

Lack of a Pharmacokinetic and Pharmacodynamic Interaction between Dimebon (Latrepirdine) and Warfarin in Healthy Subjects

David R. Plowchalk¹, Ruolun Qiu¹, Steven G. Terra¹, Brian Corrigan¹, Jenny Fang¹, Terence Fullerton¹, Jing Liu¹, Wonkyung Byon¹, Joyce Mordenti²

¹Pfizer Global Research and Development, Groton, CT; ²Medivation, Inc., San Francisco, CA

BACKGROUND

- Dimebon (latrepirdine) is an orally available, small synthetic molecule that is in Phase 3 clinical development as a potential treatment for Alzheimer's disease (AD) and Huntington disease (HD). Dimebon 20 mg 3 times daily (TID) is the dosing regimen which has been used to date in published clinical trials for the treatment of patients with AD or HD.^{1,2}
- For medications likely to be used in older patients (such as treatments for AD), the Food and Drug Administration (FDA) recommends that drug-drug interaction studies are conducted with warfarin,³ because S-warfarin is a sensitive cytochrome P450 2C9 (CYP2C9) substrate with a narrow therapeutic range, which is widely prescribed to elderly patients for the treatment and prevention of thromboembolic events.^{4,5}
- A single 25-mg dose of warfarin was selected for this study as it represents a supra-therapeutic oral dose that was expected to be safe and to provide quantifiable pharmacokinetic (PK) and pharmacodynamic (PD) endpoints for the statistical analyses. Furthermore, this dose has been used in a previous PK and PD study for an AD therapy (donepezil),⁶ as well as other drug-drug interaction studies.^{7,8}
- The effects of dimebon on the clinical PK, PD, and safety of a CYP2C9-sensitive substrate, such as warfarin, are currently unknown. The aim of this Phase 1 study was to confirm the lack of clinically-important PK and PD interactions between dimebon and warfarin in healthy adults. The interactions were assessed at steady-state when CYP2C9 inhibition was expected to be maximal.

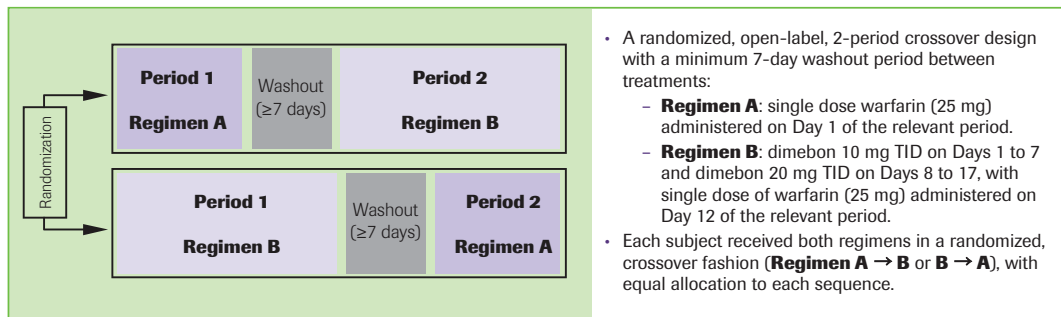
OBJECTIVES

- To demonstrate the lack of effect of steady-state dimebon 20 mg TID on the single-dose PK of warfarin 25 mg after co-administration in healthy adult subjects.
- To demonstrate the lack of effect of steady-state dimebon 20 mg TID on the single-dose PD of warfarin 25 mg after co-administration in healthy adult subjects.
- To evaluate the safety and tolerability of multiple doses of dimebon 20 mg TID in conjunction with a single dose of warfarin 25 mg in healthy adult subjects.

METHODS

Study Design

FIGURE 1 Study design depicting the dosing schedule



- A sample size of 12 subjects was required to provide at least 90% power to demonstrate the lack of an interaction for both PK and PD assessments.
- The study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization, and Good Clinical Practice Guidelines.

