®, Organic 1st Foods®, apple) followed by 3×80-mL water rinses of the mortar and pestle, and ingested. Care was taken to assure that no visible residue was left on the mortar and pestle

NG nasogastric

naturally postmenopausal for at least 24 months prior to starting the study drug. Exclusion criteria included a history of major bleeding, trauma, or surgical procedure within 6 months of the first dose; malignancy in the past 5 years; and coagulation disorders or other conditions and medications that could affect the absorption and/or excretion of the study drug.

The main covariates affecting the pharmacokinetics of edoxaban are renal function and body weight [6]. After accounting for these covariates, intrinsic factors such as age, sex, and race do not affect the pharmacokinetics of edoxaban. The crossover study design of this trial controlled these factors because the study was an intra-subject comparison of the pharmacokinetics of edoxaban, and subjects were kept in the clinical unit for the entire study.

2.3 Sample Collection and Analysis of Plasma Edoxaban

Blood samples were collected in prechilled, lithium heparin blood collection tubes. On the day of treatment (i.e., days 1, 8, and 15), blood samples were collected predose (0) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h postdose. Over the following 3 days, blood samples were collected at 24, 36, 48, 60, and 72 h post-dose.

Plasma samples were stored at a nominal temperature of $-20\,^{\circ}$C. Plasma concentrations of free-base edoxaban and M-4 were measured at Q^2 Solutions (Ithaca, NY, USA) using a validated liquid chromatography-tandem mass spectrometry method, similar to what has previously been reported [12]. The calibration curves for edoxaban and M-4 had a range of 0.764–382 and 0.0792–7.92 ng/mL, respectively. Sample preparation was conducted using Tomtec Quadra 96 Sample Processor. Edoxaban, M-4, and respective deuterium-labeled internal standards (d6-edoxaban and d3-M4) were isolated from plasma samples (200 μL) using an Oasis MCX (mixed-mode ion exchange resin) (Waters, Milford, MA, USA), 96-well solid-phase extraction plate. Extracted plasma samples were injected into

gradient chromatography (ZORBAX Eclipse XDB Phenyl, Agilent Technologies, Santa Clara, CA, USA [50-mm length, 2.1-mm internal diameter, 5-μm particle size]) at a flow rate of 0.3 mL/min, using 5 mM ammonium acetate (pH 7.0) as mobile phase A, and methanol as mobile phase B. The eluted analytes and internal standards were detected by a mass spectrometer (SCIEX API 4000 triple quadrupole with TurboIonSpray source, SCIEX, Framingham, MA, USA) in positive ionization mode. The parent $\rightarrow$ daughter ion transitions, monitored for edoxaban and its internal standards, were m/z $550.4 \rightarrow 366.3$ and m/z $556.4 \rightarrow 372.3$, respectively; the transitions for M-4 and its internal standards were m/z $521.4 \rightarrow 339.3$ and m/z $524.4 \rightarrow 342.3$, respectively. Assay validation demonstrated that, for edoxaban, the intra- and inter-assay precision (coefficient of variation) values were within 11.0 and 8.8%, respectively; the intra- and inter-assay accuracy values were within ± 6.9 and $\pm 3.8\%$, respectively. For M-4, the intra- and inter-assay precision (coefficient of variation) values were within 12.3 and 11.5%, respectively; the intra- and inter-assay accuracy values were within ± 18.5 and $\pm 8.8\%$, respectively.

2.4 Pharmacokinetic Assessments

Pharmacokinetic parameters for edoxaban and M-4 were calculated using Phoenix™ WinNonlin® Professional (Certara, Princeton, NJ, USA). These included area under the plasma concentration–time curve (AUC) from time zero to the time of the last measurable concentration (AUC$_{last}$), AUC from time zero to infinity (AUC$_{\infty}$), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal half-life, and apparent total body clearance.

2.5 Safety and Tolerability Assessments

Adverse events (AEs) were monitored up to 30 days after the last dose of study medication, and were coded using the

Medical Dictionary for Regulatory Activities coding dictionary.

2.6 Planned Sample Size and Statistical Analysis

A total of 30 participants, five per treatment sequence, was planned for enrollment, with the expectation that 24 participants would complete the study. The sample size was not based on statistical power considerations; a planned sample size of 24 participants was selected because it is a typically robust subject number for a crossover study.

