Integrated Pharmacogenomic Analysis Reveals OATP1B1 T521C Polymorphism (rs4149056) Does Not Affect the Pharmacokinetics of Edoxaban

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Background

- Edoxaban is a once-daily, selective, orally administered direct factor Xa inhibitor approved for the reduction of risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and for the treatment of venous thromboembolism in the United States[1,2]
- Edoxaban undergoes minimal metabolism, yielding the major metabolite M4, which accounts for <10% of edoxaban exposure[3]
  - M4 and edoxaban have similar anticoagulant potency (data on file)
- The organic anion transporter protein 1B1 (OATP1B1), encoded by the *SLCO1B1* gene, mediates the hepatic uptake of M4[4]
- The T521C single nucleotide polymorphism (rs4149056) of the *SLCO1B1* gene is associated with decreased transport activity of OATP1B1
  - In individuals carrying this polymorphism, exposure to certain drugs that are OATP1B1 substrates may be increased[5-9]
- Pharmacological inhibition of OATP1B1 may contribute to increased M4 exposure[10, 11]
- The objective of this integrated analysis was to investigate the association between the *SLCO1B1* genotype and the pharmacokinetics (PK) of edoxaban and M4 in healthy subjects who had participated in an edoxaban phase 1 study

Methods

- Clinical data and DNA samples from 458 healthy subjects (365 males and 93 females) from 14 edoxaban phase 1 clinical studies were analyzed
- As part of each study, following a single oral dose of edoxaban 60 mg, blood samples were collected to determine edoxaban and M4 plasma concentrations and PK parameters
- The *SLCO1B1* rs4149056 genotypes were generated in duplicate using a validated Taqman assay in a commercial genomic laboratory in compliance with Clinical Laboratory Improvement Amendments standards
- The PK parameters for the area under the plasma drug concentration-time curve from time 0 to infinity (AUC_{inf}), the area under the plasma drug concentration-time curve from time 0 to last measurable concentration (AUC_{last}), the maximum observed plasma concentration (C_{max}), and the observed plasma concentration at 24 hours postdose (C_{24}) were computed using a noncompartmental approach with WinNonlin Professional software Version 4.0 or 5.2
- Metabolite-to-parent ratios (MPR) were calculated for AUC_{last}, AUC_{inf}, and C_{max} with adjustments for molecular weights and summarized by genotype of *SLCO1B1* (TT and C carriers)
- PK parameters were statistically compared between genotypes using analysis of variance (ANOVA) in SAS® Proc MIXED, with genotype and study ID as fixed effects
- Point estimates and 90% confidence intervals (CIs) for the ratios of the PK parameters between different allele variations of *SLCO1B1* (C carriers vs TT) were calculated using multiple pair-wise comparisons by applying exponential transformation to the difference in least squares (LS) means calculated using ln-transformed values and CIs obtained from the ANOVA model
- Assuming the expected mean ratio was within the range of 95% to 105% for subgroup comparison, a genotype subgroup of at least 26, 75, and 70 subjects for edoxaban AUC_{inf}, C_{max}, and C_{24}, respectively, was required in order to have at least 80% power so that the 90% CI for the mean ratio would fall within the range of 80% to 125%
- Assuming the expected mean ratio was within the range of 95% to 105% for subgroup comparison, a genotype subgroup of at least 57, 103, and 96 subjects for M4 AUC_{inf}, C_{max}, and C_{24}, respectively, was required in order to have at least 80% power so that the 90% CI for the mean ratio would fall within the range of 80% to 125%

Results

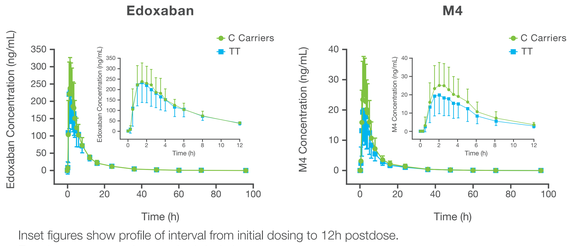
- Most baseline characteristics and demographics were similar across genotype groups
- As expected, genotype frequencies varied across racial groups and were similar to those previously reported[12]
- The genotype call rate was 100%, and the *SLCO1B1* SNP was in Hardy-Weinberg Equilibrium for all race groups examined

TABLE 1. Demographic Summary (Integrated Study Population)

