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Influence of Laropiprant, a Selective Prostaglandin D_2 Receptor 1 Antagonist, on the Pharmacokinetics and Pharmacodynamics of Warfarin

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Laropiprant (LRPT), a prostaglandin D_2 receptor 1 antagonist shown to reduce niacin-induced flushing symptoms, is being developed in combination with niacin for the treatment of dyslipidemia. This study assessed the pharmacokinetics/pharmacodynamics of single-dose warfarin in the presence/absence of multiple-dose LRPT. Thirteen subjects received 2 treatments in random order separated by ≥10-day washout: (1) multiple-dose LRPT 40 mg/d for 12 days (days −5 to 7) with coadministered single-dose warfarin 30 mg (day 6) and (2) single-dose warfarin 30 mg (day 1). R(+)- and S(−)-warfarin and international normalized ratio (INR) were assayed predose and up to 168 hours postdose. Comparability was declared if the 90% confidence intervals (CIs) for the geometric mean ratio (GMR; warfarin + LRPT/warfarin alone) of area under the plasma concentration curve from zero to infinity ($AUC_{0-\infty}$) for R(+)- and S(−)-warfarin were contained within (0.80, 1.25). The estimated GMRs of $AUC_{0-\infty}$ (90% CIs) were 1.02 (0.96, 1.09) and 1.04 (0.98, 1.09) for R(+)- and S(−)-warfarin, respectively. The estimated GMRs of maximum plasma concentration (C_{max}) (90% CIs) were 1.13 (1.02, 1.26) and 1.11 (0.99, 1.24) for R(+)- and S(−)-warfarin, respectively. The estimated GMRs of area under the prothrombin time INR curve from 0 to 168 hours on day 21 (INR AUC_{0-168h}) and average maximum observed prothrombin time INR (INR_{max}) were 1.02 (0.99, 1.05) and 1.04 (0.98, 1.10), respectively. There was no evidence of clinically meaningful alterations in the pharmacokinetics and pharmacodynamics (ie, INR) of R(+)- or S(−)-warfarin after coadministration of multiple-dose LRPT and single-dose warfarin.

Keywords: laropiprant, warfarin, pharmacokinetics, pharmacodynamics

INTRODUCTION

Niacin (nicotinic acid) has broad beneficial effects on the overall plasma lipid profile, including raising high-density lipoprotein cholesterol and lowering low-density lipoprotein cholesterol, triglycerides, and lipoprotein (a) levels.[1] Long-term administration of niacin has been shown to improve cardiovascular outcomes when administered as monotherapy or in combination with other lipid-altering agents.[2–4] However, widespread use of niacin in clinical practice is limited due to flushing symptoms experienced by many patients taking niacin therapy.[5–8] These bothersome side effects limit niacin dose escalation and patient acceptance and often lead to discontinuation of therapy.

Niacin-induced flushing is mediated primarily by prostaglandin D_2 (PGD_2), which activates prostaglandin D_2 receptors-1 (DP1 receptors) in the skin, resulting in cutaneous flushing of the face, neck, and trunk.[9–15] Laropiprant (LRPT, previously known as MK-0524) is a potent, orally active, once-daily, highly selective DP1 receptor antagonist, being developed in combination

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with niacin for the treatment of dyslipidemia.[15–19] In patients with dyslipidemia, concomitant administration of LRPT with extended release niacin was shown to reduce the incidence and intensity of niacin-induced flushing symptoms without diminishing the lipid-altering benefits of niacin therapy.[20] These findings suggest that LRPT could significantly improve the tolerability and optimal therapeutic dosing of niacin, thereby improving the clinical effectiveness of niacin therapy.

