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Evaluation of Regional Gastrointestinal Absorption of Edoxaban Using the Enterion Capsule

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Abstract

Two studies in healthy subjects assessed the absorption of edoxaban when delivered to specific locations within the gastrointestinal tract using Enterion capsules. In study 1 (single-dose, 4-way crossover), 8 participants received edoxaban 60 mg as immediate-release (IR) tablets (treatment A), as powder formulation delivered to the distal small bowel (treatment B) or ascending colon (treatment C), or as an aqueous suspension delivered to the ascending colon (treatment D). In study 2 (single-dose, 2-way crossover), 10 participants received edoxaban 30 mg as IR tablets (treatment E) or in granulate formulation with fumaric acid 50 mg, added to acidify the local gastrointestinal tract and enhance solubility, delivered to the ascending colon (treatment F). Peak and total exposure following targeted drug delivery to the distal gastrointestinal tract were significantly lower than with IR tablet delivery. In study 1, total exposure ratios of treatments B, C, and D compared with A were 14.9%, 7.9%, and 6.1%, respectively. In study 2, relative total exposure was 12.6% for treatment F despite the fumaric acid. Time to peak concentration was longer with higher variability for edoxaban delivered to the distal gastrointestinal tract compared with the IR tablet. These data indicate that edoxaban absorption occurs predominantly in the proximal small intestine.

Keywords

edoxaban, Enterion capsule, absorption, pharmacokinetics, dissolution

Edoxaban is a highly selective, direct, and reversible inhibitor of the serine protease factor Xa (FXa).[1] Inhibition of FXa in the coagulation cascade reduces thrombin generation, prolongs clotting time, and reduces the risk of provoked thrombus formation. In vitro, edoxaban inhibits the human FXa in a concentration-dependent and competitive manner, with an inhibition constant (K_i) value of 0.561 nM.[1] Edoxaban 60 mg once daily was recently approved in the United States for the treatment of deep vein thrombosis and pulmonary embolism and for reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. A dose of 30 mg is recommended for patients with CrCl 15 to 50 mL/min for both indications; edoxaban should not be used in patients with CrCl < 15 mL/min or > 95 mL/min.[2] Edoxaban is also approved in Japan for these indications and is undergoing regulatory review in other regions.

Edoxaban is the predominant circulating active moiety in plasma, with an oral bioavailability of approximately 62%.[3,4] After administration of an oral dose, peak plasma concentrations are achieved in 1 to 2 hours,[5] followed by a biphasic decline and a terminal elimination half-life of 10–14 hours.[6,7] Edoxaban is cleared equally through renal and nonrenal routes, mostly as unchanged drug.[3] Nonrenal elimination comprises metabolism and biliary secretion.[3] Edoxaban undergoes metabolism by carboxylesterase-1, resulting in formation of M-4, the major metabolite, with relative abundance less than 10% of edoxaban, and via CYP3A4/5 to a lesser extent.[3] A glucuronide metabolite has been detected but not quantified.[3] Edoxaban is a substrate of the efflux transporter P-glycoprotein, but not a substrate of OATP1B1.[8]

Many oral medicines are based on immediate-release (IR) formulations, which deliver the drug product into the small intestine for absorption following the disintegration

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of the drug product within the stomach.[9] Rapid absorption of the drug molecule typically results in maximal plasma concentrations of the drug product within 3 hours of dosing and with threshold concentrations maintained over a 24-hour period.[9] Drug absorption along the length of the gastrointestinal (GI) tract can be affected by a variety of factors, including pH and transporters, and not all compounds reach optimal absorption via an IR formulation because of poor solubility or poor permeability.[9] Therefore, analyzing the site of drug absorption through scintigraphy and delivery targeted to specific regions of the GI tract can provide useful information for assessment of drug formulation as well as identifying factors that may affect drug absorption.

