No Pharmacokinetic Drug–Drug Interaction Between Prasugrel and Vorapaxar Following Multiple-Dose Administration in Healthy Volunteers

Matt S. Anderson, Teddy Kosoglou, Paul Statkevich, Jing Li, Jennifer Rotonda, Alan G. Meehan, and David L. Cutler

Abstract

Vorapaxar is a first-in-class antagonist of the protease-activated receptor-1, the primary thrombin receptor on human platelets, which mediates the downstream effects of thrombin in hemostasis and thrombosis. Prasugrel is a platelet inhibitor that acts as a P2Y12 receptor antagonist through an active metabolite, R-138727. This study investigated the interaction of these 2 platelet antagonists when coadministered. This was a randomized, open-label, multiple-dose study in 54 healthy volunteers consisting of a fixed-sequence crossover and a parallel group design. In sequence 1, 36 subjects received prasugrel 60 mg on day 1 and then prasugrel 10 mg once daily on days 2 to 7, followed by vorapaxar 40 mg and prasugrel 10 mg on day 8 and then vorapaxar 2.5 mg and prasugrel 10 mg orally once daily on days 9 to 28. In sequence 2, 18 subjects received vorapaxar 40 mg on day 1 and then vorapaxar 2.5 mg once daily on days 2 to 21. The geometric mean ratios (90% confidence intervals) for AUC\(\tau\) and C\(_{\text{max}}\) of coadministration/monotherapy for vorapaxar (0.93 ng·h/mL [0.85–1.02 ng·h/mL] and 0.95 ng/mL [0.86–1.05 ng/mL]) and R-138727 (0.91 ng·h/mL [0.85–0.99 ng·h/mL] and 1.02 ng/mL [0.89–1.17 ng/mL]) were within prespecified bounds, demonstrating the absence of a pharmacokinetic interaction between vorapaxar and prasugrel. There was no specific safety or tolerability risk associated with multiple-dose coadministration of vorapaxar and prasugrel. In conclusion, in this study in healthy volunteers, there was no pharmacokinetic drug–drug interaction between vorapaxar and prasugrel. Multiple-dose coadministration of the 2 drugs was generally well tolerated.

Keywords

vorapaxar, prasugrel, pharmacokinetics, drug–drug interaction, PAR-1, thrombin receptor antagonist

Vorapaxar sulfate (Zontivity®; hereafter referred to as vorapaxar) is a first-in-class antagonist of the protease-activated receptor-1, the primary thrombin receptor on human platelets, which mediates the downstream effects of thrombin in hemostasis and thrombosis. Thrombin-induced platelet activation has been implicated in a variety of cardiovascular disorders including thrombosis, atherosclerosis, and restenosis following percutaneous coronary intervention. Based on a large phase 3 placebo-controlled study conducted in 26,449 adult patients, the Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events trial, vorapaxar administered in addition to standard of care was approved to reduce the risk of thrombotic cardiovascular events in the United States and the European Union in patients with a history of myocardial infarction and in the United States also in patients with peripheral arterial disease.\(^1\)\(^,\)\(^2\)

When administered orally, vorapaxar shows high bioavailability (~100%), with peak concentration (C\(_{\text{max}}\)) occurring 1 hour postdose (range, 1 to 2 hours), and shows no meaningful food effect.\(^3\)\(^,\)\(^4\)

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Vorapaxar exhibits multiexponential disposition, with an effective half-life of 3–4 days and an apparent terminal elimination half-life of 8 days. Steady state is achieved by 21 days following once-daily dosing, with an accumulation of 5–6-fold. Vorapaxar is eliminated primarily through metabolism. Cytochrome P450 (CYP) 3A4 and CYP2J2 enzymes play important roles in the formation of M20, the circulating metabolite of vorapaxar, and M19, the predominant metabolite in excreta. M20 is an active metabolite with in vitro pharmacological activity similar to vorapaxar. M20 is highly bound to plasma proteins (99%) and is a major circulating plasma metabolite (~20% of total exposure to vorapaxar) when steady state for the parent drug is achieved. M20 exhibits formation-rate-limited pharmacokinetics such that the terminal phase of plasma concentration–time profiles largely parallel those of vorapaxar. A small percentage (approximately 10%–25%) of drug-related metabolites is excreted in urine.