Prior human pharmacokinetic studies indicate that LRPT is rapidly absorbed after oral administration. The major circulating metabolite is an inactive acyl glucuronic acid conjugate which is likely formed via uridine disphosphate-glucuronosyltransferases 1A1, 1A3, 1A9, and 2B7 and excreted into the bile and urine.[21,22] LRPT is also subject to oxidative metabolism via cytochrome P450 (CYP) 3A4 isozyme with a minor contribution from CYP2C9; however, the rate of oxidative metabolism was minimal compared with that of glucuronidation.[21,23] In the in vitro CYP inhibition studies using human liver microsomes, LRPT exhibited moderate inhibition on CYP2C8-mediated reactions. Little or no inhibition was observed on CYP1A2-, CYP2B6-, CYB2C9-, CYP2C19-, CYP2D6-, CYP2E1-, and CYP3A4-mediated reactions for IC_{50} values greater than 64 μM (data on file, Merck & Co, Inc). Previous studies have demonstrated that LRPT administered in doses of 30–450 mg attain steady-state concentration by day 2 for all dose levels.[24]

Warfarin is a vitamin K antagonist widely used for the long-term prevention of thrombosis. Treatment with warfarin reduces coagulation by interfering with the vitamin K–dependent posttranslational modification of several procoagulant clotting factors (factors II, VII, and X).[25] Prothrombin time (PT) is the most commonly used parameter to assess the therapeutic anticoagulant effect of warfarin.[26] Standardization of PT across studies is achieved by calculation of the international normalized ratio (INR), which provides a more reliable measure of blood coagulation compared with the nonstandardized PT measurement.[27] Warfarin has a narrow therapeutic index with large inter- and intraindividual variations in dose response, necessitating close monitoring of PT to minimize the risk of excessive bleeding in overdose and risk of thromboembolic events due to inadequate dosing.[28,29] Although a single therapeutic range for warfarin may not be optimal for all indications, a moderate-intensity INR (2.0–3.0) is effective for most indications.[30]

Warfarin is administered as a 1:1 racemic mixture of 2 enantiomers, R(+)- and S(−)-warfarin. The anticoagulant potency of the S(−) enantiomer is approximately 5–6 times higher than that of the R(+) enantiomer.[31] Warfarin is largely metabolized by hepatic microsomal enzymes, with CYP2C9 being primarily responsible for the oxidative conversion of the S(−) enantiomer, with minor contributions from CYP2C19 and CYP3A4.[31–34] In contrast, no single CYP isoenzyme dominates the metabolism of R(+)–warfarin, which occurs via CYP1A2, CYP3A4, and CYP2C19.[31,32,34] In addition, both enantiomers of warfarin are reduced to alcohols by a ketoreductase.[35,36] Warfarin has a high propensity for drug interactions, which may occur by different mechanisms, including inhibition or induction of metabolism and altered protein binding.[28,29] Sufficient alterations in the pharmacokinetic profile of warfarin can lead to clinically important changes in its therapeutic anticoagulant effects, as measured by INR.

The current study assessed the potential influence of multiple-dose LRPT on the pharmacokinetics of (S)- and (R)-warfarin due to the likelihood that these 2 compounds will be concomitantly administered in clinical practice. LRPT 40 mg was selected for use in this study because it represented the highest dose tested in the Phase III clinical program.[37] The main objective of this study was to evaluate the potential effects of LRPT 40 mg dosed to steady state on the pharmacokinetics [primary endpoint: area under the plasma concentration curve from zero to infinity ($AUC_{0-\infty}$); secondary endpoint: maximum plasma concentration (C_{max})] and pharmacodynamics (INR) of single-dose warfarin in healthy male and female subjects. The safety and tolerability profile of the combined administration of LRPT and warfarin also was examined in this study. The primary study hypothesis stated that once-daily administration of LRPT 40 mg for 12 days would not substantially alter the plasma pharmacokinetics of single-dose warfarin 30 mg [ie, the geometric mean ratios (GMR) for $AUC_{0-\infty}$ of S(−)- and R(+)-warfarin measured in the presence and absence of LRPT will be entirely contained within the prespecified comparability bounds of (0.80, 1.25)].

MATERIALS AND METHODS

Subjects

Eligible participants included healthy, nonsmoking male subjects and female subjects of nonchildbearing potential (ie, hysterectomy, bilateral oophorectomy, tubal ligation, or postmenopausal) between 18 and 50 years of age with a body mass index between 18.5 and 32 kg/m^2 who agreed to comply with all study restrictions. Additional entry criteria included normal prestudy laboratory test results for PT, activated partial thromboplastin time, platelet count, and negative stool occult