All PK parameters were calculated using the PK analysis set, which included all participants with no major deviations from treatment intake (e.g., vomiting) for whom the primary PK data were considered sufficient and interpretable. The edoxaban and M-4 concentrations across scheduled times are presented using descriptive statistics by treatment. AUC_{last}, AUC_∞, and C_{max} for treatments B (NG tube) and C (apple puree) were compared with the reference treatment A (oral tablet) using a mixed-effect analysis of variance on the *ln*-transformed PK values with sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. The resulting geometric least-squares means (LSM) and LSM ratios ±90% confidence intervals (CIs) are presented. Time to maximum plasma concentration comparisons were conducted using the Wilcoxon signed-rank test and the Hodges–Lehmann estimate of median difference. All statistical analyses were conducted using SAS Version 9.3 (SAS Inc., Cary, NC, USA).

3 Results

3.1 Demographics and Baseline Clinical Characteristics

All randomized participants ($n = 30$) received at least two doses of the study drug; 30 participants were included in the PK analysis set. One participant was discontinued from the study after treatment period 2 and did not receive reference treatment A (oral tablet) because it was discovered that he was a participant in another clinical study. The majority of participants were male, 50% were White, and the mean ± standard deviation age was $40.3 ± 11.0$ years (Table 2).

3.2 Pharmacokinetic Properties

In general, the mean plasma concentrations of edoxaban over time were similar for all three treatments (Fig. 1a, b). However, the mean peak concentration occurred earlier for

**Table 2** Subject demographics and baseline characteristics

Characteristics	Overall ($n = 30$)
Age (years)	
18–39, n (%)	15 (50.0)
40–60, n (%)	15 (50.0)
Mean (SD)	40.3 (11.0)
Sex, n (%)	
Male	17 (56.7)
Female	13 (43.3)
Race, n (%)	
White	15 (50.0)
Black	13 (43.3)
Other	2 (6.6)
BMI (kg/m^2)	
Mean (SD)	26.3 (2.6)

BMI body mass index, *SD* standard deviation

the tablet crushed and adminstered either via a NG tube or mixed in apple puree relative to the intact tablet (inset Fig. 1a).

A summary of the PK parameters of edoxaban is shown in Table 3. The total exposure of edoxaban was similar between the whole tablet and crushed tablet formulations, with mean AUC_∞ values of 2132, 2021, and 2076 ng·h/mL for the whole tablet, suspension administered via a NG tube, and mixture with apple puree, respectively. Mean C_{max}, AUC_{last}, terminal half-life, and apparent total body clearance values were also similar between the whole tablet and oral suspension formulations. Time to maximum plasma concentration was significantly shorter by 0.5 h for the NG route and when mixed in apple puree vs. the intact tablet [Hodges–Lehmann estimate of median difference (90% CI): -0.75 (-1.25, -0.28); $p = 0.0003$ and -0.62 (-0.99, -0.26); $p = 0.0024$, respectively]. However, the C_{max}, AUC_∞, and AUC_{last} values for all three treatment regimens were similar, with 90% CIs of the geometric LSM ratios falling within the predefined 80–125% bioequivalence criterion stipulated by regulatory agencies (Table 4). The mean concentration–time profiles for the edoxaban metabolite M-4 were also similar for all three treatments (Fig. 2a, b). A summary of the PK parameters of M-4 is shown in Table 5. M-4 mean C_{max}, AUC_∞, AUC_{last}, and terminal half-life values were similar when edoxaban was administered as a whole tablet or as a crushed tablet via a NG tube or mixed with apple puree; median T_{max} was 2.0 h for the whole tablet and 1.5 h for the crushed tablet formulations. The mean metabolite-to-parent ratios for M-4 were 8.6, 8.3, and 8.4% for the whole tablet, crushed suspension administered via a NG tube, and mixed with apple puree, respectively.

