





BRIEF REPORT

Rivaroxaban thromboprophylaxis for gastric/gastroesophageal junction tumors versus other tumors: A post hoc analysis of the randomized CASSINI trial

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Abstract

Background: Prophylactic anticoagulation with rivaroxaban significantly reduced the risk of cancer-associated thrombosis during the intervention period in the CASSINI trial. Direct oral anticoagulants may increase the risk of gastrointestinal (GI) tract bleeding in patients with an in situ GI tract cancer or lesion.

Objective: This post hoc analysis characterized the efficacy and safety of rivaroxaban in patients with and without gastric/gastroesophageal junction (G/GEJ) tumors.

Methods: Primary and secondary efficacy end points and adjudicated bleeding events, including bleeding sites, were analyzed for the intent-to-treat population by cancer type (G/GEJ vs non-G/GEJ) for the 180-day observation period.

Results: In patients with G/GEJ tumors, the rates for the primary efficacy end point were 3.4% for rivaroxaban versus 6.9% for placebo (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.11-1.80). In patients with non-G/GEJ tumors, the rivaroxaban group had a lower risk of the primary end point (6.6% vs 9.3%; HR, 0.70; 95% CI, 0.40-1.21). Rates of major bleeding in patients with G/GEJ tumors were 4.6% (4/88) versus 1.2% (1/85) for rivaroxaban and placebo; rates in patients with non-G/GEJ tumors were 1.3% (4/317) versus 0.9% (3/319), respectively.

Conclusions: Excluding patients with G/GEJ tumors resulted in a definable population of cancer patients who achieved an improved benefit-risk balance from rivaroxaban prophylaxis.

KEYWORDS

anticoagulants, cancer, gastric, gastroesophageal junction, prophylaxis, rivaroxaban, thrombosis, venous thromboembolism

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Essentials

- Patients with cancer have an increased risk of thrombosis, and bleeding risk may vary by cancer type.
- This post hoc analysis assessed rivaroxaban in patients with and without gastric cancer.
- Rivaroxaban reduced the risk of thrombosis in both patients with and patients without gastric cancer.
- Bleeding risk was increased in patients with gastric cancer but not those with other cancers.

1 | INTRODUCTION

Venous thromboembolism (VTE) is a major cause of morbidity and mortality among patients with cancer.¹ The standard of care has been to treat cancer-associated venous thromboembolism (CAT) with anticoagulation using a low-molecular-weight heparin (LMWH) or a direct oral anticoagulant (DOAC).²⁻⁶ The CASSINI (Efficacy and Safety of Rivaroxaban Compared With Placebo in Ambulatory Cancer Patients Initiating Systemic Cancer Therapy and at High Risk for Venous Thromboembolism) trial evaluated the role of rivaroxaban prophylaxis in the primary prevention of VTE among patients with a Khorana score ≥ 2 .⁷ The study demonstrated a significant reduction of CAT for rivaroxaban compared with placebo during the intervention period. Furthermore, the safety profile was favorable, with a nonsignificant 1.0% increase of major bleeding while on the drug.

The Hokusai VTE Cancer study compared the DOAC edoxaban with the LMWH dalteparin for treatment of CAT and demonstrated noninferiority of the combined end point of recurrent thrombosis and major bleeding.³ Of note, in that study, there was a trend toward improved efficacy but at a trade-off of increased major bleeding, particularly in the gastrointestinal (GI) and genitourinary (GU) tracts.³ With further analysis, it was indicated that the increased major bleeding was largely in the subset of patients with GI bleeding in conjunction with GI cancers.^{3,8}

SELECT-D (Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism) was a similar study that compared the DOAC rivaroxaban with dalteparin for treatment of CAT.⁴ The SELECT-D study also showed a trend toward improved efficacy and increased major bleeding with the DOAC. The data safety monitoring committee of the study observed a nonsignificant increase in major bleeding in the rivaroxaban treatment arm among 19 patients with cancer of the esophagus or gastroesophageal junction and subsequently excluded these cancers from further enrollment.⁴ Based on the findings of the Hokusai VTE Cancer and SELECT-D studies, as well as other reports,⁹ cancer treatment guidelines caution against the use of DOACs in patients with active GI or GU cancers or other luminal lesions.^{5,10}

The purpose of targeting an intervention to patients with a Khorana score ≥ 2 is to improve the benefit of intervention. Similarly, stratifying patients by bleeding risk on prophylactic anticoagulation may allow for further improvement in the number needed to harm for primary prophylaxis. Thus, we analyzed efficacy and bleeding events from the CASSINI trial in cohorts of patients with and without gastric or gastroesophageal junction (G/GEJ) tumors to potentially define a patient population that could obtain clinical benefit from VTE prophylaxis with rivaroxaban but for which the risk of clinically important bleeding could be further reduced.