The Enterion site-specific delivery capsule represents an easy-to-use and noninvasive approach for assessing regional drug absorption from the GI tract.[9,10] The capsule can deliver solutions, suspensions, or powders to specific sites within the GI tract, with the location of the capsule determined using gamma scintigraphy. Capsule activation (drug delivery) is confirmed using a signal that is emitted from the capsule and is relayed to the activation unit.[10]

An IR formulation of edoxaban was used in phase 2 and 3 clinical trials. Early in the clinical development program for edoxaban, the 2 studies described here were undertaken to assess if the absorption of edoxaban from the distal GI tract might facilitate improved oral drug bioavailability. The primary objective of study 1 was to investigate the pharmacokinetics (PK) of edoxaban following release in the distal small intestine and ascending colon compared with the IR tablet formulation. The primary objective of study 2 was to investigate edoxaban PK when coadministered with fumaric acid, an acidification agent, and released in the ascending colon, compared with the standard IR-tablet formulation. Fumaric acid was added to modulate the pH of the colonic microenvironment and to potentially improve dissolution in the large bowel.

Materials and Methods

Study Designs

Study 1 was approved by the Quorn Research Review independent ethics committee. Study 2 was approved by the Plymouth independent ethics committee. Both studies were conducted in healthy subjects and in accordance with the respective protocols, the International Conference on Harmonisation Good Clinical Practice guideline, the requirements of the Administration of Radioactive Substances Advisory Committee, and according to the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to screening.

Study 1 was a phase 1, single-site, randomized, open-label, single-dose, 4-way crossover study. During 4 separate study periods, 8 participants received a 60-mg dose of edoxaban delivered as either an IR formulation (two 30-mg tablets; treatment A), powder formulation delivered to the distal small bowel via the Enterion capsule (treatment B), powder formulation delivered to the ascending colon via the Enterion capsule (treatment C), or an aqueous suspension delivered to the ascending colon via the Enterion capsule (treatment D). Subjects were confined to the study site for 24 hours postdose/activation during each treatment period, with a minimum washout period of 4 days between periods. A dose of 60 mg was chosen to ensure sufficient plasma concentrations for analysis while minimizing the likelihood of any adverse events (AEs).

Study 2 was a phase 1, single-site, randomized, open-label, single-dose, 2-way crossover study. Ten participants received edoxaban as a 30-mg IR tablet formulation (treatment E) or edoxaban (30 mg) plus fumaric acid (50 mg) in a granulate formulation delivered to the ascending colon via the Enterion capsule (treatment F). Subjects were confined to the study site for 48 hours postdose/activation in each of the 2 treatment periods, with a 5-day washout between periods. For this study, the 30-mg dose was chosen, as it was predicted to provide measureable plasma concentrations with a low risk for AEs, based on additional clinical study data not available when study 1 was designed.

Participants

Both studies enrolled healthy male adult subjects (18–55 years of age in study 1; 18–65 years of age in study 2), with a body mass index between 19 and 29 kg/m^2. In addition, participants were to have been in good health as determined by a medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations that included blood coagulation activity. Subjects were not to be receiving any prescription or over-the-counter medications, with the exception of the occasional use of paracetamol ($\leq$4 g daily). Subjects who were not willing or unable to eat the provided standard meals; had previously participated in earlier edoxaban studies; were allergic to anticoagulants or had ongoing allergic disease; had a history of GI disease, surgery, or injury; had a history of alcohol or drug abuse; or had any other illness or condition that would interfere with participation in the studies were excluded.

Treatments

For study 1, edoxaban tablets (treatment A), edoxaban-formulated powder, and the active pharmaceutical ingredient (API) of edoxaban in powder form were supplied by Daiichi Pharmaceutical Co., Ltd (Tokyo, Japan). The aqueous suspension was prepared at the study site from the API powder. Enterion capsules were filled at the study site with the edoxaban powder formulation

(treatments B and C) and the aqueous suspension formulation (treatment D).

For study 2, edoxaban tablets (treatment E) and the granulate fumaric acid formulation were supplied by Daiichi Pharmaceutical Co., Ltd (Tokyo, Japan). Enterion capsules were filled at the study site with the granulate formulation (treatment F).

In study 1, a treatment allocation list was employed, although treatment allocations for individual subjects could be revised during the study. Treatments were administered at least 4 hours following consumption of a standard light breakfast. For treatment A, 2×30-mg IR tablets were administered with 240 mL of water. For treatments B, C, and D, each prepared Enterion capsule was administered with 210 mL of water followed by 30 mL of the radiolabeled ^{99m}Tc-DTPA drink to allow visualization of GI tract anatomy.

