For patients with asthma who remain uncontrolled despite inhaled corticosteroid (ICS) therapy, a long-acting inhaled β₂-agonist (LABA) may be added. Combination therapy improves symptoms, reduces severe exacerbation rate and achieves better asthma control in more patients than ICS monotherapy. However, poor adherence to bid therapy may account for poor asthma control in some patients. For these patients, once-daily therapy could offer them greater convenience, thereby improving adherence.

Vilanterol (VI) (GW642444M) is a LABA with inherent 24-h activity in development as a once-daily treatment in combination with the novel ICS fluticasone furoate (FF) for asthma and COPD. Three dose-ranging
FF studies in patients with persistent asthma showed significant improvements from baseline in lung function relative to placebo, with the 100 and 200 μg doses of FF (over 8 weeks) providing optimal efficacy with an acceptable tolerability profile.⁷⁸ A VI dose-ranging study with concurrent ICS, also in persistent asthma, showed that the 25-μg dose of VI administered once daily over 4 weeks provided the most beneficial therapeutic ratio.¹⁰

The main aim of the current study was to compare the efficacy of FF/VI 100/25 μg administered once daily in the evening with fluticasone propionate (FP)/salmeterol (SAL) 250/50 μg administered bid over a 24-week treatment period in patients aged ≥12 years with persistent asthma uncontrolled on medium-dose of ICS. The dose of FP/SAL selected was considered suitable for the patient population to be studied.

**Materials and Methods**

**Patients**

Patients aged ≥12 years with asthma were eligible if they could demonstrate a ≥12% and ≥200-mL reversibility of FEV₁, following albuterol inhalation at screening and had a best evening FEV₁ of 40% to 85% of the predicted normal value at screening and at randomization.¹¹ Before screening, patients had been taking ICS for ≥12 weeks, with a stable medium dose of ICS (FP 250 μg bid or equivalent) for ≥4 weeks. Key exclusion criteria are outlined in e-Appendix 1. The study was approved by the local ethics review committees (e-Table 1) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave written informed consent.

**Study Design and Treatments**

This phase 3, multicenter, randomized, double-blind, double-dummy, parallel group study was conducted between June 16, 2010, and July 27, 2011. After screening, eligible patients entered a 4-week run-in period during which they replaced their current asthma medication with FP 250 μg bid, and their short-acting bronchodilator with albuterol delivered through a metered-dose inhaler. After the run-in period, patients received (1:1) either FF/VI 100/25 μg (emitted dose, 92/22 μg) once daily in the evening, administered through an ELLIPTA dry powder inhaler (GlaxoSmithKline), or FP/SAL 250/50 μg bid (morning and evening) through DISKUS/ACCUHALER (GlaxoSmithKline) for 24 weeks. The central randomization schedule was generated by the sponsor with a validated computerized system (RandAll; GlaxoSmithKline). Patients were randomized by the Registration and Medication Ordering System. Neither the patients nor the investigator knew which study medication the patient was receiving. A summary of permitted and prohibited medications is provided in e-Appendix 2. Compliance with study medication was measured by reviewing the dose counter on the dry powder inhaler and DISKUS/ACCUHALER.

**Outcome Measurements**

The primary end point was change from baseline in 0- to 24-h serial weighted mean (wM) FEV₁ after 24 weeks of treatment. Secondary end points were individual serial FEV₁ assessments at week 24 (FEV₁ at each time point on day 168), time to onset of bronchodilator effect (the time point when FEV₁ first exceeded the 12% and 200-mL increase over baseline [taken from serial measurements]) at randomization visit only, 0- to 4-h serial wMFEV₁ postdose at the randomization visit and at week 24, percentage of patients experiencing a ≥12% and ≥200-mL increase from baseline in FEV₁, at 12 and 24 h at week 24, and change from baseline in clinic visit trough (prebronchodilator and predose) FEV₁ at week 24.

Other efficacy end points were scores on the Asthma Quality of Life + 12 Questionnaire (AQLQ+12), the Asthma Control Test, and the European Quality of Life-5 Dimensions (EQ-5D) test, and unscheduled health-care resource utilization. Patients were asked to complete questionnaires at baseline and end of treatment. A post hoc analysis of the individual AQLQ+12 domains and minimally important difference (≥0.5-point improvement in AQLQ+12 score) was also performed. Results from this analysis are shown in e-Appendix 3.