2 | METHODS

The methods and results of the CASSINI trial have previously been published.^{7,11} The study was performed in accordance with the Declaration of Helsinki and local regulations. The protocol was approved by institutional review boards at each study site. For this post hoc analysis, patients were categorized as those with either primary G/GEJ tumors or other sites of primary malignancy (non-G/GEJ tumors). We evaluated efficacy and safety end points in these subgroups consistent with definitions used in the main trial during the 180-day intention-to-treat population observation period. The primary efficacy end point was a composite of the first occurrence of objectively confirmed symptomatic lower-extremity proximal deep vein thrombosis (DVT), asymptomatic lower-extremity proximal DVT, symptomatic lower-extremity distal DVT, symptomatic upper-extremity DVT, symptomatic nonfatal pulmonary embolism (PE), incidental PE, or VTE-related death. Key secondary efficacy end points included symptomatic VTE events, VTE-related deaths, and all-cause mortality. The primary safety end point was the occurrence of major bleeding defined by the ISTH (bleeding leading to transfusion or to a decrease in the hemoglobin level of >2 g/dL) during the intervention period. ISTH-defined clinically relevant nonmajor bleeding (CRNMB) was a key secondary safety end point.⁷

For each of these two subgroups, hazard ratios (HRs) and 95% confidence intervals (CIs) for efficacy and safety outcomes were estimated from the Cox proportional hazards model. *P* values were determined by a log-rank test.

3 | RESULTS AND DISCUSSION

3.1 | Patients

Of 841 randomized patients in the CASSINI trial, 176 patients had G/GEJ tumors (rivaroxaban, $n = 89$; placebo, $n = 87$), and 665 patients did not have G/GEJ tumors (rivaroxaban, $n = 331$; placebo, $n = 334$). Demographic and baseline characteristics of the two cohorts are provided in Table 1.

3.2 | Efficacy

In the CASSINI trial, the primary efficacy end point occurred in 6.0% in the rivaroxaban group and 8.8% in the placebo group (HR, 0.66; 95% CI, 0.40-1.09; $P = .10$) in the observation period up to day 180.⁷ In a prespecified analysis during the intervention period, the primary

TABLE 1 Baseline demographics and clinical characteristics of patients with and without G/GEJ tumors

| Characteristic | With G/GEJ tumors | | Non-G/GEJ tumors | |
|---|----------------------|------------------|-----------------------|-------------------|
| | Rivaroxaban (n = 89) | Placebo (n = 87) | Rivaroxaban (n = 331) | Placebo (n = 334) |
| Age, y, median (range) | 60 (29-82) | 61 (29-85) | 64 (23-87) | 63 (28-88) |
| Female, n (%) | 27 (30.3) | 41 (47.1) | 171 (51.7) | 174 (52.1) |
| Race, n (%) | | | | |
| White | 76 (85.4) | 70 (80.5) | 276 (83.4) | 276 (82.6) |
| Black | 3 (3.4) | 4 (4.6) | 10 (3.0) | 14 (4.2) |
| Asian | 0 | 1 (1.1) | 6 (1.8) | 4 (1.2) |
| Other/not reported | 10 (11.2) | 12 (13.8) | 39 (11.8) | 40 (12.0) |
| Ethnicity, n (%) | | | | |
| Hispanic/Latino | 15 (16.9) | 19 (21.8) | 48 (14.5) | 50 (15.0) |
| Not Hispanic/Latino | 68 (76.4) | 65 (74.7) | 246 (74.3) | 247 (74.0) |
| Not reported/unknown | 6 (6.7) | 3 (3.4) | 37 (11.2) | 37 (11.1) |
| BMI, kg/m ² , median (range) | 24.3 (13.9-43.7) | 23.5 (16.0-33.3) | 26.2 (14.7-56.2) | 25.3 (14.2-56.5) |
| Prior DVT, n (%) | 0 | 0 | 11 (3.3) | 2 (0.6) |
| Prior PE, n (%) | 0 | 0 | 2 (0.6) | 0 |
| Pancreatic cancer, n (%) | 0 | 0 | 136 (41.1) | 138 (41.3) |
| Khorana risk score, n (%) | | | | |
| <2 | 0 | 0 | 5 (1.5) | 3 (0.9) |
| 2 | 55 (61.8) | 59 (67.8) | 226 (68.3) | 236 (70.7) |
| >2 | 34 (38.2) | 28 (32.2) | 100 (30.2) | 95 (28.4) |
| ECOG PS, n (%) | | | | |
| 0 | 32 (36.0) | 21 (24.1) | 106 (32.0) | 105 (31.5) |
| 1 | 55 (61.8) | 58 (66.7) | 190 (57.4) | 197 (59.2) |
| ≥2 | 2 (2.2) | 8 (9.2) | 35 (10.6) | 31 (9.3) |