Subjects

- Healthy men or women (of non-child bearing potential), aged 18-55 years with a body mass index 18-30 kg/m² were eligible.
- Subjects were considered healthy if they had no clinically relevant abnormalities on physical examination, normal prothrombin time/International Normalized Ratio (INR) and partial thromboplastin time (PTT), and plasma Protein C and Protein S activity within a normal reference range.
- Subjects with a known sensitivity to either dimebon or warfarin were excluded.
- Other standard exclusion criteria were imposed, including presence of any clinically significant disease or condition likely to affect the properties of the drugs under investigation.

Assessments

Warfarin drug concentration measures

- For **Regimen A**, plasma PK samples were collected before dosing on Day 1 (blank) and at 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 hrs post-dose.
- For **Regimen B**, plasma PK samples were collected before dosing on Day 1 (blank) and on Day 12 at 0 (pre-dose) and 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 hrs post-dose.
- Warfarin plasma samples were assayed for S- and R-warfarin concentrations using a validated, sensitive, and specific HPLC-MS/MS method. The lower limit of quantification (LLOQ) was 2.5 ng/mL for both analytes.

Warfarin pharmacokinetic (PK) parameters

- PK parameters (**Table 1**) were calculated for warfarin from the concentration-time data on Day 1 (**Regimen A**) or Day 12 (**Regimen B**) of each treatment period, using standard non-compartmental methods.

TABLE 1 Warfarin pharmacokinetic parameters

Parameter	Definition	Method of determination
AUC _{inf} (ng-hr/mL)	Area under the S- and R-warfarin plasma concentration-time profiles from time 0 extrapolated to infinity	AUC _{max} + (C _{last} */k _e), where C _{last} * is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis, k _e as defined below
AUC _{last} (ng-hr/mL)	Area under the plasma concentration-time curve from T ₀ to time of the last quantifiable concentration	Linear/log trapezoidal method
C _{max} (ng/mL)	Maximum plasma concentration within the dosing interval on Day 14	Observed directly from data
T _{max} (hr)	Time for C _{max}	Observed directly from data as time of first occurrence
t _{1/2} (hr)	Terminal phase half-life	Log _e (2)/k _e , where k _e is the terminal phase rate constant calculated by linear regression of the log-linear concentration time curve

Warfarin pharmacodynamic (PD) assessments

- For **Regimen A**, plasma PD samples were collected prior to dosing on Day 1 (blank) and at 12, 24, 36, 48, 72, 96, 120, and 144 hrs post-dose.
- For **Regimen B**, plasma PD samples were collected prior to dosing on Day 1 (blank) and on Day 12 at 12, 24, 36, 48, 72, 96, 120, and 144 hrs post-dose. Nominal blood sampling times were used in the derivation of PD parameters.
- The primary warfarin PD parameter was the International Normalized Ratio (INR), calculated as follows:

$$INR = (PT_{test}/PT_{mean\ of\ the\ normal\ range})^{ISI}$$

- where PT is the prothrombin time, and ISI is the International Sensitivity Index for the thromboplastin used in the assay.
- The INR values in the presence and absence of dimebon were summarized to provide the maximum INR (INR_{max}) and the area under the INR-time curve (AUC-INR) over the 144-hr post-dose interval. The AUC-INR was calculated using the linear-trapezoidal method.

Safety and tolerability analyses

- Safety evaluations included monitoring of adverse events (AEs), vital signs, 12-lead ECGs, physical examination including blood pressure and pulse rate, and safety laboratory tests.
- A 3 mL blood sample was collected at Day 0 (Period 1 only) for pharmacogenomic analysis of vitamin K epoxide reductase complex, subunit 1 (VKORC1) and CYP2C9 metabolizer status.