**Safety Evaluations**

Adverse events (AEs) could be reported throughout the study. Other safety assessments were 24-h urinary cortisol (UC) excretion at baseline and at the end of the 24-week treatment period (subset of patients); vital signs (diastolic and systolic BP, pulse rate); incidence of severe asthma exacerbations; liver safety; and ECG, clinical chemistry, and hematology screening assessments. Patients were withdrawn from the study because of lack of efficacy if they experienced a severe exacerbation or worsening of asthma or at the investigator’s discretion. A severe exacerbation was defined as deterioration of asthma requiring treatment with systemic or oral corticosteroids for ≥3 days or an inpatient hospitalization or ED visit that required systemic corticosteroids. Worsening asthma was defined as a requirement for any treatment other than study medication or use of rescue albuterol. Severe asthma exacerbations were not recorded as an AE unless they met the definition of a serious adverse event (SAE).
Sample size calculations were based on the primary end point of 0- to 24-h serial \( \text{wmFEV}_1 \) at the end of the 24-week treatment period for the treatment comparison of FF/VI 100/25 \( mg \) once daily vs FP/SAL 250/50 \( mg \) bid. It was estimated that approximately 348 patients with evaluable data per treatment group would provide 90% power to detect a difference of 80 mL between FF/VI 100/25 \( mg \) and FP/SAL 250/50 \( mg \); this assumed an SD of 325 mL. Details about the analysis populations and power calculation are provided in e-Appendix 4.

The primary analysis was performed on the intention-to-treat population with an analysis of covariance model allowing for the effects of baseline \( \text{FEV}_1 \), region, sex, age, and treatment group. A two-sided 5% risk (significance level) associated with incorrectly rejecting the null hypothesis was considered acceptable for this study. For the secondary and other efficacy end points, if the statistical test for the primary end point failed to reject the null hypothesis of no treatment difference at the 0.05 significance level, the tests for the secondary and other efficacy end points were to be interpreted as descriptive only.

As a consequence of site audits conducted by the study sponsor GlaxoSmithKline, concerns about the quality of data supplied were identified for two study centers. These centers contributed 57 patients (7% of enrolled patients) to the study. Because of these concerns, analysis of the primary end point was repeated, excluding the data from these two centers. Results were consistent with the primary analysis. The authors and study sponsor are satisfied that the exclusion of data derived from these centers did not materially change the findings of the study; therefore, we present a complete data set from all the centers.

### Study Population

Patient disposition is shown in Figure 1. Most patients (89%) in both treatment groups completed the 24-week treatment period (Fig 1). Patient demographics and baseline lung function are shown in Table 1.

### Efficacy Assessments

**Lung Function:** Improvements from baseline in 0- to 24-h serial \( \text{wmFEV}_1 \) were seen with both FF/VI (341 mL) and FP/SAL (377 mL); however, the adjusted mean treatment difference was not statistically significant (-37 mL; 95% CI, -88 to 15 mL; \( P = .162 \)) (Fig 2). There were no differences in key secondary end points, including the change from baseline in individual serial \( \text{FEV}_1 \) assessments over time at week 24. These showed sustained 24-h duration of action for both once-daily FF/VI and bid FP/SAL at all time points (Fig 3). The adjusted mean treatment differences between FF/VI and FP/SAL ranged from 2 to 58 mL. No important differences were seen between FF/VI vs FP/SAL for the secondary end points of time to onset of bronchodilator effect, 0- to 4-h serial \( \text{wmFEV}_1 \) postdose at randomization and at week 24, percentage

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**Figure 1.** Consolidated Standards of Reporting Trials patient flow diagram. AE = adverse event; BD = twice daily; FF = fluticasone furoate; FP = fluticasone propionate; ITT = intention to treat; OD = once daily; SAL = salmeterol; VI = vilanterol. a Main reason was that patients did not meet inclusion/exclusion criteria (n = 613 [39%]). b Main reason was that patients did not meet continuation criteria (n = 103 [7%]).
Improvements from baseline in the AQLQ+12, Asthma Control Test, and EQ-5D asthma health outcomes assessments were observed for both FF/VI and FP/SAL. There was no difference between treatments (Table 3).

