

Switching from rivaroxaban to warfarin: an open label pharmacodynamic study in healthy subjects

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Patients receiving rivaroxaban may require transitioning to vitamin K antagonists.
- It takes several days for vitamin K antagonists such as warfarin to achieve therapeutic anticoagulation.
- In the absence of a co-administration period between rivaroxaban and a vitamin K antagonist, patients may be under-coagulated and, therefore, at higher risk of thromboembolism.

WHAT THIS STUDY ADDS

- Healthy subjects can be transitioned from steady-state rivaroxaban to warfarin while maintaining therapeutic anticoagulation by employing a co-administration period.
- International normalized ratio measurements to guide warfarin dosing during co-administration should occur at the time of trough rivaroxaban concentration to minimize interference by rivaroxaban on the international normalized ratio.

AIMS

The primary objective was to explore the pharmacodynamic changes during transition from rivaroxaban to warfarin in healthy subjects. Safety, tolerability and pharmacokinetics were assessed as secondary objectives.

METHODS

An open label, non-randomized, sequential two period study. In treatment period 1 (TP1), subjects received rivaroxaban 20 mg once daily (5 days), followed by co-administration with a warfarin loading dose regimen of 5 or 10 mg (for the 10 mg regimen, the dose could be uptitrated to attain target international normalized ratio [INR] ≥ 2.0) once daily (2–4 days). When trough INR values ≥ 2.0 were attained, rivaroxaban was discontinued and warfarin treatment continued as monotherapy (INR 2.0–3.0). During treatment period 2, subjects received the same warfarin regimen as in TP1, but without rivaroxaban.

RESULTS

During co-administration, maximum INR and prothrombin time (PT) values were higher than with rivaroxaban or warfarin monotherapy. The mean maximum effect (E_{\max}) for INR after co-administration was 2.79–4.15 (mean PT E_{\max} 41.0–62.7 s), compared with 1.41–1.74 (mean PT E_{\max} 20.1–25.2 s) for warfarin alone. However, rivaroxaban had the smallest effect on INR at trough rivaroxaban concentrations. Neither rivaroxaban nor warfarin significantly affected maximum plasma concentrations of the other drug.

CONCLUSIONS

The combined pharmacodynamic effects during co-administration of rivaroxaban and warfarin were greater than additive, but the pharmacokinetics of both drugs were unaffected. Co-administration was well tolerated. When transitioning from rivaroxaban to warfarin, INR monitoring during co-administration should be performed at the trough rivaroxaban concentration to minimize the effect of rivaroxaban on INR.

Introduction

Rivaroxaban is an orally bioavailable, selective direct Factor Xa inhibitor that has been approved for several thromboembolic disorders including prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery, treatment of deep vein thrombosis and pulmonary embolism, prevention of deep vein thrombosis and pulmonary embolism recurrence, and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF) in both the European Union and the US [1, 2]. For patients receiving anticoagulant therapy, various clinical situations may arise in which it is necessary to transition from one type of anticoagulant to another, for example, from rivaroxaban to warfarin. When transitioning to and from warfarin, it is crucial that anticoagulation is adequately maintained, because warfarin has a narrow therapeutic index with a risk of bleeding if overdosed and a risk of thromboembolic events if administered at subtherapeutic concentrations.

To establish a safe transition paradigm, the general clinical pharmacology profile of the drugs involved in the transition should be considered. When transitioning from rivaroxaban to warfarin, it is important to take into account the half-life of rivaroxaban (5–9 h in young subjects and 11–13 h in elderly subjects) [1, 2] and both its plasma concentrations and its pharmacodynamic (PD) effects just prior to dosing (or the trough plasma concentration [C_{trough}]), as well as the delayed PD effects of warfarin (which lag behind warfarin's plasma concentration) [3]. In view of these characteristics, in particular the delayed PD effect of warfarin, it is believed that a period of rivaroxaban and warfarin co-administration is necessary to ensure adequate anticoagulation is maintained when transitioning between these two drugs [1, 2].

The therapeutic efficacy of warfarin requires physicians to measure the patient's international normalized ratio (INR) of the prothrombin time (PT) regularly during therapy. Therefore, this parameter should be monitored carefully during any transition [3]. However, because rivaroxaban has a direct effect on PT, and subsequently on INR, it is important to measure INR values near the end of the rivaroxaban dosing interval, when rivaroxaban plasma concentrations are lowest, and not during the time of peak concentrations, when the potential for a greater than additive effect on the INR is expected [1, 2].

Recently, the switch from warfarin to rivaroxaban has been investigated in healthy subjects [4]. The primary objective of the current study was to assess the PD changes during the transition from rivaroxaban to warfarin in healthy subjects, to mimic a potential clinical scenario in which such a transition would have to be undertaken in a patient. PD data (specifically PT and INR) were characterized during the transition phase when both drugs were co-administered. The pharmacokinetics

(PK), safety and tolerability were assessed as secondary objectives.

Methods

Subjects and study design

This was an open label, single centre, sequential two treatment period study performed in healthy subjects between 18 and 60 years of age with a body mass index between 18 and 30 kg m⁻² and body weight \geq 50 kg. Coagulation test results (INR, PT and activated partial thromboplastin time) recorded prior to the start of the study had to be within the normal ranges defined by the central laboratory analyzing the samples. Female subjects were not to be of child-bearing potential (post-menopausal with no spontaneous menses for at least 2 years or surgically sterile). In addition, all subjects were required to provide a blood sample for pharmacogenomic testing and have fewer than three of the variant *CYP2C9* and *VKORC1* gene alleles associated with increased warfarin sensitivity.