Statistical Analyses

- Natural log transformed AUC_{inf} (if data permitted), AUC_{last}, and C_{max} for S-warfarin and R-warfarin were analyzed separately using a mixed effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect.
- Natural log transformed INR_{max} and AUC-INR were analyzed using the same mixed effects model specified for the PK parameters.
- Warfarin alone (**Regimen A**) was the Reference, and warfarin plus dimebon (**Regimen B**) was the Test treatment.
- For PK and PD parameters, estimates of adjusted mean differences (Test – Reference) and corresponding 90% confidence intervals (CIs) were obtained from the model, and were then exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.
- Lack of warfarin interaction was to be concluded if the 90% CI for all 6 endpoints (S- and R-warfarin AUC_{inf}, C_{max}, INR_{max}, and AUC-INR) were contained within 80% to 125%.
- Lack of CYP2C9 interaction was concluded if 90% CIs for S-warfarin AUC_{inf} and C_{max} was contained within 80% to 125%.

RESULTS

Subject Disposition

- Fourteen male subjects (aged 26–55 years) were assigned to treatment (**Table 2**). All subjects completed both **Regimens A** and **B** and were included in the PK, PD, and safety analyses.

TABLE 2 Demographic characteristics

Demographics	
Male, n (%)	14 (100%)
Age, years, mean ± SD	41.5 ± 8.0
Race*, n (%)	
white	6 (42.9%)
black	6 (42.9%)
other	2 (14.3%)
Body mass index, kg/m ² , mean ± SD (range)	26.9 ± 2.9 (21.9–30.4)
CYP2C9 extensive metabolizer, n (%)	14 (100%)
VKORC1 predicted phenotype, n (%)	
Heterozygous	3 (21.4%)
Homozygous variant	2 (14.3%)
Homozygous wild type	9 (64.3%)

*One participant was Latino/Hispanic and one bi-racial (black/white). VKORC1, vitamin K epoxide reductase complex, subunit 1; SD, standard deviation

Warfarin Pharmacokinetic Assessments

- When warfarin (25 mg) was administered in the presence of steady-state dimebon (20 mg TID) (**Regimen B**), median plasma S- and R-warfarin concentrations over the 144 hr sampling interval were similar to when warfarin was administered alone (**Regimen A**) (**Figure 2**).
- Plasma S- and R-warfarin C_{max} concentrations were achieved, on average, 2 to 4 hrs post-dose for both treatment regimens. Following attainment of C_{max}, plasma S- and R-warfarin concentrations declined with t_{1/2} of approximately 35 and 47 hrs, respectively, irrespective of dimebon treatment (**Table 3**).
- AUC_{inf}, AUC_{last}, and C_{max} estimates for S- and R-warfarin were similarly variable (as judged by coefficient of variation [CV]%) for both treatment regimens (**Table 3**).
- Based on the ratios of the adjusted geometric means (**Regimen B/A**), when warfarin was administered in the presence of steady-state dimebon, S- and R-warfarin AUC_{inf}, AUC_{last}, and C_{max} estimates were similar to the corresponding values when warfarin was administered alone (**Table 4**).
- The 90% CIs of the ratios for AUC_{inf}, AUC_{last}, and C_{max} for **Regimen A** and **B** were all contained within the acceptance range (80%, 125%) (**Table 4**).

FIGURE 2 Median (range) plasma warfarin concentration-time profiles for S-warfarin (Panel A) and R-warfarin (Panel B) for Regimen A (warfarin alone) or Regimen B (warfarin + dimebon)