In study 2, participants were randomly assigned to 1 of 2 treatment sequences: treatment E followed by treatment F or vice versa. Treatments were administered following a fast commencing from midnight on the day prior to dosing and continuing until 5 hours postdose, at which time a standard lunch was provided. Similar to study 1, in treatment F, the prepared Enterion capsule was administered with 210 mL of water followed by 30 mL of the radiolabeled ^{99m}Tc-DTPA drink.

Assessments

Scintigraphy. The Enterion capsule was radiolabeled with indium-111 (^{111}In) to allow tracking of location in the GI tract. In addition, a ^{111}In-labeled marker was fixed externally to the skin where the midclavicular line meets with the right costal margin so that it was positioned in approximately the same transverse plane as the pylorus.

Scintigraphic images were acquired every 10 minutes during study 1 until capsule activation, every 10 minutes until 4 hours after activation, then every 20 minutes until 8 hours after activation, and then at 12, 16, and 24 hours after activation or defecation (whichever was sooner). In study 2, scintigraphic images were collected approximately every 20 minutes until 2 hours after gastric emptying, approximately every 10 minutes until device activation, and every 20 minutes until 4 hours after activation or defecation (whichever was sooner). In both studies, fecal collection occurred after capsule administration until capsule retrieval (treatments B, C, D, and F only).

Pharmacokinetics. For the determination of edoxaban plasma concentrations in study 1, blood samples were collected at predose, preactivation (B, C, and D), and 1, 2, 4, 6, 8, 12, 16, and 24 hours postdose/activation. In study 2, blood samples were collected at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 30, and 48 hours postdose for treatment E, and at preactivation, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, and 48 hours postactivation for treatment F.

Determination of edoxaban concentrations in plasma samples was carried out using liquid chromatography/tandem mass spectrometry (Quotient Bioresearch, Inc., Rushden, United Kingdom). The validated linear calibration curve (with 1/x weighting) ranged from 1 ng/mL (lower limit of quantitation) to 500 ng/mL (upper limit of quantitation), and included 7 levels of nonzero standards. Plasma samples (200 μL) were mixed with Tris buffer (50 mM, pH 8.5, 800 μL) and internal standard solution. Edoxaban and the deuterium-labeled internal standard (d6-DU-176) were extracted by liquid–liquid extraction using 3 mL of methyl tert-butyl ether. Chromatographic separation was achieved using a Luna C18 (2) high-performance liquid chromatography column (50 mm length, 2.0 mm internal diameter, 5-μm particle size). The mobile phase was methanol:ammonium acetate (10 mM, pH 5) 3:1 v/v, at an isocratic flow rate of 0.20 mL/min. The analyte and internal standard were detected and quantified using a SciexAPI3000 tandem mass spectrometer. Intra- and interassay precision (CV) was $\leq$10.1% and $\leq$ 12.5%, respectively, whereas accuracy (RE) was $\leq \pm$ 16.0% and $\leq \pm$ 6.4%, respectively.

Pharmacokinetic assessments were determined from plasma concentrations of edoxaban using noncompartmental procedures and included area under the plasma concentration–time curve (AUC) from time zero/activation to the last quantifiable concentration (AUC_{0-last}) and from time zero/activation to infinity ($AUC_{0-\infty}$), maximum observed plasma concentration (C_{max}), and time of maximum plasma concentration (T_{max}).

Safety. Safety assessments included recording of vital signs, ECGs, physical examination, laboratory analyses, and recording of AEs as reported by the study investigator or subject. AEs were coded according to the Medical Dictionary for Regulatory Activities (version 5 in study 1 and version 8.0 in study 2).

Statistical Analyses. All participants who received edoxaban and completed the treatment periods with evaluable data were included in the PK analysis. C_{max} and AUC parameters were log-transformed prior to analysis, and each was subject to analysis of variance using subject and treatment as factors in study 1 and sequence, period, and treatment as fixed factors and subjects nested within sequence as a random factor in study 2. Least-squares (LS) means were obtained for each treatment and the difference between each treatment (ie, treatments B–D), and treatment A together with 95% confidence intervals (CIs), were assessed in study 1, and between treatment E and treatment F, together with 90%CI were assessed in study 2. Differences between treatments and corresponding CIs were back-transformed to provide the ratio of treatments together

Table 1. Scintigraphy Data Demonstrating the Delivery Site of Edoxaban From Enterion Capsules

	Study 1			Study 2
	Treatment B	Treatment C	Treatment D	Treatment F
Time of successful Enterion activation (hour after dose)				
n	8	8	8	9
Median	5.0	5.9	5.8	8.2
Range	3.9–18.0	5.6–27.7	5.4–17.1	3.1–28.0
Location of successful Enterion activation				
Ascending colon	0	8	4	9
Distal small bowel	6	0	0	0
Mid-small intestine/distal small bowel	1	0	0	0
Hepatic flexure	0	0	2	0
Hepatic flexure/transverse colon	0	0	2	0
Ileocecal junction	1	0	0	0
Not activated	0	0	0	1

with the CI for the ratio. T_{max} was analyzed similarly, but without transformation.