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; ECOG PS, Eastern Cooperative Oncology Group performance status; G/GEJ, gastric/gastroesophageal junction; PE, pulmonary embolism.

efficacy end point occurred in 11 of 420 patients (2.6%) receiving rivaroxaban and 27 of 421 (6.4%) receiving placebo (HR, 0.40; 95% CI, 0.20-0.80).⁷

In this post hoc analysis, for the observation period up to day 180, rivaroxaban treatment reduced the rate of the primary efficacy end point in patients with G/GEJ tumors (3.4% vs 6.9%; HR, 0.45; 95% CI, 0.11-1.80; Table 2). In the study population, excluding patients with G/GEJ tumors, during the observation period up to day 180, the primary efficacy endpoint event rate showed a similar benefit with rivaroxaban versus placebo (6.6% vs 9.3%; HR, 0.70; 95% CI, 0.40-1.21).

Symptomatic VTE events and VTE-related deaths occurred less frequently while patients received rivaroxaban versus placebo in both cohorts: patients with G/GEJ tumors (rivaroxaban, 2.2%; placebo, 3.4%) and patients with non-G/GEJ tumors (rivaroxaban, 5.7%; placebo, 7.2%).

There was no significant interaction effect by subgroup for tumor type and treatment on efficacy outcomes ($P = .96$) or bleeding end points ($P = .43$).

3.3 | Bleeding

In the overall CASSINI trial, bleeding events were low and not statistically different between the rivaroxaban arm and placebo arm (major bleeding: 2.0% vs 1.0%; HR, 1.96; 95% CI, 0.59-6.49; CRNMB: 2.7% vs 2.0%; HR, 1.34; 95% CI, 0.54-3.32).⁷ Because rates of bleeding were too low to allow for meaningful separate analysis of major bleeding and CRNMB, these events were combined for the primary analysis.

In this post hoc analysis, adjudicated bleeding rates for rivaroxaban versus placebo were not significantly different in both patients with and without G/GEJ tumors (Table 3). Among the 19 patients in the rivaroxaban arm who experienced a hemorrhage (8 major bleeding, 11 CRNMB), 4 patients had G/GEJ tumors. In contrast, only 1 of the 12 patients in the placebo arm who experienced a hemorrhage (4 major bleeding and 8 CRNMB) had G/GEJ cancer.

In patients with G/GEJ tumors, major bleeding was observed in 4.6% (4/88) of those treated with rivaroxaban compared with 1.2% (1/85) patients treated with placebo (HR, 3.77; 95% CI, 0.42-33.73;

TABLE 2 Incidence rates and hazard ratios for time to first occurrence of primary efficacy end point for patient cohorts with and without G/GEJ tumors and by treatment during observation period up to day 180^a

| End point | With G/GEJ tumors | | Non-G/GEJ tumors | | Total ⁷ | |
|---|--------------------|----------------|---------------------|-----------------|---------------------|-----------------|
| | Rivaroxaban (n=89) | Placebo (n=87) | Rivaroxaban (n=331) | Placebo (n=334) | Rivaroxaban (n=420) | Placebo (n=421) |
| Primary efficacy composite end point, n (%) | 3 (3.4) | 6 (6.9) | 22 (6.7) | 31 (9.3) | 25 (6.0%) | 37 (8.8%) |
| HR (95% CI) | 0.45 (0.11-1.80) | | 0.70 (0.40-1.21) | | 0.66 (0.40-1.09) | |
| P value | 0.25 | | 0.20 | | 0.10 | |
| Components of primary efficacy composite endpoint, n (%) ^b | | | | | | |
| Symptomatic lower-extremity proximal DVT | 2 (2.3) | 1 (1.2) | 7 (2.1) | 7 (2.1) | 9 (2.1%) | 8 (1.9%) |
| Symptomatic lower-extremity distal DVT | 0 | 0 | 2 (0.6) | 5 (1.5) | 2 (0.5%) | 5 (1.2%) |
| Symptomatic upper-extremity DVT | 0 | 1 (1.1) | 4 (1.2) | 5 (1.5) | 4 (1.0%) | 6 (1.4%) |
| Symptomatic nonfatal PE | 0 | 0 | 5 (1.5) | 5 (1.5) | 5 (1.2%) | 5 (1.2%) |
| Asymptomatic lower-extremity proximal DVT | 1 (1.1) | 3 (3.4) | 3 (0.9) | 8 (2.4) | 4 (1.0%) | 11 (2.6%) |
| Incidental PE | 0 | 1 (1.2) | 6 (1.8) | 9 (2.7) | 6 (1.4%) | 10 (2.4%) |
| VTE-related death | 0 | 1 (1.2) | 1 (0.3) | 2 (0.6) | 1 (0.2%) | 3 (0.7%) |