Fig. 1 Plasma edoxaban concentration–time profiles following administration of a single, oral 60-mg edoxaban tablet with water (Treatment A), a 60-mg edoxaban tablet crushed and given as a suspension via a nasogastric tube (Treatment B), or a 60-mg edoxaban tablet crushed and given orally mixed with apple puree (Treatment C). **a** Mean plasma edoxaban concentration–time profiles. **b** Semi-logarithmic mean plasma edoxaban concentration–time profiles. *Inset* Concentration–time profiles for the first 10 h only. *Error bars* represent the standard deviation
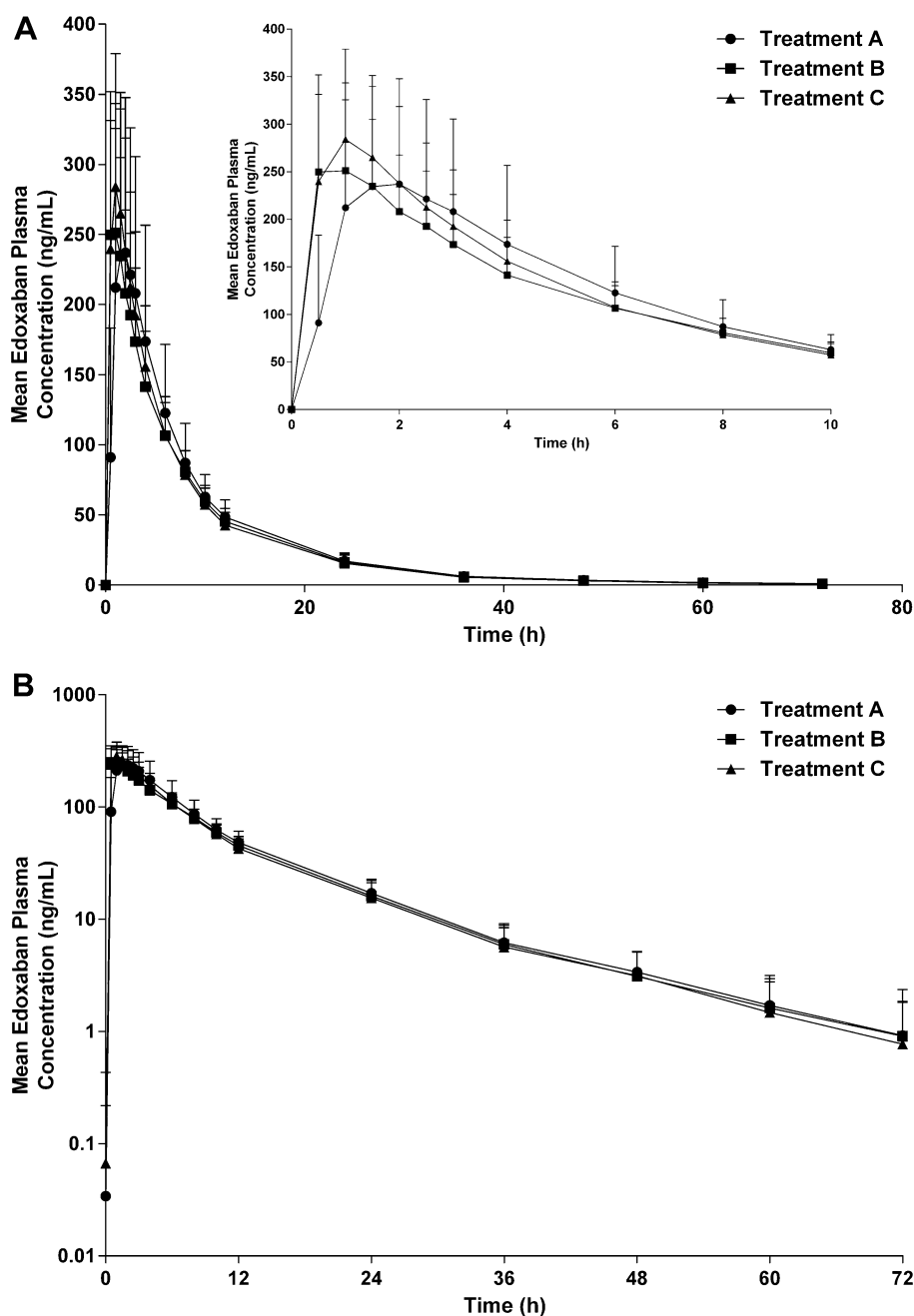
3.3 Safety and Tolerability

There were no clinically significant changes in physical examinations, clinical laboratory test results, vital signs, or ECGs attributable to edoxaban. All treatment-emergent AEs reported were of mild intensity, self-limited, did not require any medical therapy, and resolved without any sequelae. Of the treatment-emergent AEs that were related to study drug, one subject developed vaginal hemorrhage and another had conjunctival hemorrhage after receiving edoxaban via a NG tube or with apple puree, respectively. Other treatment-emergent AEs during the study included

neutropenia ($n = 2$), constipation ($n = 2$), facial pain ($n = 1$), vessel puncture-site pain ($n = 1$), laceration ($n = 1$), muscle spasm ($n = 1$), menstruation irregularity ($n = 1$), dysphonia ($n = 1$), nasal congestion ($n = 1$), oropharyngeal discomfort ($n = 1$), and rhinorrhea ($n = 1$).