Subjects were excluded from the study if they had a history of, or current, clinically significant medical illness that could interfere with the interpretation of the study results; presence or history of disorders known to be associated with increased risk of bleeding (e.g. prior haemorrhage, haematologic disease, coagulation disorders, significant haemoptysis, excessive bruising); clinically significant abnormal values for haematology, clinical chemistry or urinalysis; clinically significant abnormal physical examination, vital signs or 12-lead electrocardiogram; concomitant use (\leq 2 weeks prior to the start of the study) of drugs that either influence the coagulation system or inhibit/induce cytochrome P450 (CYP) 3A4 or CYP2C9 metabolism or P-glycoprotein and ABCG2 (also known as BCRP) transport systems; or a positive test for drugs of abuse, or a history of drug or alcohol abuse within the previous 2 years.

The study consisted of a screening phase (approximately 28 days), followed by two open label treatment periods. The first treatment period (TP1) had a duration of approximately 14 days and the second treatment period (TP2) had a duration of approximately 8 days. The duration of both treatment periods varied from subject to subject because of the individual durations required for each subject to attain a trough INR \geq 2.0 (measured at trough rivaroxaban concentrations) during the co-administration phase of the study. A washout period of at least 14 days separated the two treatment periods. After TP2 and subsequent discharge from the study centre, subjects returned within 7 days for an end of study final assessment of safety and study discharge (Figure 1).

The study protocol and amendment (see the next section for further details) were reviewed by both an Independent Ethics Committee at the University Hospital at Antwerp, Belgium and the Belgium Health Authority

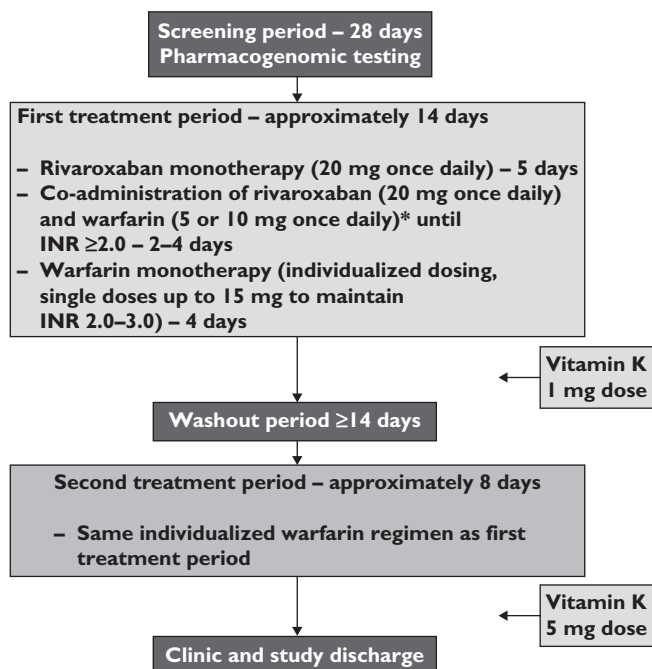


Figure 1

Study design. *Initially, subjects received warfarin 5 mg once daily during the first treatment period but because only a small proportion of subjects reached the trough INR ≥ 2.0 within the time frame allowed by the study (maximum of 4 days), the protocol was amended to allow all subsequent subjects to receive warfarin 10 mg once daily instead. INR, international normalized ratio

(Clinicaltrials.gov number: NCT01400646). Additionally, the study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and consistent with Good Clinical Practices. Subjects provided individual written consent for both the pharmacogenomic component and the general study after having been informed about the nature and purpose of the study, study conditions and the risks and benefits of treatment.

Study medication and conduct

Treatment period 1 Study drugs were administered in the morning, after a standardized meal. Subjects received rivaroxaban monotherapy 20 mg once daily for 5 days, followed by the co-administration of rivaroxaban 20 mg once daily and warfarin, given either as a loading dose regimen of 5 mg once daily (before protocol amendment) or 10 mg once daily (after protocol amendment, see below for further details), for 2–4 days. When trough INR values ≥ 2.0 were achieved during this co-administration phase, rivaroxaban was stopped and subjects continued to receive individualized warfarin maintenance doses as monotherapy (doses ranged up to 15 mg once daily), which was given for 4 days to maintain a trough INR within the range of 2.0–3.0 by at least the last day of warfarin monotherapy. To ensure that no subject was required to

undergo an unacceptable amount of blood sampling, those who did not reach a trough INR ≥ 2.0 within the 4 day co-administration phase of the study were discontinued from the study and were replaced by new subjects. A single oral 1 mg dose of vitamin K was given to each subject after TP1 in order to return coagulation parameters to normal levels.

Based on the initial design of the study, the first 17 subjects enrolled received a warfarin 5 mg once daily loading dose regimen during the co-administration phase of TP1. However, because only a small proportion of subjects reached the target trough INR ≥ 2.0 within the time frame allowed by the study (maximum of 4 days), the protocol was amended to treat all subsequent subjects with a warfarin 10 mg once daily loading dose regimen instead. For the warfarin 10 mg once daily loading dose regimen, the investigator could adjust the warfarin dose after the first 2 days of concomitant treatment (if needed) to ensure subjects reached the target INR.

Treatment period 2 During this treatment period, subjects received warfarin monotherapy, using the same loading and maintenance doses and regimens as in TP1 but without the 5 day rivaroxaban lead-in period, followed by a single oral 5 mg dose of vitamin K to return coagulation parameters to normal levels prior to their release from the study.

In both treatment periods, rivaroxaban and/or warfarin were administered immediately after a standardized breakfast that was to be consumed within a maximum of 30 min. The content of the meals consisted of food items that do not typically affect the PK or PD of warfarin (e.g. foods that are not high in vitamin K content). All drugs were swallowed whole and taken with 240 ml of non-carbonated water.

