ORIGINAL RESEARCH ARTICLE

Genetics and clinical response to warfarin and edoxaban in patients with venous thromboembolism

Alexander G. Vandell,1 Joseph Walker,2 Karen S. Brown,2 George Zhang,3 Min Lin,3 Michael A. Grosso,4 Michele F. Mercuri4

ABSTRACT

Objective The aim of this study was to investigate whether genetic variants can identify patients with venous thromboembolism (VTE) at an increased risk of bleeding with warfarin. Methods Hokusai-venous thromboembolism (Hokusai VTE), a randomised, multinational, double-blind, non-inferiority trial, evaluated the safety and efficacy of edoxaban versus warfarin in patients with VTE initially treated with heparin. In this subanalysis of Hokusai VTE, patients genotyped for variants in CYP2C9 and VKORC1 genes were divided into three warfarin sensitivity types (normal, sensitive and highly sensitive) based on their genotypes. An exploratory analysis was also conducted comparing normal responders to pooled sensitive responders (ie, sensitive and highly sensitive responders). Results The analysis included 47.7% (3956/8292) of the patients in Hokusai VTE. Among 1978 patients randomised to warfarin, 63.0% (1247) were normal responders, 34.1% (675) were sensitive responders and 2.8% (56) were highly sensitive responders. Compared with normal responders, sensitive and highly sensitive responders had warfarin therapy discontinued earlier (p<0.001), had a decreased final weekly warfarin dose (p<0.001), spent more time overanticoagulated (p<0.001), had a decreased final weekly warfarin dose (p<0.001) and had an increased bleeding risk with warfarin (sensitive responders HR 1.38 [95% CI 1.11 to 1.71], p=0.0035; highly sensitive responders 1.79 [1.09 to 2.99]; p=0.0252). Conclusion In this study, CYP2C9 and VKORC1 genotypes identified patients with VTE at increased bleeding risk with warfarin.

Trial registration number NCT00986154.

INTRODUCTION

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant health problem with an estimated annual incidence of approximately 1–2 per 1000 people among the general population.1 Vitamin K antagonists (VKAs) with initial heparinisation have long been considered a mainstay for the management of VTE.2 However, there is a high degree of interindividual variability in the dose–response relationship to VKAs, which necessitates frequent inconvenient laboratory monitoring of coagulation status.2 Possibly due to this variability and the narrow therapeutic window of VKAs, their use is often associated with serious bleeding complications.2 To overcome some of the limitations of VKAs, direct oral anticoagulants such as edoxaban, a potent factor Xa inhibitor, were developed. As a class, compared with VKAs, these agents are at least as efficacious, are associated with a lower risk of major bleeding, have more predictable pharmacodynamics and require less frequent laboratory monitoring in individuals with VTE.3

The individual response to VKAs, such as warfarin, is influenced by demographics, clinical characteristics and genetic factors.3 6–9 Genetic factors influencing the response to VKAs include polymorphisms in the vitamin K epoxide reductase (VKORC1) and cytochrome P450 2C9 (CYP2C9) genes.6 8–10 The CYP2C9 alleles that are the most associated with increased warfarin sensitivity are more common in individuals of European descent compared with African or Asian descent.11 Conversely, the prevalence of the VKORC1 allele that is associated with greatest increase in warfarin sensitivity is the highest in individuals of Asian descent.11 12 Together, the polymorphisms in these two genes account for up to 50% of the variability in warfarin dose in patients of European descent.6

In a recent subanalysis of the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) study, a large double-blind, double-dummy, randomised study comparing edoxaban to warfarin for the prevention of stroke and systemic embolic events in patients with atrial fibrillation (AF), patients randomised to receive warfarin and classified as sensitive or highly sensitive warfarin responders, based on CYP2C9 and VKORC1 genotypes, experienced more warfarin-associated bleeding and spent more time over-anticoagulated relative to normal responders.13 This effect was observed during the first 90 days of warfarin therapy, but was not present afterwards, suggesting that the effect of genetics on warfarin-induced bleeding risk is strongest during the initiation of therapy when the warfarin dose is still being optimised. These results confirmed that for stroke prevention in patients with AF, compared with warfarin, edoxaban was associated with a greater reduction in bleeding risk in sensitive and highly sensitive responders than in normal responders in the first 90 days. However, it is not known whether similar genetically based elevated bleeding risks associated with warfarin also exist for patients with VTE when transitioning from heparin to oral anticoagulants.