Safety Assessments

The overall incidence of AEs and SAEs reported while on treatment are presented in Table 4. The most frequently occurring AEs reported by both groups were nasopharyngitis and headache; treatment-related AEs were similar between groups (Table 4). Nine patients reported on-treatment SAEs (four receiving FF/VI and five receiving FP/SAL) (Table 4). SAEs were single events with the exception of asthma exacerbation and pneumonia (one pretreatment and one on treatment [FP/SAL]). None of the SAEs was considered treatment related. No deaths were reported during the study.

There was no statistically significant difference between FF/VI and FP/SAL in 24-h UC excretion at week 24 (adjusted treatment ratio, 0.85; 95% CI, 0.72-1.02; \(P = .075\)) (Fig 4). However, 24-h UC excretion did increase in both groups from baseline to week 24 (ratio to baseline, 1.11 and 1.21 for FF/VI and FP/SAL, respectively).

The incidence of asthma exacerbations was low, and there was no difference between groups (3% vs 2% on FP/SAL vs FF/VI, respectively [on-treatment events]). Eight (2%) patients in the FF/VI group and seven (2%) in the FP/SAL group withdrew because of their exacerbation. One patient in the FF/VI group and two in the FP/SAL group were hospitalized because of their exacerbations. None of the exacerbations were considered treatment related. No clinically relevant treatment effects on vital signs (e-Appendix 5) or liver function.
parameters were found, with the exception of one patient in the FP/SAL group who met liver stopping criteria of alanine aminotransferase levels more than eight times the upper limit of normal, which was reported as an AE but was not considered treatment related.

**Discussion**

In this study of patients aged ≥12 years with persistent asthma uncontrolled on a medium dose of ICS, FF/VI 100/25 μg once daily in the evening was not significantly different from FP/SAL 250/50 μg bid for the primary end point of 0- to 24-h serial wmFEV₁ at week 24 or for any of the secondary end points. The AE profiles for both treatments were similar, and those AEs reported with FP/SAL were consistent with those previously reported with this drug combination.²

Patients were symptomatic on a medium dose of ICS at baseline. According to current asthma guidelines, these patients would require a step up in their asthma treatment from step 3 to 4.² Lack of asthma control in the patient population at baseline was evident by an FEV₁ of approximately 68% of the predicted normal value for both groups and by the fact that ≥50% of patients had an Asthma Control Test score of <20. The goal of asthma treatment is to control asthma symp-

toms.² A number of studies have shown that nonadherence to asthma therapy is an important reason for loss of asthma control in some patients.¹⁴⁻¹⁶ Adherence to the treatment schedule was high during the study (94% in both groups), although the artificial setting of a clinical trial may have encouraged normally nonadherers to take their medication. If poor adherence to the dosing schedule is an important factor in loss of asthma control, then once-daily dosing (as opposed to bid dosing) such as that provided by FF/VI may represent a more-convenient treatment option for patients in a real-world setting.¹⁷

No differences in Asthma Control Test scores or in measures of quality of life (AQLQ+12 and EQ-5D) were shown in the present study. A difference of 1.4 was observed between groups on the EQ-5D test, but this difference was not statistically significant. The outcomes of the post hoc analysis (e-Appendix 3) suggest that FF/VI may provide clinically relevant improvements in certain patient-reported quality-of-life measures (environmental domain of the AQLQ+12 in the present study), as well as in the percentage of patients who improved by at least the minimally important difference of 0.5,¹⁸ that were not reported with FP/SAL. However, this statement is speculative and requires further evaluation in real-world studies outside the environment of a clinical trial.

### Table 2—Secondary End Points

<table>
<thead>
<tr>
<th>Secondary End Point</th>
<th>Treatment Value</th>
<th>Difference FF/VI OD PM vs FP/SAL bid, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to onset of bronchodilator effect (median time to ≥12% and ≥200 mL FEV₁ over baseline at randomization visit), min</td>
<td>61</td>
<td>0.948 (0.797 to 1.128)</td>
</tr>
<tr>
<td>FF/VI</td>
<td>0.316 ± 0.0149</td>
<td></td>
</tr>
<tr>
<td>FP/SAL</td>
<td>0.346 ± 0.0149</td>
<td></td>
</tr>
<tr>
<td>0- to 4-h serial wmFEV₁ postdose at randomization visit, L</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>0- to 4-h serial wmFEV₁ postdose at week 24, L</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>% patients obtaining ≥12% and ≥200 mL increase from baseline in FEV₁ at 12 h and at 24 h at week 24</td>
<td>56</td>
<td>1.31· (0.96 to 1.78)</td>
</tr>
<tr>
<td>12-h FF/VI</td>
<td>0.281 ± 0.0191</td>
<td></td>
</tr>
<tr>
<td>12-h FP/SAL</td>
<td>0.300 ± 0.0193</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as least squares mean ± SE change from baseline unless otherwise indicated. Intention-to-treat population, n = 403 (FF/VI 100/25 μg OD PM) and n = 403 (FP/SAL 250 μg bid). HR = hazard ratio; wm = weighted mean. See Table 1 legend for expansion of other abbreviations.