Study evaluations

Sample collection and bioanalytical procedures

Pharmacodynamics Blood samples (3 ml each) for the determination of PT and INR were collected during TP1 and TP2: pre-dose on days 6–12, serially at 2, 3, 4, 22 and 23 h post-dose on days 5 and 7 and at 2, 3 and 4 h post-dose on day 8. Plasma samples were then sent to the Clinical Laboratory ZNA Jan Palfijn (Antwerp, Belgium) and analyzed using a STAR Evolution analyzer (Stago, Roche) with STA Neoplastine R (Stago, Roche) as the reagent.

Pharmacokinetics Blood samples (1.2 ml each) for the determination of rivaroxaban plasma concentrations were collected during TP1 only, at the same time points as those for PD evaluations. Plasma samples were stored at -20°C until shipped and analyzed by the department of Drug Metabolism and Pharmacokinetics at Bayer Pharma AG (Wuppertal, Germany). Rivaroxaban concentration was determined in plasma after protein precipitation with

methanol (including an internal standard) followed by separation using high performance liquid chromatography and tandem mass spectrometric (LC/MS/MS) detection [5]. The calibration range of the procedure was between $0.500 \mu\text{g l}^{-1}$ (lower limit of quantification [LLOQ]) and $500 \mu\text{g l}^{-1}$ (upper limit of quantification). Mean inter-assay accuracy of back-calculated concentrations (except LLOQ) in calibrators ranged from 95.3% to 103.1%, and precision was $\leq 6.5\%$. Accuracy and precision at the lowest calibrator (LLOQ) were equal to 101.1% and 8.1%, respectively. Quality control samples in the concentration range from $1.35 \mu\text{g l}^{-1}$ to $398 \mu\text{g l}^{-1}$ were determined with an accuracy of 95.8–102.1%, and with precision of 3.8–4.4%.

Blood samples (2.6 ml each) for the determination of R- and S-warfarin plasma concentrations were collected during TP1 and TP2 at the same time points as those for PD evaluations. Plasma samples were stored at -20°C until shipped and analyzed by the Department of Bioanalysis at PPD Inc. (Richmond, VA, USA). R- and S-warfarin concentrations were determined using a validated LC/MS/MS method, with an analytical range of 5.0–1000 ng ml⁻¹. Mean inter-batch accuracy of R-warfarin ranged from 98.5% to 101.0% and precision ranged from 2.4% to 5.0%. Mean inter-batch accuracy of S-warfarin ranged from 98.9% to 101.0% and precision ranged from 2.9% to 6.7%.

Pharmacogenomic evaluations For subjects with a previously unknown genetic status for warfarin sensitivity, a single blood sample (10 ml) was collected for pharmacogenomic analysis prior to enrolment into the study. This mandatory pharmacogenomic component of the study allowed for the assessment of the subject's *CYP2C9* and *VKORC1* genetic status, to exclude from participation those individuals with three or more variant alleles within both genes. Blood samples were shipped to the Department of Neuroscience Biomarkers at Janssen Pharmaceuticals Research & Development (Raritan, NJ, USA). Each individual's DNA was isolated and both a composite genotype (a distillation of the detected modified alleles for a particular gene) and the predicted phenotype (the interpretation of the composite genotype, which may describe gene expression levels, enzymatic activity or drug metabolism) were determined.

Safety evaluations Safety and tolerability were evaluated continuously throughout the study in all subjects who received at least one dose of the study drug (rivaroxaban and/or warfarin) by monitoring the incidence of bleeding events and other treatment-emergent adverse events (TEAEs) and the results of laboratory tests (haematology, clinical chemistry, coagulation tests [PT, INR] and urinalysis), vital signs, electrocardiograms and physical examinations. Outcomes were analyzed descriptively and abnormalities in tests were listed.

Statistical methods

Statistical evaluations were performed using the SAS v9.1.3 software package (SAS Institute, Cary, NC, USA).

Pharmacodynamic evaluations PD parameters were calculated using WinNonlin® software (version 5.3, Pharsight Corporation, Sunnyvale, CA, USA). The parameters assessed were the maximum PD effect (E_{max}) after dosing for PT (PT E_{max}) and for INR (INR E_{max}). These were determined using absolute values. Mean values for PT and INR were plotted vs. time for each treatment. Absolute PT E_{max} and INR E_{max} values were summarized for each treatment and day of measurement. PT E_{max} and INR E_{max} were compared between similar days of the two treatment periods using descriptive statistics.

Pharmacokinetic evaluations Using the plasma concentration data obtained for rivaroxaban and R- and S-warfarin, the following PK parameters were determined for both study drugs via non-compartmental analysis using WinNonlin® software, maximum plasma concentration (C_{max}) and C_{trough} . Plasma C_{trough} was measured just prior to dosing of either drug.

Although both R- and S-warfarin PK parameters were determined, for the sake of brevity, only those for S-warfarin have been summarized in this manuscript. Plasma concentrations of rivaroxaban and warfarin were plotted vs. time for each treatment. The primary parameters of interest were C_{trough} and C_{max} , which were both summarized descriptively by day and treatment. The attainment of steady-state rivaroxaban concentrations was assessed through the visual inspection of the concentration–time plots.

Sample size determination Sample size was determined based on PD parameters as the primary objective of this study. Based on a previous rivaroxaban study [4], the inter-subject coefficient of variation (CV) for INR E_{max} after warfarin administration was estimated to be less than 20%. With an inter-subject CV of 20%, a sample size of 30 subjects was considered sufficient to estimate the mean INR and PT after warfarin administration to within 93% and 108% of the true value with 95% confidence. Additional patients were to be enrolled if the number of subjects completing the study dropped below 30.