Similar to the ENGAGE AF-TIMI 48 study, DNA samples were collected in the Hokusai-venous
thromboembolism (Hokusai VTE) trial, allowing for a comparison of clinical outcomes by genotype. The Hokusai VTE trial was a randomised, multinational, double-blind, non-inferiority study to evaluate the safety and efficacy of edoxaban versus warfarin (dosed to an international normalised ratio (INR) of 2.0 to 3.0) in patients with VTE initially treated with heparin. The trial demonstrated that, following initial parenteral anticoagulant therapy, edoxaban was non-inferior to warfarin for the treatment of VTE and the prevention of recurrent VTE and was also associated with significantly fewer bleeding events in patients with VTE.14 The present analysis was designed to replicate the ENGAGE AF-TIMI 48 findings and examine whether the previous results could be extended to patients with VTE.

METHODS

Study design and patient population
A detailed description of the study design and patient population of Hokusai VTE (ClinicalTrials.gov: NCT00986154) has been previously published.14 Briefly, Hokusai VTE was a randomised, double-blind trial comparing edoxaban with warfarin in patients with acute, symptomatic VTE (DVT, PE or both). All patients received open-label heparin treatment for at least 5 days. Patients were randomised 1:1 to receive either edoxaban 60 mg once daily or warfarin. The edoxaban dose was halved to 30 mg once daily in patients with a creatinine clearance of 30 to 50 mL/min, a body weight of 60 kg or less or who were receiving concurrent treatment with the P-glycoprotein inhibitors verapamil or quinidine. Warfarin was started concurrently with heparin and the warfarin dose was adjusted to maintain an INR between 2.0 and 3.0. To maintain blinding, sham INR measures were provided to patients randomised to edoxaban. The institutional review board at each participating centre approved the protocol. All patients provided written informed consent.

The Hokusai VTE trial enrolled 8292 patients from 439 centres worldwide. Eligible patients were ≥18 years of age with diagnosed acute, symptomatic DVT that involved the popliteal, femoral or iliac veins or with acute, symptomatic PE with or without DVT. Patients were excluded from the study if they presented contraindications to heparin or warfarin, had been treated for more than 48 hours with heparin at therapeutic doses, had taken more than 1 dose of a VKA, had cancer for which long-term treatment with low-molecular-weight heparin was anticipated, had another indication for warfarin therapy, had received treatment with aspirin (at more than 100 mg daily) or dual antiplatelet therapy or had a creatinine clearance of less than 30 mL/min.

Major bleeding was defined as overt bleeding that was associated with a reduction in haemoglobin of 2 g/dL or greater, required a transfusion of two or more units of blood, occurred at a critical site or contributed to death. Clinically relevant non-major (CRNM) bleeding was defined as overt bleeding not meeting the criteria for major bleeding but that required medical intervention, unscheduled contact with a clinician, interruption of study drug or discomfort or impairment of daily activities. Total bleeding was the composite of major bleeding, CRNM bleeding and nuisance bleeding (ie, all bleeding events not classified as major or CRNM). All bleeding events were adjudicated by an independent, central, blinded committee.

Genotypes
Genotypes were determined for CYP2C9 *2 and CYP2C9 *3 (rs1799853 and rs1057910, respectively) and VKORC1 −1639 G→A alleles (rs9923231) in accordance with Good Laboratory Practice guidelines by ILS Genomics (Morrisville, North Carolina, USA) with an analytically validated assay using Sequenom (San Diego, California, USA) technology. PCR primers were validated using a total of 165 independent samples of known genotype representing African, Asian, Caucasian and Hispanic populations. The genotyping assay was previously validated as part of the ENGAGE AF-TIMI 48 pharmacogenetic analysis.13 On the basis of the VKORC1 and CYP2C9 genotypes, patients were divided into three warfarin sensitivity types (figure 1), normal responders, sensitive responders and highly sensitive responders, that correspond with the US Food and Drug Administration (FDA)’s categories for warfarin response included in the warfarin label.15 In addition, because the total number of