	TT n = 384	CT n = 71	CC n = 3	Total N = 458
Sex, n (%)				
Male	311 (81.0)	53 (74.6)	1 (33.3)	365 (79.7)
Female	73 (19.0)	18 (25.4)	2 (66.7)	93 (20.3)
Race, n (%)				
American Indian/Alaskan	1 (0.3)	1 (1.4)	0 (0.0)	2 (0.4)
Asian	9 (2.3)	1 (1.4)	0 (0.0)	10 (2.2)
Black or African American	226 (58.9)	24 (33.8)	0 (0.0)	250 (54.6)
White	134 (34.9)	40 (56.3)	3 (100.0)	177 (38.6)
Other	14 (3.6)	5 (7.0)	0 (0.0)	19 (4.1)
Ethnicity, n (%)				
Hispanic/Latino	84 (21.9)	20 (28.2)	1 (33.3)	105 (22.9)
Not Hispanic/Latino	300 (78.1)	51 (71.8)	2 (66.7)	353 (77.1)
Age, y				
Mean ± SD	31.4 ± 7.4	29.6 ± 6.9	29.3 ± 12.1	31.1 ± 7.4
Weight, kg				
Mean ± SD	80.1 ± 12.1	78.8 ± 12.3	64.0 ± 4.0	79.8 ± 12.2
BMI, kg/m²				
Mean ± SD	26.1 ± 3.0	26.2 ± 3.2	24.9 ± 3.9	26.1 ± 3.1
CL_{cr}, mL/min				
Mean ± SD	134.5 ± 26.3	141.0 ± 22.7	146.7 ± 25.2	135.6 ± 25.9

BMI = body mass index; CL_{cr} = creatinine clearance; SD = standard deviation

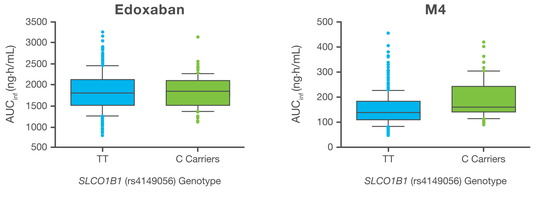
FIGURE 1. Mean Plasma Concentration-Time Profile of Edoxaban and M4 by *SLCO1B1* Genotype



Inset figures show profile of interval from initial dosing to 12h postdose.
Error bars represent the standard deviation.

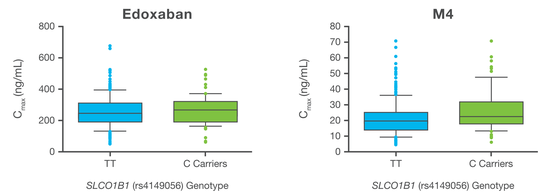
- Mean edoxaban plasma concentration-time profiles were similar across rs4149056 genotypes
- Plasma concentrations of M4 were slightly elevated in C carriers relative to TT homozygotes

FIGURE 2. AUC_{inf} Results of Edoxaban and M4 by *SLCO1B1* Genotype



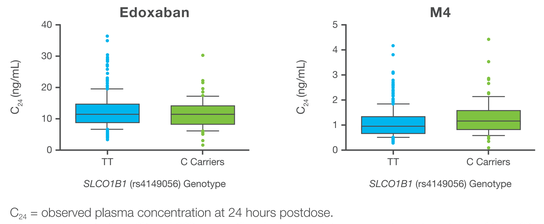
AUC_{inf} = area under the plasma drug concentration-time curve from time 0 to infinity.
Whiskers indicate the 10th and 90th percentiles; individual dots represent points outside of the 10th and 90th percentiles. Line in box plots indicates the median.

FIGURE 3. C_{max} Results of Edoxaban and M4 by *SLCO1B1* Genotype



C_{max} = maximum observed plasma concentration.
Whiskers indicate the 10th and 90th percentiles; individual dots represent points outside of the 10th and 90th percentiles. Line in box plots indicates the median.

FIGURE 4. C_{24} Results of Edoxaban and M4 by *SLCO1B1* Genotype



C_{24} = observed plasma concentration at 24 hours postdose.
Whiskers indicate the 10th and 90th percentiles; individual dots represent points outside of the 10th and 90th percentiles. Line in box plots indicates the median.

- Edoxaban AUC_{inf}, C_{max}, and C_{24} values were similar across genotypes, while C carriers had slightly higher M4 AUC_{inf} and C_{max} values compared with TT subjects; M4 C_{24} levels were comparable between the genotypes

TABLE 2. Summary of Pharmacokinetic Parameters of Edoxaban and M4 by *SLCO1B1* Genotype