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; G/GEJ, gastric/gastroesophageal junction; HR, hazard ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

^aUp to day 180 observation period includes all data from the first dose of study drug up to 180 days after randomization.

^bNote that one patient in the placebo group had an incidental PE and asymptomatic lower-extremity proximal DVT.

TABLE 3 Hazard ratios for time to first occurrence of safety end points for patient cohorts with and without G/GEJ tumors and by treatment during the on-treatment observation period^a

| End point | With G/GEJ tumors | | Non-G/GEJ tumors | | Total ⁷ | |
|--|----------------------|------------------|-----------------------|-------------------|-----------------------|-------------------|
| | Rivaroxaban (n = 88) | Placebo (n = 85) | Rivaroxaban (n = 317) | Placebo (n = 319) | Rivaroxaban (n = 405) | Placebo (n = 404) |
| Major bleeding (ISTH), n (%) | 4 (4.6) | 1 (1.2) | 4 (1.3) | 3 (0.9) | 8 (2.0) | 4 (1.0) |
| HR (95% CI) | 3.77 (0.42-33.73) | | 1.33 (0.30-5.94) | | 1.96 (0.59-6.49) | |
| P value | 0.20 | | 0.711 | | 0.26 | |
| Clinically relevant nonmajor bleeding, n (%) | 1 (1.1) | 0 (0.0) | 10 (3.2) | 8 (2.5) | 11 (2.7) | 8 (2.0) |
| HR (95% CI) | NA | | 1.22 (0.48-3.10) | | 1.34 (0.54-3.32) | |
| P value | 0.331 | | 0.671 | | 0.53 | |

Abbreviations: CI, confidence interval; G/GEJ, gastric/gastroesophageal junction; HR, hazard ratio; NA, not applicable.

^aOn-treatment observation period includes all data from the first dose of study drug to 2 days after the last dose of study drug, inclusive.

$P = .20$). CRNMB was observed in 1.1% (1/88) of patients with G/GEJ tumors treated with rivaroxaban compared with no patients treated with placebo (Table 3). Among patients with G/GEJ tumors, the site of the bleeding event was reported more frequently in the GI tract for rivaroxaban compared with placebo (major bleeding: 3.4% vs 0% [95% CI, 0.41-∞; $P = .25$]; CRNMB: 1.1% vs 0% [95% CI, 0.03-∞] $P = 1.0$) (Table 4). There was a trend toward increased GI tract bleeding with rivaroxaban prophylaxis, but the difference in GI tract bleeding was not significant ($P = 0.22$). In contrast, there was no trend toward increased bleeding from other sites, aside from the GI tract, in the cohort of patients with G/GEJ tumors receiving rivaroxaban, suggesting that G/GEJ tumors are not systemically prone to bleeding. This is consistent with our prior publications, which reported that the risk of GI bleeding with rivaroxaban is associated with G/GEJ tumors in situ and other GI luminal lesions.^{6,9}

In the patients with non-G/GEJ tumors, major bleeding was observed in 1.3% (4/317) of patients treated with rivaroxaban compared with 0.9% (3/319) of patients treated with placebo (HR, 1.33; 95% CI, 0.30-5.94; $P = .71$). CRNMB was observed in 3.2% (10/317) of patients with non-G/GEJ tumors treated with rivaroxaban compared with 2.5% (8/319) of patients treated with placebo (HR, 1.22; 95% CI, 0.48-3.10; $P = 0.67$; Table 3). Among patients with non-G/GEJ tumors, rivaroxaban treatment was not associated with a trend toward increased bleeding in the GI tract or non-GI sites (Table 4).