Prasugrel inhibits platelet activation and aggregation through the irreversible binding of an active metabolite to the P2Y12 class of adenosine diphosphate receptors on platelets. As a prodrug, prasugrel is rapidly metabolized by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19 to the pharmacologically active metabolite (R-138727) and other inactive metabolites. R-138727 has an elimination half-life of approximately 7 hours. Absorption and metabolism of prasugrel are rapid, with peak plasma concentration (C\text{max}) of the active metabolite occurring approximately 30 minutes after dosing. Prasugrel may be administered without regard to food.

Given their complementary antithrombotic mechanisms of action, the potential exists that vorapaxar and prasugrel may be coadministered in patients with atherothrombotic disease. Although there was no a priori reason to expect a pharmacokinetic drug–drug interaction between these drugs based on neither drug having been reported to be a potent inhibitor or inducer of the pharmacologic activation (prasugrel) and/or clearance pathways of the other drug; nonetheless, a pharmacokinetic interaction could not be excluded because both drugs share a common clearance pathway in CYP3A4. Thus, the present study was conducted to assess the potential for a pharmacokinetic drug–drug interaction between the 2 drugs when coadministered at clinically relevant doses to steady state in healthy subjects.

**Methods**

The study protocol (P06560) was approved by Alpha Institutional Review Board (San Clemente, California). All subjects provided written informed consent prior to participating in the trial. The study was conducted in accordance with the guidelines on Good Clinical Practice and with the ethical standards for human experimentation established by the Declaration of Helsinki. This study was conducted at a single study center in the United States (Charles River Clinical Services Northwest, Inc. [now Comprehensive Clinical Development], Tacoma, Washington) between August 16, 2010, and November 2, 2010.

**Subjects**

Healthy men and women 18 to 55 years of age with a body weight of ≥60 kg and a body mass index of 18 to 32 kg/m² were eligible for enrollment. Women were of non-childbearing potential (surgically sterilized at least 3 months prior to baseline or postmenopausal for at least 1 year) or of childbearing potential and using a reliable birth control method such as double-barrier contraception for 3 months prior to the screening period. Additional entry criteria included clinically acceptable prestudy laboratory test results (complete blood cell count, serum chemistry, and urinalysis). Subjects were required to demonstrate normal or clinically acceptable physical examination and a 12-lead electrocardiogram (ECG) recording with a QTc value ≤430 milliseconds for men and ≤450 milliseconds for women at screening. Exclusion criteria included propensity to bleed, smoking, any surgical or medical intervention that might affect the pharmacokinetics of any drug, clinically significant allergy or intolerance to foods or drugs, and recent participation in an investigational drug study.

**Study Design**

This was a randomized, open-label, multiple-dose study consisting of a fixed-sequence crossover (to assess prasugrel pharmacokinetics) and a parallel-group design (to assess vorapaxar pharmacokinetics). The study design included multiple-dose administration of vorapaxar and prasugrel to achieve or maintain steady-state plasma concentrations. A parallel design was employed because of the long elimination half-life of vorapaxar of ~187 hours. On day 1, eligible subjects were randomized to 1 of 2 treatment sequences, sequence 1 or sequence 2. In sequence 1, subjects received a loading dose of prasugrel 60 mg on day 1, followed by prasugrel 10 mg once daily on days 2 to 7. Subjects received a loading dose of vorapaxar 40 mg plus prasugrel 10 mg on day 8, followed by vorapaxar 2.5 mg and prasugrel 10 mg orally once daily on days 9 to 28. In sequence 2, subjects received a loading dose of vorapaxar 40 mg on day 1, followed by vorapaxar 2.5 mg once daily on days 2 to 21. These multiple-dose regimens were selected to achieve C\text{max} and steady-state exposure (AUC) levels expected with vorapaxar.
and prasugrel in clinical practice. Treatments were administered once daily in the morning. On pharmacokinetic evaluation days (days 7 and 28 for subjects randomized to sequence 1, and day 21 for subjects randomized to sequence 2), treatment was given following at least an 8-hour fast, and subjects continued fasting for 4 hours postdose. On nonpharmacokinetic evaluation days, treatment was administered following at least an 8-hour fast, but subjects could eat breakfast approximately 2 hours after dosing. Meals (breakfast, lunch, dinner, and snacks) were of similar nutritional composition for all subjects/groups on confinement days and were provided at approximately the same time each day. Grapefruit and grapefruit juice were excluded from the diet because substances contained in these foods have been reported to inhibit CYP3A drug-metabolizing enzymes. When meal and blood draw times coincided, blood was drawn before the meal was provided. At approximately 22:00 hours on the evenings of study days preceding full pharmacokinetic evaluation days, subjects were to have a light snack (sandwich, piece of fruit, noncaffeinated beverage), after which an overnight fast was initiated. Following an overnight fast of at least 8 hours, subjects were administered study medication with 240 mL (8 fluid ounces) of noncarbonated water. Except as required for study procedures, subjects were to remain semi-recumbent until 4 hours postdose.