		***SLCO1B1* (rs4149056) Genotypes**			
	PK Parameter	TT	n	C Carriers	n
Edoxaban	AUC_{last} (ng·h/mL)	1792.9 ± 442.8	384	1777.2 ± 380.8	74
	$AUC_{0\text{-}24}$ (ng·h/mL)	1644.1 ± 440.6	384	1643.8 ± 392.9	74
	AUC_{inf} (ng·h/mL)	1823.5 ± 444.9	381	1815.5 ± 382.4	72
	C_{max} (ng/mL)	255.1 ± 97.4	384	268.0 ± 94.7	74
	C_{24} (ng/mL)	12.3 ± 5.4	382	11.6 ± 4.8	74
M4	AUC_{last} (ng·h/mL)	147.1 ± 60.7	384	184.6 ± 75.6	74
	$AUC_{0\text{-}24}$ (ng·h/mL)	134.7 ± 57.2	384	170.0 ± 73.0	74
	AUC_{inf} (ng·h/mL)	150.2 ± 61.4	379	191.9 ± 76.4	72
	C_{max} (ng/mL)	21.2 ± 10.7	384	26.7 ± 13.6	74
	C_{24} (ng/mL)	1.1 ± 0.57	382	1.3 ± 0.74	74
	MPR AUC_{last}	8.7 ± 2.9	384	10.9 ± 3.6	74
	MPR AUC_{inf}	8.7 ± 2.9	378	11.1 ± 3.5	72
	MPR C_{max}	8.8 ± 3.1	384	10.5 ± 3.3	74

Data shown as arithmetic mean ± standard deviation. AUC_{last} = Area under the plasma drug concentration-time curve (AUC) from time zero to the last measurable concentration; $AUC_{0\text{-}24}$ = AUC from time zero to 24 hours postdose; AUC_{inf} = AUC from time 0 to infinity; C_{max} = maximum observed plasma concentration; C_{24} = observed plasma concentration at 24 hours postdose; MPR = Metabolite to parent ratio of relevant PK parameter

- Edoxaban PK parameters were similar across genotypes
- For M4, total and peak exposure were increased in C carriers compared to TT homozygotes

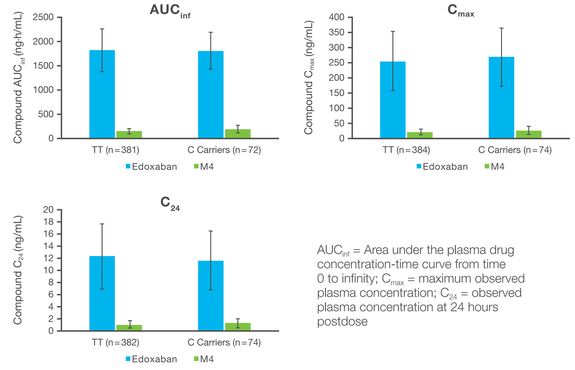
TABLE 3. Statistical Comparison of Pharmacokinetic Parameters of Edoxaban and M4 by *SLCO1B1* Genotype

		***SLCO1B1* (rs4149056) Genotypes**				
		Geometric Mean (CV%)				Ratio of Geometric LS Means (90% CI) (%)
	PK Parameter	TT	n	C Carriers	n	C Carriers vs TT
Edoxaban	AUC_{inf} (ng·h/mL)	1769 (25.4)	381	1776 (21.3)	72	100.97 (95.89, 106.32)
	C_{max} (ng/mL)	235.5 (43.9)	384	249.8 (41.6)	74	105.35 (96.47, 115.06)
	C_{24} (ng/mL)	11.25 (44.0)	382	10.56 (48.5)	74	95.25 (87.51, 103.68)
M4	AUC_{inf} (ng·h/mL)	139.1 (40.7)	379	178.9 (38.2)	72	126.86 (117.40, 137.08)
	C_{max} (ng/mL)	18.68 (55.0)	384	23.67 (52.5)	74	124.05 (111.90, 137.53)
	C_{24} (ng/mL)	0.959 (53.4)	382	1.105 (63.5)	74	114.94 (104.02, 127.00)

AUC_{inf} = Area under the plasma drug concentration-time curve from time 0 to infinity; C_{max} = maximum observed plasma concentration; C_{24} = observed plasma concentration at 24 hours postdose; CI = confidence interval; CV% = coefficient of variation; LS = least squares

- *SLCO1B1* polymorphism (rs4149056) does not affect edoxaban exposure, peak concentration, or trough level
- However, *SLCO1B1* polymorphism (rs4149056) appears to be associated with a modest increase (~25%) in M4 exposure (AUC_{inf}) and peak concentration (C_{max})

FIGURE 5. Summary Pharmacokinetics of Edoxaban and M4 in Plasma by *SLCO1B1* genotype



AUC_{inf} = Area under the plasma drug concentration-time curve from time 0 to infinity; C_{max} = maximum observed plasma concentration; C_{24} = observed plasma concentration at 24 hours postdose

Conclusions

- *SLCO1B1* polymorphism has no impact on edoxaban PK
- Exposure to the most abundant metabolite of edoxaban, M4, is marginally elevated in C carriers compared to TT homozygotes
- Given the low abundance of M4 (<10% AUC_{inf}) in proportion to edoxaban levels, the slight increase in M4 exposure is unlikely to be clinically significant in C carriers

References

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