Among patients with non-G/GEJ tumors, one patient (with pancreatic cancer) in the rivaroxaban cohort experienced gross hematuria, a CRNMB, of the GU tract. There was no other CRNMB or major bleeding of the GU tract. Among patients with G/GEJ tumors, no episodes of major bleeding or CRNMB of the GU tract were identified in either cohort. There were two intracranial hemorrhages in the

TABLE 4 Major bleeds and clinically relevant nonmajor bleeds by tumor and site of bleed while on study treatment^a

| Site of primary tumor | Gastrointestinal (major bleeding) | | | Other (major bleeding) | | |
|-----------------------|-----------------------------------|----------------|------------------------------------|---------------------------|-----------------------|------------------------------------|
| | Rivaroxaban cohort, n (%) | Placebo cohort | OR ^b ; P value (95% CI) | Rivaroxaban cohort, n (%) | Placebo cohort, n (%) | OR ^b ; P value (95% CI) |
| G/GEJ | 3/89 (3.4) | 0/87 (0) | ∞; 0.25 (0.41-∞) | 1/89 (1.1) | 1/87 (1.1) | 0.98; 1 (0.012-77.55) |
| Non-G/GEJ | 2/331 (0.6) | 3/334 (0.9) | 0.67; 1 (0.06-5.90) | 2/331 (0.6) | 0/334 (0) | ∞; 0.25 (0.19-∞) |
| Total | 5/420 (1.2) | 3/421 (0.7) | 1.68; 0.51 (0.32-10.87) | 3/420 (0.7) | 1/421 (0.2) | 3.02; 0.37 (0.24-158.87) |
| Site of primary tumor | Gastrointestinal (CRNMB) | | | Other (CRNMB) | | |
| | Rivaroxaban cohort, n (%) | Placebo cohort | OR ^b ; P value (95% CI) | Rivaroxaban cohort, n (%) | Placebo cohort, n (%) | OR ^b ; P value (95% CI) |
| G/GEJ | 1/89 (1.1) | 0/87 (0) | ∞; 1 (0.03-∞) | 0/89 (0) | 0/87 (0) | 0; 1 (0-∞) |
| Non-G/GEJ | 6/331 (1.8) | 3/334 (0.9) | 2.03; 0.34 (0.43-12.68) | 4/331 (1.2) | 5/334 (1.5) | 0.81; 1 (0.16-3.78) |
| Total | 7/420 (1.7) | 3/421 (0.7) | 2.36; 0.22 (0.53-14.23) | 4/420 (1.0) | 5/421 (1.2) | 0.80; 1 (0.16-3.75) |

Abbreviations: CI, confidence interval; CRNMB, clinically relevant nonmajor bleeding; G/GEJ, gastric/gastroesophageal junction; OR, odds ratio.

^aIncludes all randomized patients for the duration of the study in each group.

^bORs reported as ∞ were due to zero-valued numbers in the 2 × 2 tables from which the calculations were performed.

rivaroxaban cohort (one each in patients with G/GEJ and non-G/GEJ tumors) and none in the placebo cohort. There was only one fatal bleed in the rivaroxaban arm in which a patient with a G/GEJ tumor died from an upper GI hemorrhage. There was no signal of increased bleeding from any other site.

3.4 | Discussion

The current analysis provides additional guidance for the potential use of rivaroxaban to prevent CAT. Rivaroxaban was associated with a lower rate of the composite efficacy end point of VTE, PE, and death due to VTE versus placebo in patients who had G/GEJ tumors and patients with other tumor types. However, there was a trend toward increased GI bleeding in patients with G/GEJ tumors receiving rivaroxaban prophylaxis. In contrast, there was no evidence of a trend toward increased major bleeding or CRNMB in patients with non-G/GEJ tumors receiving rivaroxaban. Thus, clinicians may be less inclined to use primary prophylactic anticoagulation in a G/GEJ patient, particularly in patients with the primary tumor in situ. However, these data provide reassurance for prophylactic anticoagulation with rivaroxaban for patients without a G/GEJ tumors.

In the analysis of bleeding events, one case of gross hematuria was reported in a patient receiving rivaroxaban with pancreatic cancer (ie, non-G/GEJ tumors). We reviewed the data for patients with GU cancer and found no data to suggest an increased hemorrhagic risk in this small population of patients (n = 32) in the CASSINI trial.⁷ We did not have information regarding residual or persistent primary GU cancers or GU tract instrumentation, such as stents or nephrostomy tubes. The paucity of GU tract bleeding may simply reflect low numbers of patients with an anatomic contraindication.