blood test. Subjects should not be involved in any activities that would place them at high risk of hemorrhage (eg, contact sports). Subjects also had to agree to restrict their intake of alcohol, caffeinated beverages, grapefruit and grapefruit juice, and quinine-containing beverages. Subjects were excluded if they had any relevant history of pulmonary, hepatic, gastrointestinal, renal, cardiac, cerebrovascular, psychiatric, or neurological disease; diabetes; hypertension; any condition predisposing them to immunodeficiency; or any condition contraindicating use of warfarin (eg, hemorrhagic tendencies, recent or pending surgery, ulceration, or overt bleeding of gastrointestinal system). Subjects with an estimated creatinine clearance ≤60 mL/min or serum creatinine >1.5 mg/dL were excluded. Additional exclusion criteria included a history of multiple and/or severe allergies to drugs or foods.

Study design

This open-label, randomized crossover study consisted of 2 treatments administered in random order. Treatment A consisted of once-daily open-label dosing of LRPT 40 mg (administered as 1 × 25 mg and 3 × 5 mg) for 12 days (day −5 to 7) with coadministration of a single, open-label oral dose of warfarin 30 mg (administered as 6 × 5 mg, COUMADIN; Bristol-Myers Squibb Company) on day 1 (after 5 days of dosing with LRPT). Treatment B consisted of a single, open-label oral dose of warfarin 30 mg (administered as 6 × 5 mg) on day 1. Patients were allocated to receive the 2 treatments in random order using a computer-generated allocation schedule. The single doses of warfarin administered in the 2 treatment periods were separated by at least a 10-day washout interval. The doses on day 1 for both treatment periods were administered with 240 mL of water in the morning after an overnight fast with water intake restricted 1 hour before and after study drug administration.

The use of prescription and nonprescription medications was not allowed within 14 days of study start and throughout the entire study period. Subjects could be discontinued from the study for the following predefined reasons: any adverse experience that jeopardized the subject's safety and/or well-being, deviation from dosing regimen, use of excluded concomitant medications, and positive or borderline pregnancy test.

This study was conducted at a single study center in the United States (SFBC International, Miami, FL). Each subject provided written informed consent before the administration of study procedures. The study protocol was approved by an independent ethics committee (Independent Investigational Review Board, Inc, Plantation, FL) and was conducted in accordance with the guidelines established by the Declaration of Helsinki.

Pharmacokinetic assessments

Blood (4 mL) was drawn in sodium heparin–containing tubes predose and 0.5, 1, 2, 4, 12, 24, 48, 72, 96, 120, 144, and 168 hours after the administration of study drug on day 1 in both treatment periods for measurement of S(−) and R(+) enantiomers of warfarin. Plasma was prepared and stored at −20°C until assayed and shipped on dry ice to the central laboratory (Advion BioScience, Inc, Ithaca, NY) for assay.

Pharmacokinetic parameters were calculated via noncompartmental analysis using WinNonlin software version 5.0.1 (Pharsight Corporation, Mountain View, CA). Apparent terminal rate constant (λ) was estimated from the terminal portion of the log-transformed plasma concentration–time profile using linear regression. Terminal half-life ($t_{1/2}$) was calculated as the quotient of ln(2) and λ. The AUC to the last time point with a detectable plasma concentration (AUC_{0-last}) was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. $AUC_{(0-\infty)}$ (μg·h/mL) was estimated as the sum of AUC to the last measured concentration and the extrapolated area given by the quotient of the last measured concentration and λ. Peak plasma concentration (C_{max}, ng/mL) and its time of occurrence (T_{max}, hours) were obtained by inspection of the plasma concentration–time profile.

Pharmacodynamic assessments

The effect of LRPT on the anticoagulant effect of warfarin was evaluated through measurement of PT and calculation of INR using a single lot of thromboplastin with a known international sensitivity index at various time points throughout the study. All measurements of PT and calculations of INR were done at the site's local laboratory. Blood samples (3 mL) for PT/INR measurement were collected predose on days 1 and 1, 2, 4, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose on day 1 of both treatments A and B. Plasma was prepared and used for PT determination in duplicate within 2 hours of collection. PT values were reported both as raw data in absolute time (seconds) and as INR calculations. Standardization of PT across studies is achieved by calculation of the INR, which provides a more reliable measure of blood coagulation compared with the nonstandardized PT ratio.[27]

Analytical methods

Plasma samples were analyzed for S(−)- and R(+)-warfarin concentrations using a dilution procedure, turbo ion spray liquid chromatography–tandem mass spectrometry (LC/MS/MS) assay by a central laboratory (Advion BioScience, Inc). The lower limit of

quantification was 10 ng/mL and the linear calibration range was 10–2500 ng/mL for both enantiomers of warfarin.