Results

Forty-eight subjects were screened for the study, 46 of whom were enrolled. In total, 31/46 (67.4%) subjects completed the study, which was sufficient to meet the calculated required sample size. Among the 15 subjects who withdrew, three did so because of adverse events, 11 required more than 4 days of rivaroxaban and warfarin

Table 1

Demographic and baseline characteristics

Rivaroxaban + warfarin (n = 46)	
Age (years)	
Mean (SD)	47.7 (8.8)
Median	49
Minimum–maximum	24–60
Gender, n (%)	
Female	18 (39)
Male	28 (61)
Race, n (%)	
Black or African American	1 (2)
Caucasian	45 (98)
Weight (kg)	
Mean (SD)	75 (13.2)
Median	75
Minimum–maximum	51–114
Height (cm)	
Mean (SD)	171 (10.4)
Median	171
Minimum–maximum	150–198
Body mass index (kg m⁻²)	
Mean (SD)	26 (3.1)
Median	26.2
Minimum–maximum	18.2–30.2

SD, standard deviation.

concomitant therapy to reach a trough INR value ≥ 2.0 and one had a positive drug screen.

Demographic and baseline characteristics of subjects who received at least one dose of drug are shown in Table 1. Subjects had a median age of 49 (range 24–60) years, a mean baseline weight of approximately 75 kg, and a mean baseline body mass index of approximately 26 kg m⁻². The population comprised 61% men and 39% women.

Prior to the protocol amendment, 17 subjects were enrolled and received the 5 mg once daily warfarin loading dose regimen. Of these 17 subjects, 11 were discontinued for not having attained the target INR within 4 days. The remaining six subjects reached the target INR and completed both treatment periods. After the protocol amendment, 29 subjects were enrolled and received the 10 mg once daily warfarin loading dose regimen. Of these 29 subjects, three were discontinued owing to an adverse event and one was discontinued owing to a positive drug screen. Twenty-five subjects reached the target INR and completed both treatment periods. Because most of the enrolled subjects who received the warfarin 5 mg loading dose regimen did not complete the study (65%), only the PK and PD data from subjects who completed the study were included in the respective PK and PD analyses. After the protocol amendment, all subjects who had PK and/or PD samples collected, regardless of completion status, were included in the respective PK and PD analyses.

Pharmacodynamics

Effect on international normalized ratio Upon reaching steady-state in TP1, rivaroxaban monotherapy produced a mean INR E_{\max} of approximately 2.12. However, it had a minimal effect on INR at trough plasma concentrations because the mean trough INR was similar to the mean baseline INR value on day 0 (Figure 2A, B). With the addition of warfarin co-administration starting on day 6, INR at trough rivaroxaban concentrations and E_{\max} values both progressively increased. For both warfarin loading dose regimens that were given during this co-administration phase of TP1 (5 mg once daily and 10 mg once daily), mean INR E_{\max} values were higher during this phase than those observed with either agent alone (Table 2). During this phase, the mean absolute INR E_{\max} values ranged from 2.55 to 4.33 for subjects who received the warfarin 5 mg once daily loading dose regimen with rivaroxaban and from 2.79 to 4.20 for those who received the warfarin 10 mg once daily loading dose regimen with rivaroxaban (Table 2). When a target trough INR ≥ 2.0 was reached during this co-administration phase, rivaroxaban was discontinued. On the first day of the warfarin monotherapy phase (i.e. day 8), mean peak INR values were markedly decreased, whereas mean trough INR values were similar to the respective values on the last day of dosing in the co-administration phase. Mean INR levels were maintained in the therapeutic range of 2.0–3.0 for up to 24 h after the last dose of individualized warfarin monotherapy (Figure 2A, B).

For the 17 subjects who received the 5 mg warfarin loading dose regimen, 11 did not achieve the target INR within 4 days of rivaroxaban and warfarin co-administration and were consequently discontinued from the study. For the remaining six subjects who achieved the target INR (as shown in Table 3), two subjects attained the target INR by day 7.1 and the remaining four subjects attained the target INR by day 7.2. The mean warfarin doses required to maintain the target INR range (2.0–3.0) during the warfarin monotherapy phase of TP1 (days 8–11) were similar to the mean warfarin loading doses administered during the co-administration phase of TP1 (days 6–7.2).

For the 28 subjects who received the 10 mg warfarin loading dose regimen, nine subjects attained the target INR by day 7, 17 subjects attained the target INR by day 7.1, and the remaining two subjects attained the target INR by day 7.2 (Table 4). The mean warfarin doses required to maintain the target INR range (2.0–3.0) during the warfarin monotherapy phase of TP1 were 40–75% lower than the mean warfarin loading doses administered during the co-administration phase of TP1.

During TP2, in which subjects received the same warfarin loading dose regimen (5 or 10 mg once daily) as they received in TP1 but without co-administration of rivaroxaban, mean absolute peak and trough INR values observed during the first 4 days of warfarin dosing