**Pharmacokinetic Assessments and Analytic Methods**

Blood samples for vorapaxar pharmacokinetic evaluation in subjects assigned to treatment sequence 1 were obtained at predose (0 hour) on days 1 and 28 and 0.5, 1, 1.5, 2, 3, 4, 6, 12, and 24 hours postdose on day 28. Blood samples for vorapaxar pharmacokinetic evaluation in subjects assigned to treatment sequence 2 were obtained predose (0 hour) on days 1 and 21 and 0.5, 1, 1.5, 2, 3, 4, 6, 12, and 24 hours after the last dose on day 21. Blood samples for prasugrel’s active metabolite (R-138727) pharmacokinetic evaluation were also obtained from subjects assigned to treatment sequence 1 at predose (0 hour) on days 1, 7, and 28 and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose. The following pharmacokinetic parameters were determined for vorapaxar, M20, and R-138727 from their plasma concentration data: AUCτ, area under the plasma concentration–time curve during a dosing interval (0 to 24 hours); Cmax, maximum observed plasma concentration; Tmax, time of maximum observed plasma concentration; CL/F, apparent total body clearance; and metabolite-to-parent (M/P) ratio, based on the AUCτ ratio for the M20 metabolite to unchanged (parent) vorapaxar (ie, AUCτ metabolite/AUCτ parent).

Plasma concentrations of vorapaxar and its M20 metabolite were measured using previously described methods.8 Plasma concentrations of R-138727 were also determined using previously described methods.9

**Safety Assessments**

The safety and tolerability of study medication were assessed by clinical evaluation of adverse events (AEs) and inspection of other safety parameters, including physical examination, vital sign measurement, 12-lead ECG, and routine laboratory safety tests (hematology, blood chemistry, and urinalysis). AEs were monitored throughout the study and evaluated in terms of intensity (mild, moderate, or severe), duration, severity, outcome, and relationship to study drug.

**Statistical Analysis**

The primary pharmacokinetic parameters were AUCτ and Cmax. AUCτ was determined by noncompartmental pharmacokinetic analyses. Cmax was determined from observed values. The log-transformed Cmax and AUCτ for vorapaxar were analyzed using a linear mixed-effects model extracting the effect of treatment. The geometric mean ratio (GMR; expressed as a percentage) and the 90% confidence interval (CI) of the Cmax and AUCτ for vorapaxar for sequence 1, day 28 (vorapaxar + prasugrel) compared with sequence 2, day 21 (vorapaxar alone) were determined. The log-transformed Cmax and AUCτ for R-138727 were analyzed using an analysis of variance model extracting the effect of treatment (fixed effect) and subject (random effect). The GMR and the 90%CI of the Cmax and AUCτ for R-138727 compared with sequence 1, day 7 (prasugrel alone) were determined. The log-transformed AUCτ for the M20 metabolite was also analyzed using a linear mixed-effects model extracting the effect of treatment. The GMR and 90%CI of the AUCτ for M20 for sequence 1, day 28 (vorapaxar + prasugrel) compared with sequence 2, day 21 (vorapaxar alone) were determined. The limits of pharmacokinetic change for vorapaxar were set to 2-fold, consistent with the effects of a strong CYP3A inhibitor on vorapaxar pharmacokinetics (PK).8 More conservative bounds were selected for prasugrel to limit the potential for meaningful change. Thus, if the 90%CIs for the GMRs for vorapaxar fell within the prespecified bounds of 0.50–2.00 and the 90%CIs for the GMRs for R-138727 fell within the prespecified bounds of 0.70–1.43, then no clinically meaningful pharmacokinetic drug–drug interaction was to be claimed between vorapaxar and prasugrel.