4 Discussion

The results of this study conclude that the administration of a 60-mg edoxaban tablet that is crushed and given either via a NG tube in a water suspension or orally mixed with

Table 3 Summary of plasma pharmacokinetic parameters of edoxaban

Treatment ($n = 30$)	C_{max}[a] (ng/mL)	AUC_∞[a] (ng·h/mL)	AUC_{last}[a] (ng·h/mL)	T_{max}[b] (h)	$t_{1/2}$[a] (h)	CL/F[a] (L/h)
Treatment A	293 (107)[c]	2132 (547)[d]	2089 (548)[c]	1.5 (0.5–8.0)[c]	11.5 (3.3)[d]	30.1 (8.0)[d]
Treatment B	283 (95)	2021 (423)	1993 (413)	1.0 (0.5–3.0)	10.8 (3.7)	31.0 (6.5)
Treatment C	303 (96)	2076 (453)	2051 (451)	1.0 (0.5–1.5)	10.9 (3.3)	30.2 (6.3)

AUC_∞ area under the plasma concentration–time curve from time zero to infinity, AUC_{last} area under the plasma concentration–time curve from time zero to the time of the last measurable observation, CL/F apparent total body clearance, C_{max} maximum plasma concentration, $t_{1/2}$ terminal half-life, T_{max} time to maximum plasma concentration

[a] Arithmetic mean (standard deviation) unless indicated otherwise

[b] Median (range)

[c] $n = 29$

[d] $n = 28$

Treatment A = single oral dose of an intact 60-mg edoxaban tablet with water; Treatment B = single dose of a 60-mg edoxaban tablet crushed and suspended in water and administered via a nasogastric tube; Treatment C = single oral dose of a 60-mg edoxaban tablet crushed and given orally mixed with apple puree and ingested

Table 4 Statistical analysis of the pharmacokinetic parameters of edoxaban

Treatment ($n = 30$)	C_{max}[a] (ng/mL)	AUC_∞[a] (ng·h/mL)	AUC_{last}[a] (ng·h/mL)	Ratio C_{max}[b] (%)	Ratio AUC_∞[b] (%)	Ratio AUC_{last}[b] (%)
Treatment A	265.4	2064.2	2019.3			
Treatment B	267.6	1978.8	1952.2	100.8 (91.2–111.4)	95.9 (92.1–99.8)	96.7 (92.7–100.9)
Treatment C	288.2	2031.0	2006.0	108.6 (98.3–120.0)	98.4 (94.5–102.4)	99.3 (95.2–103.7)

AUC_∞ area under the plasma concentration–time curve from time zero to time infinity, AUC_{last} area under the plasma concentration–time curve from time zero to the time of the last measurable observation, C_{max} maximum plasma concentration

[a] Geometric least-squares mean

[b] Geometric least-squares mean ratio vs. reference (90% confidence interval)

Treatment A = single oral dose of an intact 60-mg edoxaban tablet with water; Treatment B = single dose of a 60-mg edoxaban tablet crushed and suspended in water and administered via a nasogastric tube; Treatment C = single oral dose of a 60-mg edoxaban tablet crushed and given orally mixed with apple puree and ingested

apple puree does not impact the extent of edoxaban absorption relative to an intact tablet. The C_{max} and AUC geometric LSM ratios for crushed tablet formulations were bioequivalent with the whole uncrushed tablet, according to the predefined 80–125% bioequivalence criterion. These results are consistent with the results of a previous food effect study, which concluded that food does not have a clinically significant effect on the bioavailability of edoxaban [3]. Furthermore, an edoxaban tablet crushed and administered either via a NG tube or with apple puree displays similar total exposure, and metabolite-to-parent ratios for the main active metabolite of edoxaban, M-4, compared with a whole tablet administered orally, suggesting that the biotransformation of edoxaban is not affected by the mode of drug administration.