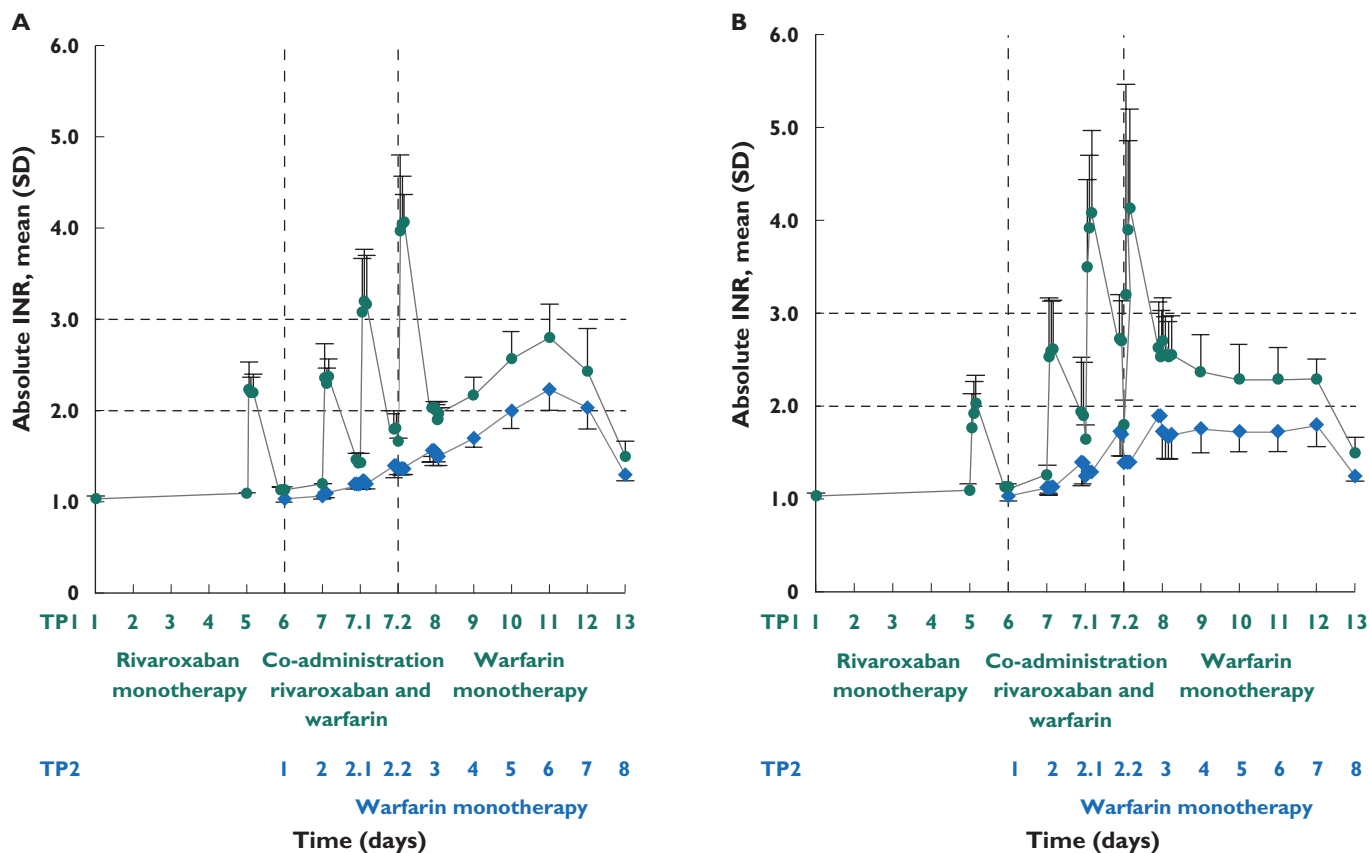


Figure 2

Mean (SD) international normalized ratio–time profile with (A) 5 mg and (B) 10 mg warfarin loading dose regimens during both treatment periods for subjects who completed both periods. Days 7.1 and 7.2 are repeats of day 7 sampling for subjects requiring additional days of rivaroxaban and warfarin co-administration to reach the required INR (part of the maximum 4 day co-administration phase) during TP1. Days 2.1 and 2.2 are the corresponding days during TP2. These are equivalent to days 7.1 and 7.2 TP1 but without the 5 day lead-in period of rivaroxaban dosing. INR, international normalized ratio; SD, standard deviation; TP1, treatment period 1; TP2, treatment period 2. ●, TP1; ◆, TP2

displayed a similar increasing trend to that observed in TP1 during the co-administration phase. However, mean peak INR values in TP2 were much lower than those in TP1 for both the 5 mg and 10 mg warfarin loading dose regimens. Mean trough INR values were slightly lower in TP2 than in TP1 for the 5 mg warfarin loading dose regimen, whereas a greater difference between TP1 and TP2 was observed for the 10 mg warfarin loading dose regimen (Figure 2A, B). For both peak and trough INR values, the difference in values between TP1 and TP2 became more pronounced with continued dosing during the co-administration phase. After completion of the co-administration phase, the differences in mean trough INR values between TP1 and the same corresponding times in TP2 were maintained until 24 h after the final warfarin maintenance dose. Mean trough INR was consistently lower in TP2, with only a few subjects reaching a trough INR value ≥ 2.0 by the end of treatment (Figure 2A, B).

Effect on prothrombin time In general, changes observed in mean absolute PT values over time followed a similar trend to those observed with INR (data not shown). Peak PT values after co-administration with warfarin were higher than those observed with either agent administered alone, with mean absolute E_{max} values ranging from 37.2 to 65.2 s for subjects receiving warfarin 5 mg once daily with rivaroxaban and from 41.0 to 63.5 s for those receiving warfarin 10 mg once daily with rivaroxaban. This is in comparison with a mean PT E_{max} of 30.9 s obtained with rivaroxaban monotherapy upon reaching steady-state (Table 2).

Pharmacokinetics

Visual inspection of pre-dose/trough plasma values taken from days 1–5 of TP1 showed that rivaroxaban reached steady-state by day 3.

Table 2Pharmacokinetic and pharmacodynamic parameters for rivaroxaban and S-warfarin alone and during co-administration ($n = 46$)

Treatment period and drug/regimen	Day	PD parameters, mean (SD)				PK parameters, mean (SD)		
		E_{\max} INR	E_{\max} PT		Rivaroxaban C_{\max}	Warfarin C_{\max}		
Treatment period 1 (TP1)								
Rivaroxaban 20 mg once daily monotherapy	5	2.12 (0.32)	30.9 (5.02)		294 (84.8)	N/A		
Rivaroxaban 20 mg once daily + warfarin* once daily		5 mg	10 mg	5 mg	10 mg	5 mg	10 mg	
		warfarin†	warfarin	warfarin†	warfarin	warfarin†	warfarin	
	7	2.55 (0.26)	2.79 (0.51)	37.2 (3.94)	41.0 (7.89)	291 (82.4)	365 (84.4)	759 (159)
	7.1‡	3.55 (0.52)	4.20 (0.90)	49.9 (8.32)	63.5 (14.4)	296 (99.4)	477 (138)	1055 (268)
	7.2‡	4.33 (0.54)	4.15 (1.06)	65.2 (8.41)	62.7 (17.3)	264 (103)	541 (262)	1070 (368)
Treatment period 2 (TP2)								
Warfarin* once daily monotherapy	2	1.22 (0.04)	1.41 (0.25)	17.0 (0.53)	20.1 (3.79)	N/A	392 (89.5)	781 (151)
	2.1‡	1.40 (0.11)	1.74 (0.27)	20.2 (1.42)	25.2 (4.06)	N/A	471 (122)	1072 (280)
	2.2‡	1.58 (0.10)	N/A	22.4 (1.49)	N/A	N/A	579 (238)	1110 (N/A)