Safety measurements

The safety and tolerability of study medication were assessed by clinical evaluation of adverse experiences and inspection of other safety parameters including physical examinations, vital signs, routine laboratory safety measurements (hematology, blood chemistry, and urinalysis), serum β-human chorionic gonadotropin, and 12-lead electrocardiograms (12-lead ECG). Adverse experiences were monitored throughout the study and evaluated in terms of intensity (mild, moderate, or severe), duration, severity, outcome, and relationship to study drug. All patients who took at least 1 dose of study medication (treatment A or B) were included in the safety/tolerability analyses.

Statistical analysis

Primary and secondary pharmacokinetic endpoints in this study included the $AUC_{0-\infty}$ and C_{max} values, respectively, for S(−)- and R(+)-warfarin. The primary study hypothesis stated that multiple-dose LRPT 40 mg (12 days) would not substantially alter the plasma pharmacokinetics of single-dose warfarin 30 mg as assessed by measurement of S(−)- and R(+)-warfarin $AUC_{0-\infty}$ in the absence and presence of LRPT [ie, the true GMRs (warfarin + LRPT/warfarin) for the plasma $AUC_{0-\infty}$ of warfarin enantiomers, S(−) and R(+), would be contained within the prespecified comparability bounds of (0.80, 1.25)]. The secondary study hypothesis stated that multiple-dose LRPT 40 mg (12 days) would not substantially alter the plasma C_{max} of S(−)- and R(+)-warfarin [ie, the true GMRs for the plasma C_{max} of warfarin enantiomers, S(−) and R(+), would be contained within the prespecified comparability bounds of (0.80, 1.25)].

A mixed linear effects model appropriate for a 2-period crossover study design was used to compare the pharmacokinetic parameters of S(−)- and R(+)-warfarin in the absence and presence of LRPT. The model included terms for sequence, period, and treatment as fixed effects and subject within sequence as a random effect. The $AUC_{0-\infty}$ and C_{max} values were analyzed after transformation to the natural log scale. Ninety percent confidence intervals (CIs) were constructed for the GMRs (warfarin + LRPT/warfarin) for both warfarin S(−) and R(+) $AUC_{0-\infty}$ and C_{max} from the model after back transformation. If the 90% CIs for both the GMRs of warfarin S(−) and R(+) $AUC_{0-\infty}$ were contained within the prespecified bounds of (0.80, 1.25), then the primary study hypothesis was supported. Similarly, if the 90% CIs for both the GMRs of warfarin S(−) and R(+) C_{max} were contained within the prespecified bounds of (0.80, 1.25), then the secondary study hypothesis was supported. Nonparametric methods were used to analyze T_{max}, and the results were summarized by providing the estimates for median differences and the associated 90% CI using the Hodges–Lehmann estimator. Harmonic mean was provided for apparent terminal $t_{1/2}$.

The influence of multiple-dose LRPT on the pharmacodynamics of single-dose warfarin was assessed through the measurement of area under the prothrombin time INR curve from 0 to 168 hours on day 21 (INR AUC_{0-168h}) and average maximum observed prothrombin time INR (INR_{max}) and analyzed using the same mixed model as described above for the pharmacokinetic analyses. The natural log transformation was applied to both of these parameters before analysis.

RESULTS

Study population

Thirteen healthy subjects (8 males and 5 females) with a mean age of 40.0 years (range 21–50 years), a mean height of 168.4 cm (range 157.5–180.3 cm), and a mean weight of 76.6 kg (range 60.0–90.0 kg) were enrolled in the study. A total of 8 (62%) Hispanic, 3 (23%) white and 2 (15%) black subjects participated in this study. Twelve subjects (92%) completed the study per protocol. One subject withdrew from the study due to a family emergency after finishing period 1 and before starting period 2. This subject was included in the safety analyses but was not included in the pharmacokinetic and pharmacodynamic analyses.