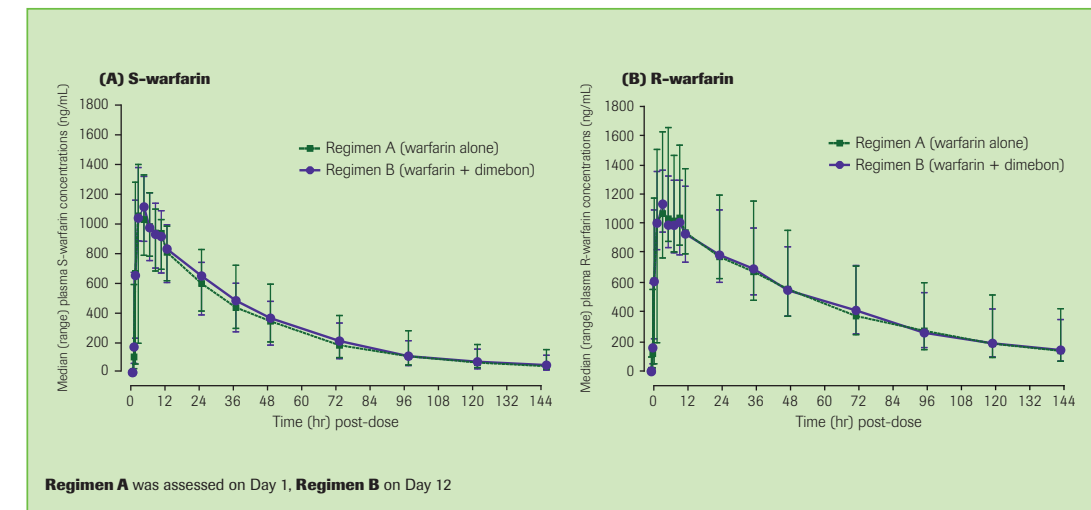


TABLE 3 Geometric mean* (coefficient of variation [CV] %) of plasma warfarin pharmacokinetic values

PK parameter (units)	Regimen A (warfarin alone) (N=14)	Regimen B (dimebon + warfarin) (N=14)
S-warfarin		
AUC _{inf} (ng-hr/mL)	45100 (26)	46700 (21)
AUC _{last} (ng-hr/mL)	42600 (22)	44300 (18)
C _{max} (ng/mL)	1130 (11)	1160 (9)
T _{max} (hr) median (range)	2.00 (1.0–6.0)	3.98 (1.0–4.0)
t _{1/2} (hr) arithmetic mean (SD)	34.7 (4.9)	34.4 (5.1)
R-warfarin		
AUC _{inf} (ng-hr/mL)	73700 (21)	72800 (16)
AUC _{last} (ng-hr/mL)	66700 (22)	67400 (20)
C _{max} (ng/mL)	1130 (13)	1150 (11)
T _{max} (hr) median (range)	4.0 (1.0–10.0)	4.0 (1.0–4.0)
t _{1/2} (hr) arithmetic mean (SD)	47.6 (6.6)	47.1 (7.2)

*Data are geometric mean (CV%) unless otherwise specified

TABLE 4 Summary of statistical analysis of plasma S- and R-warfarin exposure

Parameter (units)	Dimebon + warfarin (Test*)	Warfarin alone (Reference*)	Ratio (%) [†]	90% CI	
				Lower	Upper
S-warfarin					
AUC _{inf} (ng-hr/mL)	46748.14	45065.96	103.73	100.62	106.94
AUC _{last} (ng-hr/mL)	44308.11	42605.27	104.00	100.96	107.13
C _{max} (ng/mL)	1155.46	1125.67	102.65	98.49	106.98
R-warfarin					
AUC _{inf} (ng-hr/mL)	74796.50	73774.88	101.38	97.43	105.50
AUC _{last} (ng-hr/mL)	67422.79	66725.18	101.05	97.36	104.87
C _{max} (ng/mL)	1149.92	1129.67	101.79	98.60	105.09

* Adjusted geometric mean values. [†] Ratio of adjusted geometric means

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Warfarin Pharmacodynamic Assessments

- As expected, based on its mechanism of action, a single 25-mg dose of warfarin produced an increase in median INR when administered alone (**Regimen A**), and there was no change in the presence of steady-state dimebon (**Regimen B**) (**Figure 3**).
- AUC-INR and INR_{max} estimates were similarly variable (as judged by CV%) for both treatment regimens (**Table 5**).
- Based on the ratios of the adjusted geometric means (**Regimen B/A**), when warfarin was administered in the presence of steady-state dimebon, AUC-INR and INR_{max} estimates were similar to the corresponding values when warfarin was administered alone (**Table 6**).
- The 90% CIs of the ratios for AUC-INR and INR_{max} were within the acceptance range (80%, 125%) (**Table 6**).