All subjects, regardless of completion status, who had PK and/or PD samples collected were included in the respective PK and PD analyses. *S-warfarin. † $N = 6$ (only subjects who completed both TP1 and TP2). ‡Days 7.1 and 7.2 are repeats of day 7 sampling for subjects requiring additional days of rivaroxaban and warfarin co-administration to reach the required INR (part of the maximum 4 day co-administration phase) during TP1. Days 2.1 and 2.2 are the corresponding days during TP2. These are equivalent to days 7.1 and 7.2 in TP1 but without the 5 day lead-in period of rivaroxaban dosing. C_{\max} , maximum plasma concentration; E_{\max} , maximum PD effect after dosing; INR, international normalized ratio; N/A, not available; PD, pharmacodynamic; PK, pharmacokinetic; PT, prothrombin time; SD, standard deviation.

Table 3

Mean (standard deviation) warfarin doses (mg) during the co-administration of rivaroxaban and warfarin and warfarin monotherapy phases of treatment period 1 for subjects who received the 5 mg warfarin loading dose regimen and attained target international normalized ratio within 4 days

	Day 6	Co-administration phase TP1				Day 8	Warfarin monotherapy phase TP1		
		Day 7	Day 7.1	Day 7.2	Day 9		Day 10	Day 11	
Mean	5.00	5.00	5.00	5.00	4.67	4.83	5.00	3.33	
SD	0.00	0.00	0.00	0.00	0.52	0.41	0.00	2.58	
n^*	6	6	6	4	6	6	6	6	

*Results for the 11 subjects who did not attain target international normalized ratio within 4 days of the co-administration phase of TP1 are not reported. TP1, treatment period 1; SD, standard deviation.

Table 4

Mean (standard deviation) warfarin doses (mg) during the co-administration of rivaroxaban and warfarin and warfarin monotherapy phases of treatment period 1 for all subjects who received the 10 mg warfarin loading dose regimen

	Day 6	Co-administration phase TP1				Day 8	Warfarin monotherapy phase TP1		
		Day 7	Day 7.1	Day 7.2	Day 9		Day 10	Day 11	
Mean	10.0	10.0	12.9	15.0	3.79	4.67	5.52	6.00	
SD	0.00	0.00	2.54	0.00	2.57	2.42	2.29	2.60	
N^*	28	28	19	2	28	27	27	27	

*Of the 29 subjects who received the 10 mg warfarin loading dose regimen, one subject was discontinued after the two rivaroxaban doses and one subject was discontinued after one dose of warfarin monotherapy in TP1. TP1, treatment period 1; SD, standard deviation.

The mean plasma C_{\max} values of rivaroxaban and warfarin when administered alone were similar to those values during the co-administration phase. Mean C_{\max} values for rivaroxaban when administered with warfarin during the transition phase of TP1 ranged from 264 to 296 ng ml⁻¹, with values for CV ranging from

approximately 28% to 39%. These values were similar to the mean C_{\max} of 294 ng ml⁻¹ and CV of 29% obtained upon reaching steady-state with rivaroxaban monotherapy (Table 2).

Mean S-warfarin C_{\max} values obtained with the warfarin 10 mg loading dose regimen when co-administered with

rivaroxaban during the transition phase of TP1 increased gradually and ranged from 759 to 1070 ng ml⁻¹ (CV 21–34%). These values were similar to the mean S-warfarin C_{max} values that ranged from 781 to 1110 ng ml⁻¹ (CV 19–26%) obtained during warfarin monotherapy in TP2, using the same dose. A similar response was observed for mean S-warfarin C_{max} values with the warfarin 5 mg loading dose regimen between TP1 and TP2 (Table 2). R-warfarin concentrations followed similar trends to S-warfarin (data not shown).

Safety and tolerability

In total, 32 (69.6%) subjects reported at least one TEAE during the study. TEAEs were reported by 23 (50.0%) subjects during rivaroxaban monotherapy, 15 (33.3%) subjects during the rivaroxaban and warfarin combination therapy, and 19 (55.9%) subjects during warfarin monotherapy. The incidence of TEAEs with rivaroxaban monotherapy, rivaroxaban and warfarin combination therapy, and warfarin monotherapy is summarized in Table 5. The most commonly reported TEAEs were headache (32.6%), nasopharyngitis (15.2%) and muscle spasm (15.2%).

No significant bleeding events were observed, even in subjects with elevated INR values and no discontinuations occurred because of bleeding events. Three subjects withdrew from the study because of adverse events (headache, pyrexia and wound infection). Two patients withdrew during TP1 (co-administration of warfarin and rivaroxaban) and one patient withdrew during TP2 (warfarin monotherapy). All of these events resolved by the end of the study. No deaths, serious adverse events, clinically meaningful abnormalities or trends for adverse changes in clinical laboratory, vital signs or physical examinations were observed.