Plasma pharmacokinetics

The mean plasma concentration–time curves for S(−)- and R(+)-warfarin after treatment with single-dose warfarin 30 mg administered in the absence and presence of multiple-dose LRPT 40 mg/d (12 days) are shown in Figure 1. The plasma concentration–time curves showed that the pharmacokinetic profiles of S(−)- and R(+)-warfarin were comparable during both treatments. Summary statistics for $AUC_{0-\infty}$, C_{max}, T_{max}, and apparent terminal $t_{1/2}$ as well as the associated GMRs (90% CI) for S(−)- and R(+)-warfarin are provided in Table 1. The model-based geometric mean $AUC_{0-\infty}$ values measured in the absence and presence of LRPT, respectively, were 59.0 and 61.1 μg·h/mL for S(−)-warfarin and 101.3 and 103.5 μg·h/mL for R(+)-warfarin. The model-based

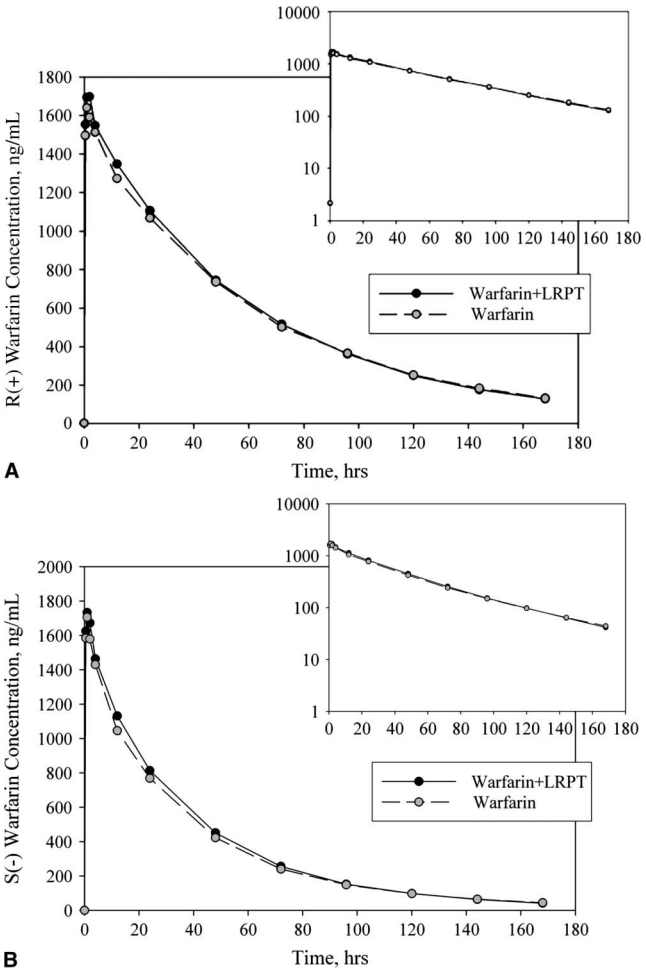

FIGURE 1. Mean plasma concentration profiles for (A) R(+)-warfarin and (B) S(−)-warfarin after a single oral dose of warfarin 30 mg administered in the absence (treatment B) and presence (treatment A) of steady-state LRPT 40 mg. Data are plotted as mean (ng/mL) plasma levels up to 168 hours postdose (inset: semi-log plot).

geometric average C_{max} values measured in the absence and presence of LRPT, respectively, were 1946 and 2154 ng/mL for S(−)-warfarin and 1868 and 2118 ng/mL for R(+)-warfarin. There were no statistically significant differences in T_{max} for S(2)- and R(+)-warfarin between the 2 treatments. The apparent terminal $t_{1/2}$ of S(2)- and R(+)-warfarin were also comparable.

The $AUC_{0-\infty}$ (primary endpoint) and C_{max} (secondary endpoint) of S(−)- and R(+)-warfarin were used to evaluate the pharmacokinetics of warfarin in the presence and absence of LRPT 40 mg. The estimated GMRs (warfarin + LRPT/warfarin; 90% CI) for $AUC_{0-\infty}$ of S(−)- and R(+)-warfarin were 1.04 (90% CI: 0.98, 1.09) and 1.02 (90% CI: 0.96, 1.09), respectively (Table 1). The 90% CIs for GMRs $AUC_{0-\infty}$ of S(−)- and R(+)-warfarin all fell within the predetermined comparability bounds of (0.80, 1.25), thus supporting the primary study hypothesis.