Solid oral formulations crushed and mixed in food or provided as a water suspension via a NG tube represent viable alternative methods of administration for patients who have difficulty swallowing [11]. Based on the results

of studies on alternative methods of administration of non-vitamin K oral anticoagulants conducted to date, crushed apixaban and rivaroxaban tablets are well tolerated when administered either with food or via a NG tube. Specifically, when rivaroxaban 20-mg or apixaban 5-mg crushed tablets were administered as suspensions via a NG tube, mean exposure decreased by only 5–11% [AUC_∞ (90% CI); 0.89 (0.86–0.92) and 0.95 (0.91–1.00), respectively] [13, 14]. Furthermore, while C_{max} for the rivaroxaban 20-mg crushed tablet administered as a suspension via a NG tube was slightly below the lower bioequivalence limit [0.82 (0.78–0.86)], it was within the bioequivalence limits for the apixaban 5-mg crushed tablet [0.88 (0.83–0.94)]. However, when rivaroxaban 20-mg and apixaban 2 × 5-mg crushed tablets were administered as applesauce suspensions, the mean exposure decreased by only 5–16% [AUC_∞ (90% CI); 0.95 (0.92–0.98) and 0.84 (0.80–0.88), respectively]. Furthermore, while C_{max} for the rivaroxaban 20-mg crushed tablet in the applesauce suspension was

Fig. 2 Plasma M-4 concentration–time profiles following administration of a single, oral 60-mg edoxaban tablet with water (Treatment A), a 60-mg edoxaban tablet crushed and given as a suspension via a nasogastric tube (Treatment B), or a 60-mg edoxaban tablet crushed and given orally mixed with apple puree (Treatment C). **a** Mean plasma M-4 concentration–time profiles. **b** Semi-logarithmic mean plasma M-4 concentration–time profiles. *Inset* Concentration–time profiles for the first 10 h only. *Error bars* represent the standard deviation
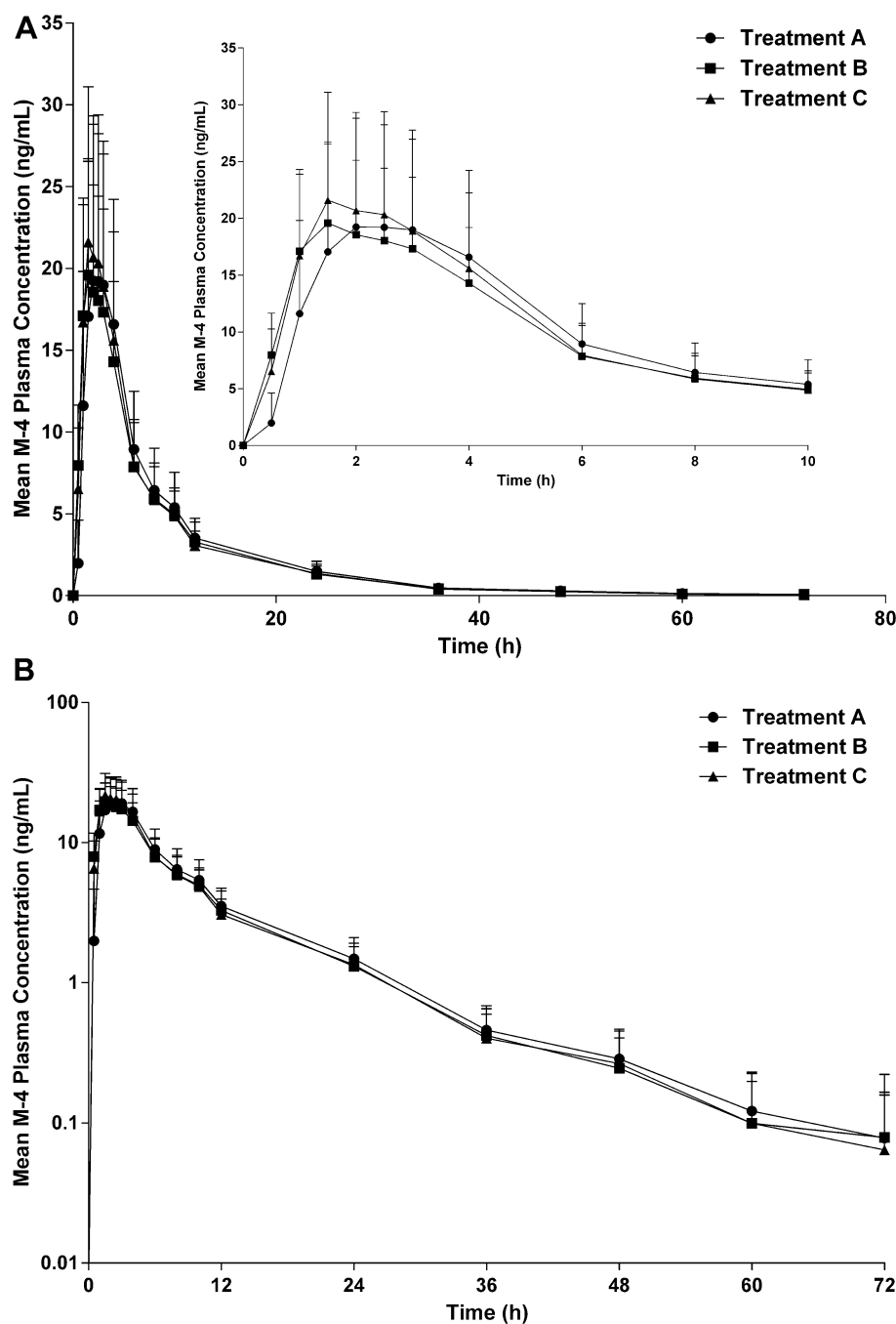
within the bioequivalence limits [0.90 (0.86–0.94)], it was slightly below the lower bioequivalence limit for the apixaban 2 × 5-mg crushed tablet in applesauce suspension [0.79 (0.74–0.84)] [13–15].