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9 *1/*1</th>
<th>CYP2C9 *1/*2</th>
<th>CYP2C9 *1/*3</th>
<th>CYP2C9 *2/*2</th>
<th>CYP2C9 *2/*3</th>
<th>CYP2C9 *3/*3</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/G</td>
<td>Normal responders 25.7% (n = 1016)</td>
<td>Normal responders 7.1% (n = 282)</td>
<td>Sensitive responders 4.4% (n = 174)</td>
<td>Sensitive responders 0.6% (n = 22)</td>
<td>Sensitive responders 0.7% (n = 27)</td>
<td>Highly sensitive responders 0.3% (n = 10)</td>
</tr>
<tr>
<td>G/A</td>
<td>Normal responders 29.3% (n = 1161)</td>
<td>Sensitive responders 8.6% (n = 339)</td>
<td>Sensitive responders 4.4% (n = 174)</td>
<td>Sensitive responders 0.6% (n = 24)</td>
<td>Highly sensitive responders 0.6% (n = 25)</td>
<td>Highly sensitive responders 0.2% (n = 9)</td>
</tr>
<tr>
<td>A/A</td>
<td>Sensitive responders 12.2% (n = 481)</td>
<td>Sensitive responders 3.2% (n = 125)</td>
<td>Highly sensitive responders 1.6% (n = 63)</td>
<td>Highly sensitive responders 0.3% (n = 12)</td>
<td>Highly sensitive responders 0.2% (n = 7)</td>
<td>Highly sensitive responders 0.1% (n = 5)</td>
</tr>
</tbody>
</table>

Figure 1  Distribution of genotypes and genotype bins. Bold border line demarcates the patient population included in the sensitive responders group for the two-bin exploratory analysis. CYP2C9, cytochrome P450 2C9; VKORC1, vitamin K epoxide reductase.

2 Vandell AG, et al. Heart 2017;0:1–6. doi:10.1136/heartjnl-2016-310901
patients included in this analysis was substantially smaller than in the ENGAGE AF-TIMI 48 pharmacogenetic analysis (3956 vs 14 348),13 exploratory analyses were also conducted using a two-bin system in which sensitive and highly sensitive responders were pooled together (ie, pooled sensitive responders) and compared with normal responders to increase statistical power (figure 1).

Statistical analysis and data presentation
All statistical analyses were conducted using SAS V9.3 or higher by Quintiles (Durham, North Carolina, USA) and Daiichi Sankyo (Parsippany, New Jersey, USA). All patients who received at least one dose of the study drug consented to be included in the pharmacogenetic analysis and provided a pharmacogenetic sample were included in the analysis. All statistical significant conclusions are based on two-sided tests with a significance level of 0.05.

The demographics and baseline clinical characteristics, as well as time until discontinuation of heparin therapy, were compared across genetically defined warfarin sensitivity groups using Kruskal-Wallis tests. In warfarin-treated patients, final weekly warfarin dose and time in therapeutic range (TTR; defined as the percentage of days over the first 90 days and over the entire duration of the study that patients spent within INR 2.0–3.0) were also compared using Kruskal-Wallis tests. Global p values are based on the Kruskal-Wallis tests. Multiple comparisons were performed using Dwass-Steel-Critchlow-Fligner multiple comparison analysis, which is based on pairwise two-sample Wilcoxon comparisons; only comparisons in which the global p value was significant are shown.

All on-treatment bleeding events occurring within 90 days of treatment or over the entire duration of the study were included in the analysis. Cox proportional hazards models were used to compare the bleeding outcomes (ie, total bleeding, major or CRNM bleeding and major bleeding) associated with edoxaban relative to warfarin stratified by genetically defined warfarin sensitivity types. Covariates used in the hazards model included presenting diagnosis (PE with or without DVT vs DVT only), baseline risk factors (temporary risk vs other) and the need for edoxaban dose adjustment. Kaplan-Meier methodology was used to assess the time-to-bleeding event curves for patients treated with warfarin during the first 90 days of treatment; p values are based on the Cox proportional hazards model with genotype of responder as covariate.