*Results are for all secondary end points other than the end point individual serial FEV₁ assessments at week 24 (see Fig 3).

¹HR.

²OR.
In the present study, no clinically relevant effects of FF/VI or FP/SAL were found in measures of BP or pulse rate. It may be considered a limitation that the study duration was too short to reliably collect information on important end points such as exacerbations. Also, while a once-daily dosing schedule could provide greater convenience to the patient and may therefore increase compliance to treatment, the double-blind, double-dummy nature of the study, together with the very high compliance levels during the study, means that the full benefit of once-daily dosing compared with bid dosing could not be realized in this study. This can only be investigated in a real-world effectiveness study, such as the Salford Lung Study, which is now under way.

It is possible that prestudy ICS adherence was lower than anticipated by the protocol, as suggested by the high degree of FEV₁ reversibility seen at screening. Patient compliance with run-in medication was not formally assessed. Once-daily FF/VI had similar treatment effects to bid FP/SAL in improving lung function and health status in this double-blind study.

FF/VI and FP/SAL were well tolerated, and FF/VI had a similar AE profile to FP/SAL. The AE profile with FF/VI reported in the present study is consistent with that seen in the two FF dose-ranging studies that included the 100 μg once-daily dose and the two studies of VI 25 μg plus concurrent ICS. Most of the SAEs reported in the present study were single events, and none were considered treatment related. Asthma exacerbations requiring hospitalization occurred in one patient receiving FF/VI and two patients receiving FP/SAL.

A potential effect of ICS treatment is reduction in UC levels as a result of suppression of the hypothalamic-pituitary-adrenal axis, although this usually only occurs at higher doses of ICS. In earlier phase dose-ranging studies, once-daily FF 100 or 200 μg did not significantly inhibit 24-h UC levels relative to placebo. In the current study, clinically insignificant increases in UC levels from baseline were reported, and no statistically significant differences were observed between the groups at week 24. LABAs have occasional side effects, such as headache, tremor, and hypertension.

In the present study, no clinically relevant effects of FF/VI or FP/SAL were found in measures of BP or pulse rate.

It may be considered a limitation that the study duration was too short to reliably collect information on important end points such as exacerbations. Also, while a once-daily dosing schedule could provide greater convenience to the patient and may therefore increase compliance to treatment, the double-blind, double-dummy nature of the study, together with the very high compliance levels during the study, means that the full benefit of once-daily dosing compared with bid dosing could not be realized in this study. This can only be investigated in a real-world effectiveness study, such as the Salford Lung Study, which is now under way.

It is possible that prestudy ICS adherence was lower than anticipated by the protocol, as suggested by the high degree of FEV₁ reversibility seen at screening. Patient compliance with run-in medication was not formally assessed. Once-daily FF/VI had similar treatment effects to bid FP/SAL in improving lung function and health status in this double-blind study.