In study 1, all participants who received edoxaban were included in the analysis of safety. In study 2, all participants who received at least 1 dose of edoxaban and had at least 1 safety assessment were included in the safety population. Safety data were described by subject and summarized by treatment.

Results

Demographics and Baseline Characteristics

Study 1 included 8 healthy male subjects who enrolled and completed all treatments, and study 2 included 10 healthy male subjects who were randomly assigned to receive the study drug. One subject in study 2 did not receive edoxaban during treatment F because the capsule did not activate; he was therefore not included in the PK and biomarker analyses. Mean ± standard deviation for age and body weight of subjects were 32.4 ± 10.0 years and 75.6 ± 7.4 kg, respectively, in study 1 and 34.7 ± 7.7 years and 82.5 ± 10.9 kg, respectively, in study 2. All participants in study 1 were white; 9 participants in study 2 were white and 1 was Asian.

Scintigraphy

Scintigraphic images and retrieved capsules obtained in study 1 confirmed the release of edoxaban at regional target locations in all 24 assessments (Table 1). Similarly, scintigraphic images in conjunction with retrieved Enterion capsules confirmed that 9 of the 10 capsules administered in study 2 were successfully activated.

Pharmacokinetics

Rate and Extent of Absorption. In study 1, peak (C_{max}) and total exposure ($AUC_{0–last}$) were significantly higher for 2 × 30-mg edoxaban IR tablets (treatment A) compared with the formulations delivered to the distal small intestine (treatment B) and ascending colon (treatments C and D); see Figure 1 and Table 2. Peak and total exposure for the powdered formulation delivered to the distal small intestine (treatment B) were slightly higher than those values for the same formulation delivered to the ascending colon (treatments C and D). Delivery of edoxaban as either a powder or aqueous formulation to the ascending colon resulted in similar peak and total exposures. Systemic exposure ratios based on geometric LS means (95%CI) for treatments B, C, and D compared with treatment A were 15.5% (8.5%–28.0%), 7.4% (4.1%–13.5%), and 6.4% (3.5%–11.5%), respectively. Corresponding peak concentration values were 7.2% (3.8%–13.5%), 3.3% (1.7%–6.1%), and 2.6% (1.4%–4.8%), respectively.

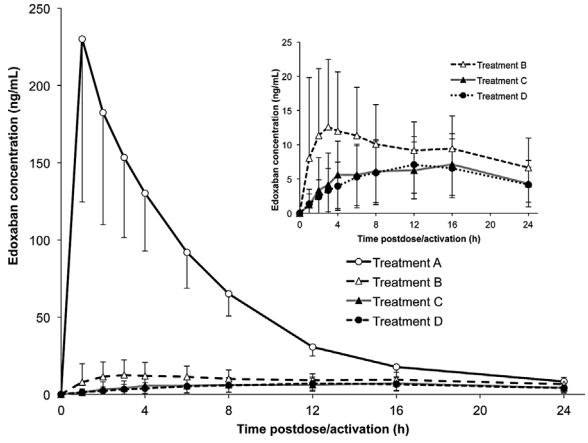

Figure 1. Mean edoxaban plasma concentration–time curves in study 1. Treatment A, two 30-mg edoxaban immediate-release tablets; treatment B, 60 mg edoxaban powder formulation delivered to the distal small bowel; treatment C, 60 mg edoxaban powder formulation delivered to the ascending colon; treatment D, 60 mg edoxaban aqueous suspension delivered to the ascending colon. Error bars represent the standard deviation.