Discussion

Rivaroxaban does not exhibit some of the limitations associated with vitamin K antagonist treatment, such as slow onset of action, narrow therapeutic window, pharmacogenomic limitations, numerous drug and food interactions, and the need for regular coagulation monitoring and frequent dose adjustments [6–9]. However, in some clinical circumstances, patients receiving rivaroxaban therapy may need to be switched to vitamin K antagonists. Owing to the potential for patients to experience over- or under-coagulation when switching from one anticoagulant to another, this study was designed to mimic a potential clinical scenario in which patients needed to transition from rivaroxaban to warfarin. The PD (specifically PT and INR) results obtained from this study in healthy subjects may provide some guidance to physicians on how to administer both warfarin and rivaroxaban together safely during this transition phase.

The rivaroxaban dose selected for this study was 20 mg once daily, because it is the currently approved dose for stroke prevention in patients with AF who have either normal renal function or mild renal impairment [1, 2]. A reduced dose of 15 mg once daily is indicated in patients with AF and moderate or severe renal impairment as per the product label [1, 2]. The warfarin loading and maintenance dosing regimens used in this study were selected such that a target INR range of 2.0–3.0 would be achieved, which is the INR range recommended for the long-term anticoagulant treatment of stroke prevention in patients with AF [10].

Results from this study suggest that steady-state plasma concentrations for rivaroxaban were reached by day 3 of rivaroxaban monotherapy, and maximum concentrations obtained at steady-state were consistent with previously conducted clinical pharmacology studies [8, 11,

Table 5

Treatment-emergent adverse events with an incidence ≥5% by MedDRA dictionary-derived term in the safety population (N = 46)

	Rivaroxaban monotherapy (n = 46)	Rivaroxaban + warfarin (n = 45)	Warfarin monotherapy (n = 34)	Total (n = 46)
Subjects with TEAEs, n (%)	23 (50.0)	15 (33.3)	19 (55.9)	32 (69.6)
Headache	8 (17.4)	3 (6.7)	10 (29.4)	15 (32.6)
Nasopharyngitis	3 (6.5)	2 (4.4)	2 (5.9)	7 (15.2)
Muscle spasms	3 (6.5)	1 (2.2)	3 (8.8)	7 (15.2)
Dizziness	1 (2.2)	1 (2.2)	2 (5.9)	3 (6.5)
Back pain	2 (4.3)	1 (2.2)	1 (2.9)	3 (6.5)
Neck pain	0	1 (2.2)	2 (5.9)	3 (6.5)
Diarrhoea	0	0	3 (8.8)	3 (6.5)
Nausea	1 (2.2)	0	2 (5.9)	3 (6.5)
Epistaxis	1 (2.2)	0	2 (5.9)	3 (6.5)
Dry eye	0	1 (2.2)	2 (5.9)	3 (6.5)

TEAE, treatment-emergent adverse event.

12]. Importantly, the co-administration of rivaroxaban and warfarin during the transition phase of the study did not meaningfully alter the C_{\max} values for either drug. Similar results were observed in a previous drug–drug interaction study conducted with the two compounds, in which warfarin did not affect either the C_{\max} or the area under the concentration–time curve (AUC) of rivaroxaban, and rivaroxaban did not have an effect on the C_{\max} or AUC of either R- or S-warfarin (data on file).

When assessing the PD changes that occurred during the co-administration phase of the study in TP1, the observed peak PT and INR values were higher than those that occurred when either drug was administered alone. This was as expected, because both drugs affect PT and INR. Mean INR E_{\max} values ranged from 2.79 to 4.15, with individual maximum INR values reaching as high as 5.90 with a warfarin 10 mg loading dose regimen during this co-administration phase of 2–4 days. Also during this co-administration phase in TP1, trough INR values increased gradually but with a greater magnitude relative to warfarin alone as the target trough INR of ≥ 2.0 was approached. These higher peak and trough INR values during the co-administration phase reflect an effect of the combined mechanisms of action of these two compounds. Peak INR values displayed greater than additive increases with concomitant administration, but increases in trough INR values were not as marked. Additionally, it should be noted that although mean and individual INR E_{\max} values surpassed the typical therapeutic range of 2.0–3.0, these changes did not coincide with an increase in the number of adverse events or the occurrence of bleeding-related adverse events during this transition phase. Despite this, these results should be interpreted with caution because this study consisted of healthy, younger subjects and not older patients who may be more likely to incur higher INR values [2]. For this reason, it is important to monitor warfarin anticoagulation closely in accordance with the guidance from the prescribing information [3].

Unlike warfarin, rivaroxaban does not require routine coagulation monitoring or dose adjustment based on a PD target. Although PT can be a sensitive PD marker for rivaroxaban, results vary based on the assay reagent used. For this study, PT samples were analyzed using Neoplastine, a sensitive reagent that was used throughout the clinical development of rivaroxaban. The results observed in this study might have differed if other, less sensitive reagents had been used [1, 2]. Because the objective of this study was to explore PD changes during the transition from rivaroxaban to warfarin, both PT and INR were reported. For the purposes of PD monitoring, greater importance would be given to the INR value during the transition, because subjects would ultimately be transitioned to warfarin therapy. Although rivaroxaban also affects INR, the INR assay is not calibrated to assess the effect of rivaroxaban and thus should not be used specifically to monitor its PD effects.

The results obtained from this study support the premise that healthy subjects can be transitioned from steady-state rivaroxaban to warfarin while maintaining therapeutic anticoagulation. One of the key findings from this study to be considered when making a transition from rivaroxaban to warfarin is that rivaroxaban can affect a patient's INR. Therefore, during the co-administration period, proper timing of blood sampling for the INR is essential to ensure that the PD effects of warfarin can be measured accurately. This can be achieved by assessing a patient's INR at trough rivaroxaban concentrations, thereby minimizing the confounding influence of rivaroxaban on this PD parameter. Once a subject's INR is within the target therapeutic range, rivaroxaban treatment can be stopped and warfarin monotherapy continued to maintain an INR within therapeutic range [1, 2].