FIGURE 3 Median (range) International Normalized Ratio (INR)-time profile for Regimen A (warfarin alone) or Regimen B (warfarin + dimebon)

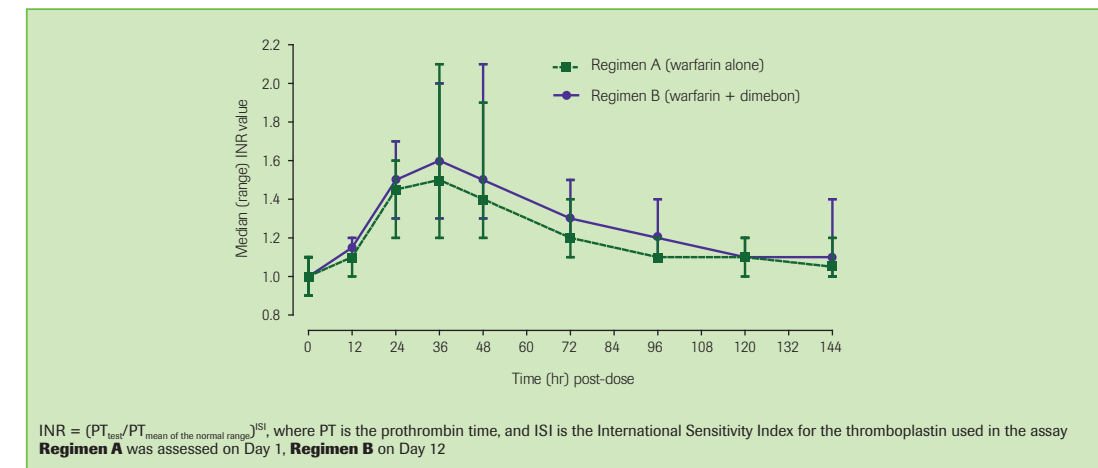


TABLE 5 Geometric mean (coefficient of variation %) of plasma warfarin pharmacodynamic values

Parameter	Regimen A (warfarin alone) (N=14)	Regimen B (dimebon + warfarin) (N=14)
AUC-INR	178 (7)	185 (5)
AUC _{max}	1.58 (19)	1.62 (13)

TABLE 6 Summary of statistical analysis of International Normalized Ratio (INR)

Parameter	Dimebon + warfarin (Test*)	Warfarin alone (Reference*)	Ratio (%) [†]	90% CI	
				Lower	Upper
AUC-INR	184.62	178.06	103.68	101.48	105.94
INR _{max}	1.62	1.58	102.62	98.61	106.79

* Adjusted geometric mean values. [†] Ratio of adjusted geometric means

Safety and Tolerability

- Co-administration of dimebon (20 mg TID) and warfarin (25 mg) was well tolerated in this trial. No subject discontinued due to AEs.
- Most AEs were mild in severity in both treatment regimens. None of the AEs were severe.
- Treatment-related AEs reported in > 1 participant included headache (3, **Regimen B**), fatigue (2, **Regimen A**; 1, **Regimen B**), and diarrhea (2, **Regimen B**).
- The incidence of laboratory abnormalities was comparable between treatments, and none were considered clinically significant.
- There were no clinically significant post-baseline values or changes from baseline in vital signs or ECG parameters observed in this study.

CONCLUSIONS

- Steady-state dimebon had no effect on the single-dose PK or PD of warfarin in healthy male adults, suggesting the two agents can be co-administered without warfarin dose adjustment.
- Multiple doses of dimebon in conjunction with warfarin were safe and well-tolerated in healthy male adults with no deaths, other serious or severe AEs, or discontinuations due to AEs.
- As S-warfarin is a substrate for CYP2C9, these results suggest dimebon is not an inhibitor of CYP2C9 and is not expected to cause drug-drug interactions with medications metabolized by CYP2C9.

DISCLOSURE Medivation Inc., and Pfizer Inc are developing dimebon (latrepirdine) for the treatment of AD and HD. All authors are employees of Medivation Inc., or Pfizer Inc.