The C_{max} values of S(−)- and R(+)-warfarin were slightly elevated in the presence of LRPT 40 mg. The GMRs (warfarin + LRPT/warfarin) for C_{max} of S(−)- and R(+)-warfarin were 1.11 (90% CI: 0.99, 1.24) and 1.13 (90% CI: 1.02, 1.26), respectively (Table 1). The 90% CI for the GMR C_{max} of S(−)-warfarin was contained entirely within the predetermined comparability bounds, indicating that the S(−) enantiomer showed comparable pharmacokinetics in the absence and presence of LRPT. The upper bound (1.26) of the 90% CI for R(+)-warfarin was slightly greater than the predetermined upper comparability bound (1.25)

Pharmacodynamics

Table 2 shows summary statistics for the INR pharmacodynamic endpoints after the administration of single-dose warfarin 30 mg with and without multiple-dose LRPT 40 mg. Coadministration of warfarin with LRPT did not seem to alter the anticoagulant efficacy of warfarin as measured by INR AUC_{0-168h} and INR_{max} (Figure 2). The estimated GMR (warfarin + LRPT/warfarin) for the INR AUC_{0-168h} was 1.02 with a corresponding 90% CI of (0.99, 1.05). The estimated GMR (warfarin + LRPT/warfarin) for the INR_{max} was 1.04 with a corresponding 90% CI of (0.98, 1.10). These results demonstrate no pharmacodynamic alterations, specifically that the INR level was not meaningfully changed after coadministration of LRPT and warfarin.

Safety and tolerability

A total of 4 subjects reported 7 clinical adverse experiences in this study; all adverse experiences were reported during coadministration of LRPT and warfarin. The individual adverse experiences included loose stools (2 subjects with 3 reports), headache (1 subject with 2 reports), stomach ache (1 subject with 1 report), and toothache (1 subject with 1 report). All clinical adverse events were transient in duration and considered mild in intensity by the study investigator. Six adverse experiences were rated possibly related to study medication by the study investigator except for the report of toothache, which was considered probably not related to study medication. No serious clinical adverse experiences and no laboratory adverse experiences were reported in this study. Additionally, there were no consistent treatment-related changes in laboratory test results, ECG parameters, or vital signs.

Table 1. Pharmacokinetic parameters of R(+)- and S(−)-warfarin after administration of a single dose of warfarin 30 mg alone (treatment B) or in combination (treatment A) with multiple-dose LRPT 40 mg in healthy subjects.

Pharmacokinetic parameter	n	Least-squares geometric mean: Coadministered warfarin + LRPT (treatment A)	Least-squares geometric mean: Warfarin alone (treatment B)	Estimated GMR (90% CI)	*P*†
R(+)-warfarin					
$AUC_{0-\infty}$(μg·h/mL)	12	103.5	101.3	1.02 (0.96, 1.09)	0.539
C_{max}(ng/mL)	12	2118	1868	1.13 (1.02, 1.26)	0.050
T_{max}(h)	12	1.0	0.8	0.0 (−0.5, 0.8)*	0.999
Apparent terminal $t_{1/2}$(h)	12	45.7	49.0	—	0.046
S(−)-warfarin					
$AUC_{0-\infty}$(μg·h/mL)	12	61.1	59.0	1.04 (0.98, 1.09)	0.278
C_{max}(ng/mL)	12	2154	1946	1.11 (0.99, 1.24)	0.141
T_{max}(h)	12	1.0	0.8	0.0 (−0.5, 0.2)*	0.797
Apparent terminal $t_{1/2}$(h)	12	35.5	37.3	—	0.353

*Hodges–Lehmann estimate of median difference with distribution-free CI for T_{max}.
†*P* value was from testing if the 2 treatments are different. $P < 0.05$ indicates that the treatments were statistically different at the significance level of 0.05.
—, not calculated; apparent terminal $t_{1/2}$, apparent terminal half-life.