An interesting finding of this study occurred when subjects returned to the study clinic for TP2. Mean trough INR values were generally lower than those observed in TP1, although the same warfarin loading and maintenance dosing regimens were administered and subsequent plasma concentrations for both R- and S-warfarin were similar. Although an exact explanation for this reduced INR response in TP2 is not known, the following factors may have contributed to this result. It has been reported that a rebound effect may occur after warfarin treatment is discontinued [13]. After withdrawal of anticoagulants, changes in vitamin K-dependent procoagulant and anticoagulant factors occur during the first few days to weeks after discontinuation. For example, after withdrawal of warfarin therapy, levels of procoagulant Factor VII return to normal levels within 2 days and to even higher levels 1–2 weeks later [13]. Similarly, Grip *et al.* reported that Factor VII levels exceeded the normal range 4 days after withdrawal of warfarin and remained above the upper limit of normal for up to 14 days after discontinuing warfarin [14]. In the present study, elevated procoagulant levels during TP2 may have contributed to a lower INR response to warfarin than that seen in TP1. This was evident for both the 5 mg and 10 mg warfarin loading dose regimens, although the difference in mean trough INR values between TP1 and TP2 was more pronounced for the 10 mg warfarin loading dose regimen. Additionally, it is possible that the administration of vitamin K, a reversal agent for warfarin, at the end of TP1 and/or the intake of vitamin K through normal consumption of vitamin K-containing foods and supplements during the washout period (during which no dietary restrictions were imposed) may have contributed to the lower INR values observed in TP2. Although a 1 mg dose of vitamin K is less likely to induce warfarin resistance compared with higher doses and the consumption of vitamin K-containing foods and supplements during the washout period was variable between subjects, an influence of these factors cannot be ruled out entirely [7]. Although there is no confirmed explanation for the observed difference in mean

trough INR values between the two treatment periods, the results of this study demonstrated that therapeutic INR values could be attained within 3–4 days of rivaroxaban and warfarin co-administration and that, after rivaroxaban was discontinued, INR values could be maintained in the therapeutic range via routine warfarin maintenance dosing.

For subjects who received the 5 mg warfarin loading dose regimen, mean trough INR values during the warfarin monotherapy phase for both TP1 and TP2 continued to rise up to and including day 11. In contrast, mean trough INR values for subjects who received the 10 mg warfarin loading regimen remained flat from days 8–12 during the warfarin monotherapy phase of TP1 and TP2. As shown in Tables 3 and 4, the differences in mean trough INR profiles during the warfarin monotherapy phase for subjects who received the 5 mg and 10 mg loading dose regimens during the co-administration phase reflect differences in the maintenance warfarin doses required to maintain therapeutic INR values for each group of subjects during this phase.

Both the warfarin package insert [3] and treatment guidelines [15] recommend a warfarin starting dose of 5 mg, hence its selection as the initial loading dose regimen for this study. However, when the first cohort of 17 healthy adults received this loading dose regimen, most subjects did not achieve a target trough INR of ≥ 2.0 within the time frame of 4 days required by the study protocol. Therefore, the protocol was amended and all subsequent subjects were administered a warfarin 10 mg loading dose regimen from the start of the transition period. This loading dose could be increased at the discretion of the investigator to achieve the target therapeutic INR. Achievement of a trough INR of ≥ 2.0 within 4 days of concomitant therapy was a prerequisite of this trial because of the need to prevent excessive blood PD and PK sampling. Therefore, the above dosing paradigm may not reflect actual medical practice. Additionally, subjects who participated in the study were healthy adults who were screened for potential genetic susceptibility to the exaggerated pharmacological effects or metabolism of warfarin and may not reflect the typical AF patient population that might be older and not have a known *CYP2C9* or *VKORC1* phenotype when initiating warfarin therapy. Patients, especially those who are elderly, may also have other intrinsic factors that predispose them to higher warfarin concentrations.

Lastly, monotherapy with rivaroxaban or warfarin and the concomitant administration of both drugs were all well tolerated in this study, with no reports of clinically significant bleeding events or discontinuations owing to bleeding. These observations, combined with the outcomes from the study, should be interpreted with the caveat that they were obtained in a relatively small number of healthy subjects. Therefore, specific clinical advice for individual patients treated for conditions in which rivaroxaban is pre-

scribed cannot be directly extrapolated from the results of the present study. Nevertheless, the results from this study suggest that this transitioning paradigm may serve as a good basis for developing a more comprehensive and practical guide for transitioning patients from rivaroxaban to warfarin.

In conclusion, this study showed that the combined PD effects of rivaroxaban and warfarin were greater during a period of co-administration than they were during administration of either drug alone. Healthy adult subjects enrolled in this study (after being screened for variant gene alleles associated with increased warfarin sensitivity or decreased warfarin metabolism) could be transitioned from steady-state rivaroxaban to warfarin therapy, achieving a target therapeutic INR range of 2.0–3.0 within 2–4 days. These subjects could subsequently be maintained in the therapeutic range with routine warfarin maintenance dosing. The combined administration of rivaroxaban and warfarin was well tolerated. No excess of adverse events was observed during co-administration compared with monotherapy with either agent alone, and no clinically significant bleeding events were observed before, during or after the co-administration phase. Co-administration of rivaroxaban and warfarin did not meaningfully alter the PK of either drug. Although co-administration of rivaroxaban and warfarin increased the PD effect (increases in PT and INR values) at both peak and trough drug concentrations, changes in these PD parameters were smallest at rivaroxaban plasma trough concentrations. This indicates that the best time to assess a patient's INR for warfarin dose adjustment during co-administration with rivaroxaban would be approximately 24 h after the last dose of rivaroxaban (and before the next dose), when rivaroxaban has a minimal effect on the INR. This will ensure that INR values better reflect the PD effect of warfarin and guide continued individual warfarin dosing correctly.

Competing Interests

All authors are employees of Janssen Pharmaceuticals, with the exception of HS, who was an employee at the time of the study.

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