The total target sample size was 54 subjects. Approximately 36 subjects were to be randomized to sequence 1 to ensure that approximately 32 subjects completed the sequence, and approximately 18 subjects were to be
randomized to sequence 2 to ensure that approximately 16 completed the sequence. Assuming the true GMR was 1.00 for all 4 primary end points, with a sample size of 32 and 16 in the vorapaxar + prasugrel group compared with the vorapaxar-alone group, respectively, there was a >99% probability that the 90%CI of the GMR fell within 0.50–2.00 for either the $C_{\text{max}}$ or $\text{AUC}_\tau$ of vorapaxar. With the same assumption about the GMRs and a sample size of 32 in the vorapaxar + prasugrel group compared with the prasugrel-alone group, power was 92% and >99% that the 90%CI of the GMR fell within 0.70–1.43 for the $C_{\text{max}}$ and $\text{AUC}_\tau$ of prasugrel, respectively. Assuming a 0.5 correlation between $C_{\text{max}}$ and $\text{AUC}_\tau$ for both vorapaxar and the prasugrel active metabolite, R-138727, and assuming that the PK parameters between vorapaxar and R-138727 were independent, the overall power of this study to demonstrate that the 90%CIs for the GMRs for $C_{\text{max}}$ and $\text{AUC}_\tau$ were contained within the prespecified bounds of 0.50–2.00 for vorapaxar and 0.70–1.43 for R-138727 was at least 90%.

Results

Demographics and Baseline Characteristics
A total of 54 adult subjects, 37 men (68%) and 17 women (31%), with a mean age of 32 years (range, 19–55 years) and a mean body mass index of 26.8 kg/m² (range, 20.1–31.8 kg/m²) were enrolled in the study (36 subjects in sequence 1 and 18 subjects in sequence 2). Of the 54 subjects, 32 (59%) were white, 19 (35%) were black or African American, 2 (3%) were multiracial, and 1 (1%) was American Indian or Alaskan Native.

Of the 36 subjects who were enrolled in sequence 1, 33 completed the study, and 3 were discontinued because of noncompliance with the protocol. Of the 18 subjects who were enrolled in sequence 2, 16 completed the study, and 2 were discontinued because of noncompliance with the protocol.

Pharmacokinetics

R-138727, Active Metabolite of Prasugrel. The R-138727 mean plasma concentration–time profile and pharmacokinetic parameters are presented in Figure 1 and Table 1, respectively. After once-daily oral doses of prasugrel (with and without vorapaxar), median time of the last quantifiable samples for R-138727 was 8 hours after the last dose of prasugrel. There was no accumulation of R-138727, with predose plasma concentrations being below the limit of quantification for all subjects treated with prasugrel. The GMR and corresponding 90%CI of [(vorapaxar + prasugrel)/(prasugrel alone)] for R-138727 $\text{AUC}_\tau$ and $C_{\text{max}}$ were 0.91 (0.85–0.99) and 1.02 (0.89–1.17), respectively (Table 2).
Table 1. R-138727, Vorapaxar, and M20 Pharmacokinetic Parameters Following Multiple-Dose Oral Administration of Prasugrel Alone, Vorapaxar Alone, or Concomitant Administration of Prasugrel and Vorapaxar to Healthy Adult Subjects

| Analyte | Treatment               | n  | Cmax (ng/mL) | Tmax (h) | AUC<sub>τ</sub> (ng·h/mL) | CL/F (L/h) | M/P Ratio |
|---------|-------------------------|----|--------------|----------|---------------------------|------------|-----------|
| R-138727| Prasugrel alone         | 35 | 51.4 (43)    | 0.5 (0.25–1) | 52.1 (32)                | –          | –         |
|         | Vorapaxar + prasugrel   | 33 | 51.6 (42)    | 0.5 (0.25–1) | 48.2 (34)                | –          | –         |
| Vorapaxar| Vorapaxar alone         | 16 | 75.9 (21)    | 1.5 (0.5–4)  | 1300 (20)               | 1.68 (23)  | –         |
|         | Vorapaxar + prasugrel   | 33 | 71.6 (17)    | 1.0 (0.5–3)  | 1200 (15)               | 1.77 (15)  | –         |
| M20     | Vorapaxar alone         | 16 | 7.48 (47)    | 3 (0.0–24.0) | 151 (50)                | –          | 12 (51)   |
|         | Vorapaxar + prasugrel   | 33 | 7.49 (55)    | 3 (0.9–24.0) | 153 (55)                | –          | 13 (49)   |