Table 2. Summary of Pharmacokinetic Parameters

	Study 1 Edoxaban 60 mg (n = 8)				Study 2 Edoxaban 30 mg (n = 9[a])	
	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E	Treatment F
Formulation	IR tablet	Powder	Powder	Suspension	IR tablet	Granulate with fumaric acid
Site of activation	—	Distal small bowel	Ascending colon	Ascending colon	–	Ascending colon
C_{max} (ng/mL)[b]	230 ± 106	15.9 ± 8.8	8.5 ± 4.8	7.3 ± 4.9	151.6 ± 63.9	6.2 ± 3.6
T_{max} (hours)[c]	1.0 (1.0–1.1)	7.5 (1.1–16.1)	14.0 (2.0–24.0)	16.0 (1.0–24.0)	1.0 (0.8–6.0)	9.0 (3.0–21.0)
AUC_{0-last} (ng · h/mL)[b]	1403 ± 359	222 ± 103	132 ± 83.5	120 ± 85.1	903 ± 193	127 ± 74.1
$AUC_{0-\infty}$ (ng · h/mL)[b]	1498 ± 312	274[d] ± 130	NC	NC	922 ± 194	123[e] ± 81.2

AUC, area under the plasma concentration–time curve; $AUC_{0-\infty}$, AUC–time curve from time zero/activation to infinity; AUC_{0-last}, AUC–time curve from time zero/activation to the last quantifiable concentration; C_{max}, maximum plasma concentration; IR, immediate release; NC, could not be calculated; T_{max}, time to maximum plasma concentration.

[a]Enterion capsule recovered from 1 participant was not activated, and this participant was excluded from the PK analysis.

[b]Arithmetic mean ± standard deviation.

[c]Represented as the median (range) values.

[d]n = 3.

[e]n = 6.

In study 2, the peak exposure of edoxaban was significantly higher with the IR-tablet formulation (treatment E) than when administered with fumaric acid and delivered to the ascending colon (treatment F); see Figure 2 and Table 2. Delivery of edoxaban with fumaric acid to the ascending colon resulted in lower total exposure than that observed with the edoxaban IR-tablet formulation (12.6% [90%CI, 8.5%–18.7%]; based on geometric LS means).

Time to Peak Plasma Concentration. In study 1, median time to peak concentration for the tablet formulation (treatment A) was 1 hour (range, 1.0–1.1 hours) after dosing, and for formulations delivered to the distal small intestine and ascending colon, time to peak concentration ranged from 7 to 16 hours (Figure 1, Table 2). The powder formulation delivered to the distal small intestine (treatment B) showed an earlier time to peak concentration compared with the powder (treatment C) and aqueous (treatment D) formulations delivered to the ascending colon.

In study 2, edoxaban was rapidly absorbed when administered as an IR tablet, with a median time to peak concentration of 1 hour (range, 0.8–6.0 hours), and absorption of edoxaban from the ascending colon was markedly slower when delivered with fumaric acid via the Enterion capsule, with a median time to peak concentration of 9 hours (range, 3–21 hours); see Figure 2 and Table 2.

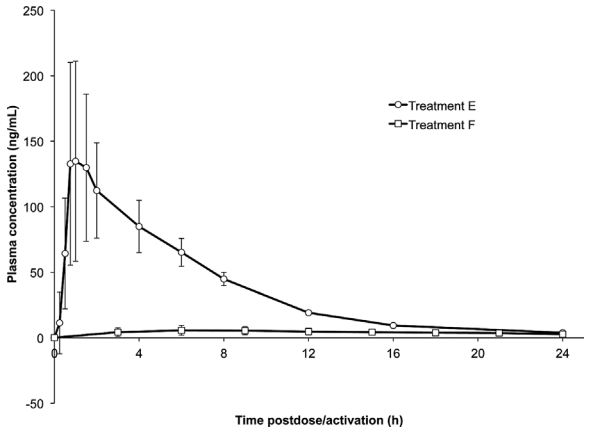

Figure 2. Mean edoxaban plasma concentration–time curves in study 2. Treatment E, 30-mg edoxaban immediate-release tablet; treatment F, 30 mg edoxaban plus 50 mg fumaric acid in a granulate formulation. Error bars represent the standard deviation. Data were collected up to 36 hours, but for clarity only the first 24 hours are shown here.