DISCUSSION

The effects of steady-state LRPT 40 mg (dosed for 12 consecutive days) on the pharmacokinetics and pharmacodynamics of single-dose warfarin 30 mg was evaluated in this study because of the narrow therapeutic index of warfarin and the high likelihood that patients requiring chronic warfarin therapy may also require treatment with LRPT in combination with niacin. In this study, the pharmacokinetic [$AUC_{0-\infty}$, C_{max}, T_{max}, and apparent plasma half-life of S(−)- and R(+)-warfarin] and pharmacodynamic parameters (INR AUC_{0-168h} and INR_{max}) of warfarin were monitored for up to 168 hours postdose to accommodate the long half-life of both warfarin enantiomers.

Previous in vitro studies have shown that LRPT is primarily metabolized by glucuronidation in the gut and liver, with minimal oxidative metabolism via CYP3A4 and CYP2C9.[21,23] The metabolic pathways suspected to be responsible for the biotransformation of the less potent R(+) enantiomer include CYP3A4 (10-hydroxywarfarin), CYP1A2 (6- and 8-hydroxywarfarin), and CYP2C19 (8-hydroxywarfarin).[31,32,34] In contrast, the more potent S(−) enantiomer is oxidized primarily to S-7-hyroxywarfarin and to a limited amount to S-6-hydroxywarfarin, predominantly by CYP2C9.[31–34] Both enantiomers are further metabolized to alcohols by reductases in endoplasmic reticulum and cytosol.[35,36] Treatment with LRPT was not expected to interfere with the metabolism of R(+)- or S(−)-warfarin because prior in vitro human liver microsome experiments conducted with LRPT demonstrated no significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 isoenzymes ($IC_{50} >$ 64 μM) (data on file, Merck & Co, Inc).

Table 2. Pharmacodynamic parameters after administration of a single dose of warfarin 30 mg alone (treatment B) or in combination (treatment A) with multiple-dose LRPT 40 mg in healthy subjects.

Pharmacodynamic parameter	n	Least-squares geometric mean: Coadministered warfarin + LRPT (treatment A)	Least-squares geometric mean: Warfarin alone (treatment B)	Estimated GMR (90% CI)†	*P*‡
INR AUC_{0-168h}	12	229.4	225.2	1.02 (0.99, 1.05)	0.336
INR_{max}	12	2.1	2.0	1.04 (0.98, 1.10)	0.305

†GMR for (warfarin + LRPT)/(warfarin alone).
‡*P* value was from testing if the true GMR is different from 1.00. $P < 0.05$ indicates that the true GMR was statistically different from 1.00 at the significance level of 0.05.

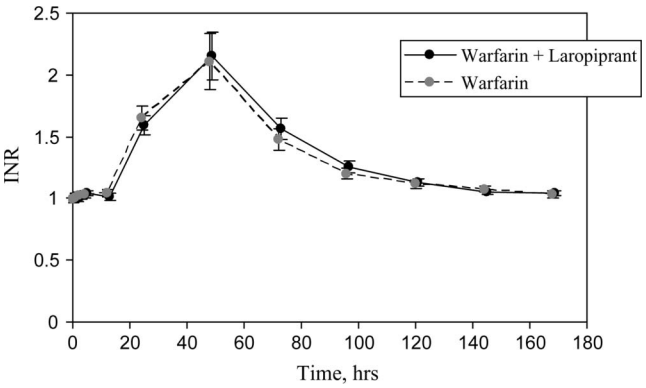

FIGURE 2. Time profile plot of prothrombin/INR measured over 168 hours after a single oral dose of warfarin 30 mg administered in the absence (treatment B) and presence (treatment A) of steady-state LRPT 40 mg.