Data are expressed as mean (% coefficient of variation), except for T<sub>max</sub>, which is expressed as median (range). AUC<sub>τ</sub>, area under the concentration–time curve during a dosing interval; Cmax, maximum observed concentration; T<sub>max</sub>, time of maximum observed concentration; CL/F, apparent total body clearance; M/P ratio, metabolite-to-parent ratio (AUC<sub>τ</sub> [metabolite]/AUC<sub>τ</sub> [parent]).

Table 2. Statistical Comparisons of Plasma Pharmacokinetic Parameters for R-138727 and Vorapaxar Following Administration of Prasugrel Alone, Vorapaxar Alone, and Prasugrel With Vorapaxar to Healthy Adult Subjects

| Analyte | Pharmacokinetic Parameter | n     | GM (95%CI) | n     | GM (95%CI) | GMR (90%CI) | rmSE<sup>b</sup> |
|---------|---------------------------|-------|------------|-------|------------|-------------|-----------------|
| R-138727| AUC<sub>τ</sub> (ng·h/mL)<sup>a</sup> | 33    | 45.2 (40.2–50.8) | 35    | 49.4 (44.0–55.5) | 0.91 (0.85–0.99) | 0.185           |
|         | C<sub>max</sub> (ng/mL)<sup>a</sup> | 33    | 47.3 (40.4–55.3) | 35    | 46.2 (39.6–53.8) | 1.02 (0.89–1.17) | 0.327           |
| Vorapaxar| AUC<sub>τ</sub> (ng·h/mL)<sup>a</sup> | 33    | 1190 (1120–1265) | 16    | 1274 (1167–1391) | 0.93 (0.85–1.02) | 0.174           |
|         | C<sub>max</sub> (ng/mL)<sup>a</sup> | 33    | 70.6 (66.1–75.5) | 16    | 74.3 (67.5–81.8) | 0.95 (0.86–1.05) | 0.190           |

GM, geometric mean; GMR, geometric mean ratio; CI, confidence interval.
<sup>a</sup>Back-transformed least-squares mean and confidence interval from mixed-effects model performed on natural log-transformed values.
<sup>b</sup>rmSE, square root of conditional mean squared error (residual error) from the linear fixed-effects model. rmSE × 100% approximates the between-subject %CV on the raw scale.

administered alone and vorapaxar coadministered with prasugrel, respectively (Table 3).

Safety and Tolerability
There were no deaths or serious AEs. No clinically significant changes in blood chemistry or hematological parameters, vital signs, or ECGs occurred in any treatment group. A total of 45 subjects (83%) reported at least 1 treatment-emergent AE during the study: 33 of the 36 subjects (92%) in sequence 1 and 12 of the 18 subjects (67%) in sequence 2.

The most common AEs in sequence 1 were ecchymosis (16 of 36, 44%), nausea (5 of 36, 14%), myalgia (4 of 36, 11%), headache (4 of 36, 11%), and occult blood (4 of 36, 11%). All reported AEs were considered by the investigator to be of mild intensity except 8, which were of moderate intensity. Of the 8 AEs of moderate intensity, 5 were considered by the investigator to be drug related (ecchymosis, nausea, vomiting, fatigue, and dysmenorrhea), and 3 (musculoskeletal chest pain, headache, and dysmenorrhea) were considered unlikely related to treatment.

The most common AEs in sequence 2 were headache (4 of 18, 22%) and occult blood (3 of 18, 17%). All reported AEs were considered by the investigator to be of mild intensity except 2 (abdominal pain and dyspepsia), both of which were of moderate intensity and considered possibly related to treatment.