The AVERT (Apixaban for the Prevention of Venous Thromboembolism in Cancer Patients) study compared apixaban with placebo for prevention of CAT in patients with a Khorana score ≥ 2 .¹² Unlike the CASSINI trial, the AVERT study did not use screening ultrasound to exclude patients with VTE at baseline. Despite this difference, apixaban was also associated with a lower rate of VTE compared with placebo. The study included only a small proportion of patients with gastric tumors (8.6% in the apixaban arm and 6.7% in the placebo arm), and no data are available on their outcomes.

This post hoc analysis is limited by a potential lack of power to draw comparisons between these subgroups and imbalances in the two arms by subgroup that may alter outcomes. Another limitation is that the available CASSINI data did not include information regarding whether the primary G/GEJ tumors were still present or if the upper GI tract anatomy was abnormal. It is possible that the signal of increased GI bleeding in these patients could have been greater, if an analysis could be performed on the subset of G/GEJ tumors with the primary tumor remaining in situ.

The benefit of therapeutic and prophylactic anticoagulation must be balanced with the risk of hemorrhage. The Khorana score has now been validated in two recent studies, allowing for identification of patients with cancer with intermediate to high risk of developing VTE. However, there are no validated tools to assess risk of bleeding in patients with cancer. This analysis, along with prior studies, provides guidance for patient selection to improve the benefit and risk balance of prophylaxis with rivaroxaban in patients with cancer.^{3-8,12}

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RELATIONSHIP DISCLOSURE

JVM has no conflict of interest or financial relationships to disclose. MBS received grant support and personal fees from Janssen for serving as the site principal investigator for the CASSINI trial and serving on an advisory board during the conduct of the study. Outside the submitted work, he received personal fees from Bayer for a continuing medical education lecture and for serving on an advisory board, from CSL Behring for serving on the outcome adjudication committee, and from Daiichi Sankyo and Pfizer for serving on an advisory board; grant support from Boehringer Ingelheim and Roche; and grant support and personal fees from Portola for a CME lecture and for serving on an advisory board. He served as an expert witness for various legal cases. AAK reports receiving personal fees for serving as co-chair of the steering committee for CASSINI and nonfinancial support for travel from Janssen during the conduct of the study; personal fees and nonfinancial support for travel from Bayer, Sanofi, Parexel, Janssen, Halozyme, Pfizer, AngioDynamics, Leo Pharma, Medscape/WebMD, and Seattle Genetics; personal fees from Pharmacyclics, Pharmocyte, Bristol-Myers Squibb, Nektar, and TriSalus; and grants to his institution from Merck, Array, Bristol-Myers Squibb, and Leap Pharma, outside the submitted work. He was also the National Coordinator of the MARINER trial for Janssen. CVD reports being employed by Janssen Scientific Affairs and owning stock in Johnson & Johnson. PW reports being employed by Janssen Scientific Affairs and owning stock in Johnson & Johnson. PB reports being employed by Janssen Pharmaceuticals, Inc., and owning stock in Johnson & Johnson. HR reports receiving reimbursement for travel from Janssen Scientific Affairs during the conduct of the study and personal fees for serving on an advisory board from Janssen Scientific Affairs. Outside the submitted work, HR reports receiving personal fees for lectures and serving on advisory boards for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer; and grant support from Charité IIT. GAS received personal fees from Janssen for participating in meetings for the planning and discussion of results during the conduct of this and another study and received grant support and personal fees from Janssen outside the submitted work. GAB has no conflicts of interest or financial relationships to disclose.

AUTHOR CONTRIBUTIONS

JVM: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, writing—original draft, review, and editing. MBS: conceptualization,

data curation, investigation, methodology, and writing—review and editing. AAK: conceptualization, data curation, investigation, methodology, and writing—review and editing. GAB: conceptualization, data curation, investigation, methodology, and writing—review and editing. CVD: conceptualization, data curation, investigation, methodology, and writing—review and editing. PW: conceptualization, methodology, resources, supervision, and writing—review and editing. PB: conceptualization, methodology, resources, supervision, and writing—review and editing. HR: conceptualization, data curation, investigation, methodology, and writing—review and editing. GAS: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, writing—original draft, review, and editing. JVM and GAS wrote the first draft of the manuscript. The corresponding author (GAS) had full access to all the data in the study and had final responsibility for the decision to submit for publication.


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