RESULTS
Genotyping
All of the 4013 samples collected were genotyped; all genotypes were concordant across samples. There was a 100% call rate for VKORC1 and CYP2C9 genotypes. The CYP2C9 and VKORC1 polymorphisms were in Hardy-Weinberg equilibrium for all three race groups examined (ie, Caucasians, African Americans and East Asians), and the observed allele frequencies within each race group were consistent with previously published findings (online supplementary table 1).11

Out of the 8292 patients in Hokusai VTE, 3956 (47.7%) participants (1978 from each treatment group) received ≥1 dose of the study drug, consented to be included in the pharmacogenetic analysis and provided a pharmacogenetic sample and were therefore included in the present analysis. Among the 1978 patients randomised to the warfarin regimen, 63.0% (1247) were normal responders, 34.1% (675) were sensitive responders and 2.8% (56) were highly sensitive responders (online supplementary figure 1).

Baseline demographics and clinical characteristics
In general, the baseline and clinical characteristics were similar across the genotype categories. However, a larger proportion of sensitive and highly sensitive responders were of Asian ancestry relative to normal responders (table 1). This variation in warfarin sensitivity by race is expected based on the known differences in allele frequencies11 and is consistent with the ENGAGE AF-TIMI 48 pharmacogenetic subanalysis.11

Duration of heparin dose, final warfarin dose, TTR and bleeding risk with warfarin
In warfarin-treated patients, but not edoxaban-treated patients, as genetically defined warfarin sensitivity increased, heparin therapy was discontinued sooner (global p<0.001; p<0.0001 vs normal responders for both sensitive and highly sensitive responders) and the final mean weekly warfarin doses decreased (global p<0.001; p<0.0001 vs normal responders for both sensitive and highly sensitive responders) (figure 2A and B). Over the first 90 days of treatment and over the entire study duration, there were no differences observed in the proportion of time warfarin-treated patients spent in normal INR therapeutic range (global p=0.0593 and 0.6313, respectively) (figure 3A and B). However, as genetically defined warfarin sensitivity increased, warfarin-treated patients tended to spend a higher percentage of time with supratherapeutic INRs during the first 90 days of treatment (global p<0.0001) and over the entire study duration (global p=0.0004) (figure 3). Among the warfarin-treated patients over the entire duration of the study, the median percentages of time with an INR value >3 were 13.1% for normal responders, 15.2% for sensitive responders.

### Table 1 Demographics and baseline clinical characteristics across genotype bins

<table>
<thead>
<tr>
<th></th>
<th>Normal responders (n=2459)</th>
<th>Sensitive responders (n=1366)</th>
<th>Highly sensitive responders (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year), mean±SD</td>
<td>55.3±15.92</td>
<td>56.5±15.58</td>
<td>56.3±17.47</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>1486 (60.4)</td>
<td>802 (58.7)</td>
<td>70 (53.4)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>2031 (82.6)</td>
<td>1122 (82.1)</td>
<td>108 (82.4)</td>
</tr>
<tr>
<td>Black</td>
<td>147 (6.0)</td>
<td>5 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>113 (4.6)</td>
<td>157 (11.5)</td>
<td>15 (11.5)</td>
</tr>
<tr>
<td>Native Hawaiian/ Pacific Islander</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>164 (6.7)</td>
<td>77 (5.6)</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Weight (kg), mean±SD</td>
<td>85.5±19.42</td>
<td>83.7±19.25</td>
<td>83.2±19.91</td>
</tr>
<tr>
<td>BMI (kg/m²), mean±SD</td>
<td>28.8±5.95</td>
<td>28.3±5.45</td>
<td>28.5±6.40</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min), mean±SD</td>
<td>108.5±40.14</td>
<td>106.2±39.69</td>
<td>103.8±40.62</td>
</tr>
<tr>
<td>Edoxaban dose adjusted at randomisation, n (%)</td>
<td>295 (12.0)</td>
<td>207 (15.2)</td>
<td>17 (13.0)</td>
</tr>
</tbody>
</table>

*Edoxaban patients meeting the dose reduction criteria (ie, creatinine clearance 30–50 mL/min, body weight ≤60 kg or receiving selective concomitant P-gp inhibitor) had their edoxaban dose reduced to edoxaban 30 mg once daily.