Discussion
The current study evaluated the safety, tolerability, and plasma pharmacokinetics of vorapaxar and prasugrel coadministration in healthy men and women. Such exposure may have important safety and/or efficacy implications, as CYP3A4 is involved in the metabolism of both drugs. Multiple-dose administration of vorapaxar and prasugrel was employed to achieve or maintain steady-state plasma concentrations. A vorapaxar loading dose of 40 mg followed by a maintenance dose of 2.5 mg was used to simulate the loading/maintenance dose regimen used in 1 of the 2 pivotal phase 3 trials evaluating the drug’s use for acute coronary syndromes. A parallel study design was employed because of the long (~187 hours) terminal
elimination half-life of vorapaxar. The selected 60-mg prasugrel loading dose is consistent with Effient labeling and clinical practice.

No clinically relevant pharmacokinetic or emergent safety interaction was observed in this study in healthy men and women, as the 90% CIs for the GMRs of coadministration/monotherapy for vorapaxar and R-138727 AUC_τ and C_{max} were contained not only within the prespecified ranges but also within bioequivalence acceptance criteria (0.80–1.25). This was expected because neither vorapaxar nor prasugrel was known to be a potent inhibitor or inducer of the pharmacological activation and/or clearance pathways of the other drug. Although both drugs share a common CYP3A4 clearance pathway, this mechanism did not appear to cause

**Table 3.** Geometric Mean and Geometric Mean Ratio and 90% CI of M20 AUC_τ and Vorapaxar AUC_τ After Administration of Vorapaxar With Prasugrel Compared With Vorapaxar Alone in Healthy Adult Subjects

| Treatment          | Analyte | n  | LS GM (90% CI) AUC_τ, ng·h/mL | %GMR M20/Vorapaxar Ratio (90% CI) |
|--------------------|---------|----|-------------------------------|-----------------------------------|
| Vorapaxar + Prasugrel | M20     | 33 | 133.2 (118.3–150.1)           | 11.2 (9.6–13.1)                   |
| Vorapaxar alone    | M20     | 16 | 1190 (1057–1341)              |                                    |
|                    | Vorapaxar | 16 | 136 (117–159)                 | 10.7 (8.9–12.9)                   |

LS GM, least-squares geometric mean; CI, confidence interval; GMR, geometric mean ratio.

*aModel-based least-squares geometric mean and 90% CI AUC_τ based on mixed-effects model extracting the effect from analyte as fixed effect and subject as random effect.
a meaningful change in exposure with either drug when prasugrel and vorapaxar were coadministered.

The safety profile of vorapaxar when coadministered with prasugrel was similar to that of the vorapaxar-alone group. Of particular note, despite multiple venipunctures for blood sample collections, no evidence of increased bleeding was observed in any treatment group, including the group receiving both vorapaxar and prasugrel. Results from laboratory tests and measurements of vital signs did not indicate any adverse effect of multiple-dose vorapaxar when administered alone or in combination with prasugrel.

The present study has some limitations that warrant caution regarding interpreting the results in relation to their applicability to the target patient populations in the clinical setting. This study was conducted in predominantly young (mean age, 32 years) healthy volunteers who were not treated with other concomitant antiplatelet medications typical of the target patient populations. Although vorapaxar itself does not prolong bleeding time,4,12,13 and mean plasma vorapaxar concentrations were not significantly affected by coadministration of prasugrel, it cannot be assumed that bleeding liability is not increased in a setting of coadministered antiplatelet drugs in view of the safety results from the vorapaxar phase 3 clinical trials.1,2

Conclusions

In the present study in healthy volunteers, there was no pharmacokinetic drug–drug interaction between vorapaxar and prasugrel. The 90% CIs of coadministration/monotherapy GMRs for vorapaxar and prasugrel's active metabolite, R-138727, AUCr and Cmax were contained within bioequivalence acceptance bounds (0.80–1.25) indicating that no significant effect on exposure to either vorapaxar or prasugrel had occurred with coadministration of the 2 drugs. There was no identifiable, specific safety or tolerability risk or concern associated with multiple-dose coadministration of vorapaxar and prasugrel.1,2

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Declaration of Conflicting Interests

M.S.A., T.K., P.S., J.L., J.R., A.G.M., and D.L.C. are or were employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, and may own stock and/or hold stock options in the company.

Disclosures

M.S.A., T.K., P.S., J.L., J.R., A.G.M., and D.L.C. are responsible for the work described in this article. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, and interpretation of data in addition to drafting the manuscript and/or revising/reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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