Safety

In both studies, edoxaban 60 mg was found to be safe and well tolerated, both when administered as an IR tablet and when delivered via the Enterion capsule and when coadministered with fumaric acid. In study 1, there were 9 treatment-emergent AEs reported by 5 subjects. These included 1 case each of cannula-site reaction (treatment D), influenza-like illness (treatment D), musculoskeletal pain (treatment D), paresthesia (treatment D), syncope (treatment A), and thirst (treatment B). There were 3 cases of dizziness; 1 occurred during treatment B and 2 during treatment D. Two of the 3 events of dizziness (once each in treatments B and D) and the 1 event of syncope were considered related to therapy.

Seven treatment-emergent adverse events were reported by 4 subjects in study 2. These included 1 case of nausea (treatment F), 1 case of somnolence (treatment F), 2 cases of upper respiratory tract infections (treatments E and F), and 3 cases of headache (treatment E). Two events

in treatment E were considered possibly or probably related to therapy (upper respiratory tract infection and headache; n = 1 for both) and 3 events in treatment F (nausea, upper respiratory tract infection, and somnolence; n = 1 for each). In both studies, the majority of AEs were mild in severity and resolved spontaneously, no deaths or serious AEs occurred, and no participants discontinued study treatment because of a study drug-related AE.

Edoxaban showed no clinically significant effects on vital signs, ECG variables, or hematologic, clinical chemistry, or laboratory data measurements, with the following exception. In 1 participant in study 2, a slight increase in mean supine heart rate was observed when edoxaban was coadministered with fumaric acid (7–11 beats/min) versus edoxaban alone (−1 to 2 beats/min) compared with baseline up to 4 hours after activation.

Discussion

The results of study 1 demonstrated that the absorption of edoxaban occurs predominantly in the proximal small intestine. Powder and aqueous formulations of edoxaban delivered to the ascending colon showed a similar rate and extent of absorption.

The solubility of edoxaban is pH dependent. It is highly soluble in an acidic pH (pH 3 to 5), slightly soluble at neutral pH (pH 6 to 7), and practically insoluble at a basic pH (8 to 9).[2] Thus, it was thought that edoxaban may undergo better absorption via improvement of its dissolution characteristics in the colon, such as through coadministration with fumaric acid to acidify the microenvironment around the drug with consequential benefits for the pH solubility profile. However, this failed to have a meaningful effect on absorption of edoxaban as demonstrated in study 2. Systemic exposure to edoxaban was no better in the colon when coadministered with fumaric acid.

As stated earlier, the 2 studies described here were undertaken early in the clinical development program for edoxaban to assess if its absorption from the distal GI tract might facilitate improved oral drug bioavailability and to determine if altering the pH of the microenvironment of the colon would facilitate improved drug dissolution and increased absorption at that site. This information is helpful in optimizing a formulation or developing extended-release formulations, if these are expected to improve either absorption or the pharmacokinetic/pharmacodynamic relationship.

The human GI tract is a complex physiological organ with many factors affecting drug absorption.[9] This complexity is challenging in terms of developing absorption, dissolution, and exposure models that are predictive of the behavior of a drug in humans. An understanding of the impact of these factors on the pharmacological behavior of a drug product is important for the rational design of orally administered treatments.[9] This study demonstrates that edoxaban absorption in the colon is limited, and this limited absorption is not related to solubility.

All single oral doses of edoxaban were safe and well tolerated, including when coadministered with fumaric acid, with no clinically significant changes in laboratory values or vital signs observed. The incidence of AEs was low for all formulations, with the majority of events being mild in severity and resolving spontaneously. A slight increase in mean supine heart rate was observed when edoxaban was coadministered with fumaric acid. However, these differences were not clinically significant and were thought to reflect the different times of day in which the measurements were obtained.

Overall, the results from this study suggest that absorption of edoxaban occurs predominantly in the proximal small intestine. The PK variables reported in this analysis for the IR formulation of edoxaban are consistent with previously reported studies, which demonstrate a peak concentration within 1 to 2 hours of dosing, followed by a biphasic decline.[4,5] As a weak base, edoxaban has poor solubility at intestinal pH, and therefore the intention of study 2 was to investigate if the corelease of a pharmaceutically relevant amount of acid with the drug would create an acidic microenvironment in the colon around the drug particles. It was hoped this would increase the amount of dissolved drug, thereby increasing the prospects for colonic permeability. The low absorption rates of edoxaban observed following targeted drug delivery to the distal small intestine or ascending colon are therefore likely due to differences in permeability along the length of the GI tract rather than poor solubility per se.

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