The results of this study showed that steady-state administration of LRPT 40 mg does not alter the pharmacokinetics of single-dose warfarin 30 mg as measured by $AUC_{0-\infty}$ of R(+)- and S(−)-warfarin enantiomers to any meaningful extent with respect to clinical application. The 90% CIs for the $AUC_{0-\infty}$ GMRs (warfarin + LRPT/warfarin) of R(+)- and S(−)-warfarin fell entirely within the predetermined comparability bounds of (0.80, 1.25), thus supporting the primary study hypothesis. With respect to the secondary hypothesis, the 90% CI for the C_{max} GMR of S(−)-warfarin fell within the prespecified bounds of (0.80, 1.25), whereas the calculated upper bound (ie, 1.26) of the 90% CI for the C_{max} GMR of R(+)-warfarin was slightly greater than 1.25. This minimal deviation in the upper bound of the prespecified limit is not likely to be clinically meaningful, considering the substantially reduced potency of the R(+) enantiomer relative to the S(−) enantiomer. Furthermore, there were no statistically significant differences in T_{max} for S(−)- and R(+)-warfarin between the 2 treatments. The apparent terminal $t_{1/2}$ values of S(−)- and R(+)-warfarin were also comparable. Because the total exposure to S(−)- and R(+)-warfarin was unchanged during coadministration of LRPT and warfarin, no clinically meaningful effects on blood coagulation were expected. However, any change in a drug therapy regimen where warfarin is being dosed warrants appropriate laboratory monitoring.

The potential effects of steady-state LRPT on the pharmacodynamics of single-dose warfarin was assessed in this study through the measurement of INR, a biomarker of the anticoagulant efficacy of warfarin.[26,27] No statistically significant or clinically important differences were detected in INR AUC_{0-168h} and INR_{max} between the 2 treatments. The estimated GMRs of INR AUC_{0-168h} and INR_{max} were 1.02 (0.99, 1.05) and 1.04 (0.98, 1.10), respectively. These findings are consistent with the expectation that small changes in plasma levels of warfarin based on the GMR and CIs are not likely to be associated with clinically meaningful effects associated with the pharmacodynamics of warfarin.

Concomitant administration of LRPT and warfarin was generally well tolerated in this population of healthy subjects. There were no instances of clinically significant bleeding or unusual changes in INR with either treatment. No subjects discontinued from this study due to adverse experiences. There were no clinically significant effects of LRPT 40 mg on blood chemistry tests (including alanine and aspartate aminotransferases), hematology parameters, vital signs, and ECG parameters. LRPT was associated with a greater incidence of gastrointestinal-related adverse experiences compared with warfarin alone. Overall, clinical adverse experiences associated with LRPT were generally mild, transient, and self-limited in nature.

This study demonstrated that LRPT 40 mg dosed to steady state had no clinically meaningful effect on the pharmacokinetics or pharmacodynamics of a 30-mg dose of racemic warfarin. However, as this was a single-dose study design, the potential pharmacokinetic and pharmacodynamic effects of chronic warfarin and LRPT coadministration are unknown. Although a single dose of warfarin 30 mg does not produce stable anticoagulant effects in vivo, this treatment has been shown to sufficiently elevate the INR value enabling the detection of clinically meaningful pharmacodynamic interactions.[38–40] In the present study, the mean INR_{max} value after single dose administration of warfarin 30 mg alone was within the clinically relevant range expected for anticoagulant therapy. Several published studies have successfully employed a similar single-dose warfarin/multiple-dose study paradigm to evaluate possible warfarin–drug interactions.[38,40–42] Furthermore, it has been demonstrated that the single-dose warfarin study paradigm yields findings similar to those obtained from a multiple-dose study design.[43] The single-dose study design has the advantage of allowing for the investigation of possible drug interactions while mitigating the safety risks associated with exposing healthy subjects to multiple doses of warfarin. Several studies have demonstrated the predictive value of the single-dose study paradigm in confirming the lack of pharmacokinetic/pharmacodynamic interactions after chronic warfarin in clinical practice.[38,39,44]

The results of the present study show that multiple-dose LRPT 40 mg, a potent and selective DP1 receptor antagonist, does not affect systemic exposure (ie,

$AUC_{0-\infty}$) to R(+)- or S(−)-warfarin or the anticoagulant effect of warfarin. A small increase in C_{max} of the less potent R(+) enantiomer was observed after coadministration of warfarin with LRPT, but this change is not likely to be clinically meaningful considering the lack of effect of LRPT on warfarin INR pharmacodynamics. Coadministration of multiple doses of LRPT 40 mg with a single oral dose of warfarin was generally well tolerated in this population of healthy male and female subjects. These results suggest that no dosage adjustment of warfarin is required when these drugs are concomitantly prescribed in clinical practice, but standard monitoring of INR should continue.

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