In vitro studies, conducted prior to the initiation of this study, demonstrated that when edoxaban was given in a water suspension by a NG tube there was no adherence of edoxaban to the tube for edoxaban concentrations used in this study. Furthermore, the edoxaban suspension was stable in aqeous media and in apple puree. However, there are several limitations of this study that could limit its

generalizability—the type of NG tube used (polyvinyl chloride), consistency of the apple puree, and the rigor in which the mortar and pestle were cleaned after crushing each tablet.

5 Conclusions

Results of this randomized, single-dose, crossover study support the use of edoxaban tablets crushed and administered either in apple puree and taken orally or as a water

Table 5 Summary of plasma M-4 pharmacokinetic parameters

Treatment ($n = 30$)	C_{max}[a] (ng/mL)	AUC_{∞}[a] (ng·h/mL)	AUC_{last}[a] (ng·h/mL)	T_{max}[b] (h)	$t_{1/2}$[a] (h)	MPR[a] (%)
Treatment A	22.0 (9.0)[c]	169 (57)[d]	164 (56)[c]	2.0 (1.0–10.0)[c]	11.0 (3.6)[d]	8.6 (2.5)[d]
Treatment B	20.5 (7.2)	158 (46)[c]	157 (46)	1.5 (1.0–3.0)	9.9 (3.2)[c]	8.3 (2.2)[c]
Treatment C	22.5 (9.9)	166 (57)[c]	161 (56)	1.5 (1.0–3.0)	9.9 (2.7)[c]	8.4 (2.4)[c]

AUC_{∞} area under the plasma concentration–time curve from time zero to infinity, AUC_{last} area under the plasma concentration–time curve from time zero to the time of the last measurable observation, C_{max} maximum plasma concentration, MPR metabolite-to-parent ratio, $t_{1/2}$ terminal half-life, T_{max} time to maximum plasma concentration

[a] Arithmetic mean (standard deviation) unless indicated otherwise

[b] Median (range)

[c] $n = 29$

[d] $n = 27$

Treatment A = single oral dose of an intact 60-mg edoxaban tablet with water; Treatment B = single dose of a 60-mg edoxaban tablet crushed and given orally suspended in water and administered via a nasogastric tube; Treatment C = single oral dose of a 60-mg edoxaban tablet crushed and mixed with apple puree and ingested

suspension via a NG tube as suitable alternative methods of administration in patients who are unable to swallow solid oral dose formulations of edoxaban. These findings further suggest that these alternate modes of administration are interchangeable with the oral edoxaban tablet swallowed whole.

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