All data are from baseline unless otherwise noted.

BMI, body mass index; P-gp, p-glycoprotein.
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(p=0.0013 vs normal responders) and 16.8% for highly sensitive responders (p=0.0639 vs normal responders). In addition, among patients randomised to warfarin, sensitive and highly sensitive responders experienced significantly more bleeding events sooner than normal responders during the first 90 days of treatment (HR: sensitive responder, 1.38 [95% CI 1.11 to 1.71], p=0.004; highly sensitive responders, 1.79 [1.09 to 2.99]; p=0.03) (figure 4).

Bleeding analysis for edoxaban versus warfarin by genotype categories
Over the first 90 days of treatment and over the entire duration of the study, there were no significant interactions observed across genotype categories for the risk of total bleeds or major and CRNM bleeds for edoxaban versus warfarin (online supplementary figure 2A). Edoxaban-treated patients had a numerically greater number of major bleeds relative to warfarin-treated individuals across genotype categories during the first 90 days and particularly during the first 28 days of treatment (online supplementary table 2, supplementary figure 3). However, because the size of the warfarin-sensitive and highly sensitive cohorts was small, there were too few major bleeds within these cohorts to reliably establish estimates of the major bleeding rate.

In an exploratory analysis using a two-bin system in which sensitive and highly sensitive responders were pooled (ie, pooled sensitive responders) and compared with normal responders, a statistically higher proportion of pooled sensitive warfarin responders experienced any bleeding events compared with normal warfarin responders during the first 90 days of treatment (HR 1.41 [95% CI 1.14 to 1.71]; p=0.0013) (online supplementary figure 4). In addition, warfarin was associated a significantly higher risk of total bleeds relative to edoxaban in the first 90 days as a function of warfarin sensitivity (p_int=0.0377; online supplementary figure 2B).

DISCUSSION
The present pharmacogenetic subanalysis of the Hokusai VTE trial was designed to confirm and extend the results of the
previously reported ENGAGE AF-TIMI 48 pharmacogenetic analysis in a distinct population of patients with VTE requiring a similar treatment. Following an approach consistent with the previously reported ENGAGE AF-TIMI 48 pharmacogenetics subanalysis, the results of this new set of analyses confirmed that genetic polymorphisms in CYP2C9 and VKORC1 affect the pharmacology and the safety of warfarin. Specifically, as genetically defined warfarin sensitivity increased, heparin therapy was discontinued earlier and the final weekly warfarin dose decreased. The proportion of time spent in a supratherapeutic INR also tended to be elevated in sensitive and highly sensitive warfarin responders relative to normal responders. In the Hokusai VTE trial, the overall time spent in therapeutic range was 63.5%, which is higher than what is typically reported in registries of clinical practice but is similar to what was reported in the ENGAGE AF-TIMI 48 pharmacogenetics analysis. Although the FDA recommends dose adjustments for warfarin in patients with warfarin-sensitive genotypes, in clinical practice, CYP2C9 and VKORC1 genotypes are not routinely assessed, and it has never been demonstrated that genotyping can reduce the risk of bleeding. The present results and the results of the previous ENGAGE AF-TIMI 48 pharmacogenetic analysis suggest that further investigations are needed into the potentially beneficial effects of genotyping prior to prescribing anticoagulation therapy in patients with AF or VTE. Genotype-informed dosing may be especially beneficial in those patients who are initiating therapy, as an individual’s genetic sensitivity could interact with existing clinical factors to exacerbate overall bleeding risk.