### Table 3—Health Outcomes Assessments

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Mean Score at Baseline</th>
<th>Mean Score at Week 24</th>
<th>LS Mean Change ± SE From Baseline*</th>
<th>Difference FF/VI OD pm vs FP/SAL bid, (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQLQ +12 (total score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF/VI</td>
<td>5.35</td>
<td>5.85</td>
<td>0.46 ± 0.043</td>
<td>0.09 (−0.03 to 0.21)</td>
</tr>
<tr>
<td>FP/SAL</td>
<td>5.37</td>
<td>5.79</td>
<td>0.37 ± 0.043</td>
<td></td>
</tr>
<tr>
<td>ACT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF/VI</td>
<td>18.9</td>
<td>21.2</td>
<td>2.3 ± 0.16</td>
<td>0.2 (−0.2 to 0.7)</td>
</tr>
<tr>
<td>FP/SAL</td>
<td>18.8</td>
<td>20.9</td>
<td>2.0 ± 0.16</td>
<td></td>
</tr>
<tr>
<td>EQ-5D dimensions, % reporting no problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF/VI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP/SAL</td>
<td>83</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF/VI</td>
<td>83</td>
<td>84</td>
<td>N/A</td>
<td>1.14 (0.38 to 3.41)</td>
</tr>
<tr>
<td>FP/SAL</td>
<td>97</td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF/VI</td>
<td>75</td>
<td>84</td>
<td>N/A</td>
<td>1.44 (0.93 to 2.24)</td>
</tr>
<tr>
<td>FP/SAL</td>
<td>74</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF/VI</td>
<td>67</td>
<td>69</td>
<td>N/A</td>
<td>1.12 (0.80 to 1.58)</td>
</tr>
<tr>
<td>FP/SAL</td>
<td>60</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF/VI</td>
<td>78</td>
<td>77</td>
<td>N/A</td>
<td>0.79 (0.52 to 1.19)</td>
</tr>
<tr>
<td>FP/SAL</td>
<td>77</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D VAS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF/VI</td>
<td>80.4</td>
<td>85.6</td>
<td>5.5 ± 0.60</td>
<td>1.4 (−0.3 to 3.0)</td>
</tr>
<tr>
<td>FP/SAL</td>
<td>80.0</td>
<td>84.2</td>
<td>4.1 ± 0.60</td>
<td></td>
</tr>
</tbody>
</table>

Intention-to-treat population, n = 403 (FF/VI 100/25 μg OD pm) and n = 403 (FP/SAL 250 μg bid). ACT = Asthma Control Test; AQLQ +12 = Asthma Quality of Life + 12 Questionnaire; EQ-5D = European Quality of Life-5 Dimensions; N/A = not applicable; VAS = visual analog scale. See Table 1 legend for expansion of other abbreviations.

* AQLQ +12, ACT, and EQ-5D VAS score, analysis of covariance was used, with covariates of baseline score, country, sex, age, and treatment; EQ-5D, logistic regression analysis was used, with covariates of baseline, region, sex, age, and treatment.

*OR.
randomized study. It remains to be seen whether it will be superior in a real-world setting. In conclusion, there was no difference in efficacy or safety between FF/VI 100/25 μg administered once daily in the evening and FP/SAL 250/50 μg administered bid.

Table 4—On-Treatment AEs ≥ 3% in Any Treatment Group, All SAEs, and Treatment-Related AEs (Intention-to-Treat Population)

<table>
<thead>
<tr>
<th>Event</th>
<th>FF/VI 100/25 μg</th>
<th>FP/SAL 250/50 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>213 (53)</td>
<td>198 (49)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>46 (11)</td>
<td>46 (11)</td>
</tr>
<tr>
<td>Headache</td>
<td>34 (8)</td>
<td>41 (10)</td>
</tr>
<tr>
<td>URTI</td>
<td>26 (6)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Cough</td>
<td>15 (4)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 (3)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>11 (3)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>12 (3)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (3)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Productive cough</td>
<td>11 (3)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Treatment-related AEs (any)</td>
<td>19 (5)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>SAEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>4 (&lt;1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>URTI</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Asthma</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>CO poisoning</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Treatment-related SAEs (any)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are presented as No. (%). AE = adverse event; SAE = serious adverse event; URTI = upper respiratory tract infection. See Table 1 legend for expansion of other abbreviations.

Acknowledgments

Author contributions: Dr Woodcock had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Woodcock: contributed to the study design, data interpretation, critical review of the manuscript, and approval of the final version to be published.

Dr Bleecker: contributed to the study design, data interpretation, critical review of the manuscript, and approval of the final version to be published.

Dr O’Byrne: contributed to the study design, data interpretation, critical review of the manuscript, and approval of the final version to be published.

Dr Bateman: contributed to the study design, data interpretation, critical review of the manuscript, and approval of the final version to be published.

Ms Medley: contributed to the study concept and design, data collection, critical review of the manuscript, and approval of the final version to be published.

Ms Ellsworth: contributed to the study design, data analysis and interpretation, critical review of the manuscript, and approval of the final version to be published.

Dr Jacques: contributed to the study design; data collection, analysis, and interpretation; critical review of the manuscript; and approval of the final version to be published.

Dr Busse: contributed to the study design, data interpretation, critical review of the manuscript, and approval of the final version to be published.

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