This pharmacogenetic subanalysis of Hokusai VTE has a number of limitations which could constrain the generalisability of the results. Hokusai VTE did not stratify patients by warfarin sensitivity genotypes prior to randomisation. There were not enough major bleeding events to determine the interaction between treatment regimen and warfarin sensitivity. In addition, the study was underpowered for the three-bin analysis and the results of the exploratory two-bin analysis should only be considered hypothesis generating. There was also a low number of black patients included in this subanalysis, and therefore additional analyses will be needed to confirm the results in the future.

During the first 90 days of warfarin treatment, the risk of any bleeding event was significantly increased by approximately 1.8 times in the highly sensitive responders and 1.4 times in the sensitive responders relative to normal responders (p<0.05 for both). However, unlike the pharmacogenetic analysis of the ENGAGE AF-TIMI 48 study, only a trend was observed towards a higher bleeding risk with warfarin versus edoxaban in sensitive and highly sensitive responders relative to normal responders (p=0.0747). In addition, warfarin-associated major bleeding during the first 90 days was lower than what was observed in the pharmacogenetics subanalysis of ENGAGE AF-TIMI 48. The lack of a significant interaction between the bleeding risk associated with warfarin versus edoxaban as a function of warfarin sensitivity may be due to the lower number of patients included in this analysis compared with the ENGAGE AF-TIMI 48 pharmacogenetic analysis. Although the FDA recommends dose adjustments for warfarin in patients with warfarin-sensitive genotypes, it has never been demonstrated that genotyping can reduce the risk of bleeding. The present results and the results of the previous ENGAGE AF-TIMI 48 pharmacogenetic analysis suggest that further investigations are needed into the potentially beneficial effects of genotyping prior to prescribing anticoagulation therapy in patients with AF or VTE. Genotype-informed dosing may be especially beneficial in those patients who are initiating therapy, as an individual’s genetic sensitivity could interact with existing clinical factors to exacerbate overall bleeding risk.
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different racial groups. It should also be noted that genotyping was not used in guiding the starting dose of warfarin and that the high TTR observed in this study is not what is typically seen in clinics. Finally, the results of this subanalysis could differ in other disease states besides VTE.

CONCLUSION
The results of this analysis extend the results of the previous ENGAGE AF-TIMI 48 pharmacogenetic analysis to demonstrate that patients with VTE who have a sensitive or highly sensitive warfarin genotype spend more time overanticoagulated, require a lower warfarin dose and have higher bleeding rates with warfarin therapy. In addition, this subanalysis suggests that compared with normal warfarin responders sensitive warfarin responders may have a higher risk of bleeding on warfarin relative to edoxaban.

Key messages

What is already known on this subject?
In a recent subanalysis of the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48, a study comparing edoxaban with warfarin for the prevention of stroke and systemic embolic events in patients with atrial fibrillation, patients randomised to receive warfarin and classified as sensitive or highly sensitive warfarin responders—based on CYP2C9 and VKORC1 genotypes—experienced more warfarin-associated bleeding and spent more time overanticoagulated relative to normal responders.

What might this study add?
The present pharmacogenetic subanalysis of the Hokusai-venous thromboembolism (Hokusai VTE) trial, a trial evaluating edoxaban versus warfarin in patients with VTE initially treated with heparin, demonstrates that patients with VTE who have a sensitive or highly sensitive warfarin genotype spend more time overanticoagulated (p<0.001), require a lower warfarin dose (p<0.001) and have higher bleeding rates with warfarin therapy (sensitive responders HR 1.38 [95% CI 1.11 to 1.71], p=0.0035; highly sensitive responders 1.79 [1.09 to 2.99]; p=0.0252).

How might this impact on clinical practice?
The results presented here may influence the practical management of warfarin therapy for the treatment of VTE in patients who are sensitive or highly sensitive responders to warfarin.

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Contributors AV, JW, KSB, GZ, ML, MAG and MFM made substantial contributions to the conception or design of the work and analysis or interpretation of data, drafted or critically revised the manuscript, and had final approval of the version to be published.

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Competing interests AV, GZ, ML, MAG and MFM are employees of Daiichi Sankyo, Inc. JW and KSB were employees at Daiichi Sankyo, Inc at the time the study was conducted.

Patient consent This manuscript does not contain identifiable medical information.

Ethics approval The institutional review board at each participating centre approved the protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES
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