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Original Article

Evaluation of the Efficacy and Safety of DW1903 in Patients with Gastritis: A Randomized, Double-Blind, Noninferiority, Multicenter, Phase 3 study

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Background/Aims: H2 receptor antagonists (H2RA) have been used to treat gastritis by inhibiting gastric acid. Proton pump inhibitors (PPIs) are more potent acid suppressants than H2RA. However, the efficacy and safety of low-dose PPI for treating gastritis remain unclear. The aim was to investigate the efficacy and safety of low-dose PPI for treating gastritis.

Methods: A double-blind, noninferiority, multicenter, phase 3 clinical trial randomly assigned 476 patients with endoscopic erosive gastritis to a group using esomeprazole 10 mg (DW1903) daily and a group using famotidine 20 mg (DW1903R1) daily for 2 weeks. The full-analysis set included 319 patients (DW1903, n=159; DW1903R1, n=160) and the per-protocol set included 298 patients (DW1903, n=147; DW1903R1, n=151). The primary endpoint (erosion improvement rate) and secondary endpoint (erosion and edema cure rates, improvement rates of hemorrhage, erythema, and symptoms) were assessed after the treatment. Adverse events were compared.

Results: According to the full-analysis set, the erosion improvement rates in the DW1903 and DW1903R1 groups were 59.8% and 58.8%, respectively. According to the per-protocol analysis, the erosion improvement rates in the DW1903 and DW1903R1 groups were 61.9% and 59.6%, respectively. Secondary endpoints were not significantly different between two groups except that the hemorrhagic improvement rate was higher in DW1903 with statistical tendency. The number of adverse events were not statistically different.

Conclusions: DW1903 of a low-dose PPI was not inferior to DW1903R1 of H2RA. Thus, low-dose PPI can be a novel option for treating gastritis (ClinicalTrials.gov Identifier: NCT05163756). **(Gut Liver 2024;18:70-76)**

Key Words: Gastritis; Phase III clinical trial; Proton pump inhibitors; Histamine H2 antagonists

INTRODUCTION

Gastric mucosal injury, including gastritis, can occur due to an imbalance between defensive mechanisms and noxious factors in the gastric mucosa. Gastric acid is one of the representative noxious factors in the stomach. Thus, acid inhibiting agents are used to treat or prevent gastric mucosal injury. In addition, acid inhibiting agents are used to control upper gastrointestinal (GI) symptoms because acid is one of the factors provoking upper GI symptoms.[1-3]

Gastritis is a common disease in Korea, causing gastric mucosal injury and/or upper GI symptoms.[4] Therefore, acid-suppressive therapy is a primary treatment for gastritis. H2 receptor antagonists (H2RAs) have been used to treat gastritis. H2RAs inhibit intragastric acid by competitively inhibiting histamine action on H2 receptors. Although H2RAs are effective acid suppressants, repeat dosing can lead to tolerance development.[5] Proton pump inhibitors (PPIs) are potent acid suppressants that can irreversibly inhibit a final acid secretion step without causing tolerance. Therefore, PPIs can be an effective treatment option for gastritis. However, until now, PPIs have not been permitted as a therapy for gastritis. DW1903 (Escorten®; Daewon Pharm Co. Ltd., Seoul, Korea) is low-dose (10 mg) esomeprazole, a PPI. The aim was to investigate the efficacy and safety of low-dose PPI (DW1903) for treating gastritis.

MATERIALS AND METHODS

1. Study population

This study was a randomized, double-blind, noninferiority, multicenter, phase 3 clinical trial conducted in Korea from November 2020 to May 2021. Patients with gastritis were enrolled from the following 27 Korean centers: Korea University Ansan Hospital (Ansan), Samsung Medical Center (Seoul), CHA Bundang Medical Center (Seongnam), Korea University Anam Hospital (Seoul), Korea University Guro Hospital (Seoul), Severance Hospital (Seoul), Seoul National University Hospital (Seoul), Chung-Ang University Hospital (Seoul), Seoul National University Bundang Hospital (Seongnam), Asan Medical Center (Seoul), Gangnam Severance Hospital (Seoul), Soonchunhyang University Hospital (Bucheon), Gangneung Asan Hospital (Gangneung), Wonju Severance Christian Hospital (Wonju), Gil Medical Center (Incheon), Kyung Hee University Hospital (Seoul), Pusan National University Hospital (Pusan), Chungnam National University Hospital (Daejeon), Pusan National University Yangsan Hospital (Yangsan), Dong-A University Hospital (Pusan), Inje University Haeundae Paik Hospital (Pusan), Kosin University Gospel Hospital (Pusan), Keimyung University Dongsan Hospital (Daegu), Kyungpook National University Chilgok Hospital (Daegu), Chonnam National University Hospital (Gwangju), Jeonbuk National University Hospital (Jeonju), and Presbyterian Medical Center (Jeonju).

Patients who were enrolled met the following inclusion criteria: (1) subjects aged 20 to 75 years with acute or chronic gastritis and (2) those with gastric erosions on baseline endoscopy. Patients could not participate in the study if they had one of the exclusion criteria: (1) patients who could not undergo endoscopy; (2) patients with peptic ulcer (except scar) or reflux esophagitis or inflammatory bowel disease or coagulopathy or Zollinger-Ellison syndrome; (3) patients who had performed a GI tract operation such as surgery to inhibit gastric acid secretion or an esophagogastric surgery; (4) patients with a history of GI tract cancer; (5) patients who had H2RAs, PPIs, gastrin receptor antagonists, anticholinergic drugs (muscarinic receptor antagonists), prokinetics, prostaglandin analogs, or gastric mucosal protective agents within 2 weeks of baseline endoscopic examination; (6) patients who needed to take corticosteroids, nonsteroidal anti-inflammatory drugs, aspirins, or anti-thrombotic agents during the study period; (7) women who were pregnant or lactating; (8) men and women of childbearing age without contraception; (9) patients with significant problems in hematologic, renal, cardiac, pulmonary, hematopoietic, or endocrine systems; (10) patients with hypersensitivity to H2RA or benzimidazole; (11) participation in clinical trial within 30 days before screening; or (12) any situation that an investigator regarded as inappropriate for this study.

This study was approved by the institutional review board of each institution including Gangnam Severance Hospital (IRB number: 3-2020-0325). The study was registered at ClinicalTrials.gov (Identifier: NCT05163756).

2. Randomization

Treatment allocation list was based on a computer-generated randomization code and distributed to each institution. Participants underwent screening tests including blood tests, urinalysis, electrocardiography, and esophagogastroduodenoscopy. After that, eligible subjects were randomly assigned to have one of the following two medications for 2 weeks at a 1:1 ratio: (1) test group (DW1903; Daewon Pharm Co. Ltd.) and (2) control group (DW1903R1; Daewon Pharm Co. Ltd.). DW1903 is a low-dose esomeprazole (10 mg) and DW1903R1 is famotidine at 20 mg. Participants received either DW1903 before noon with a placebo before bedtime or a placebo before noon with DW1903R1 before bedtime for 2 weeks (Fig. 1). All processes were a double-blind approach.

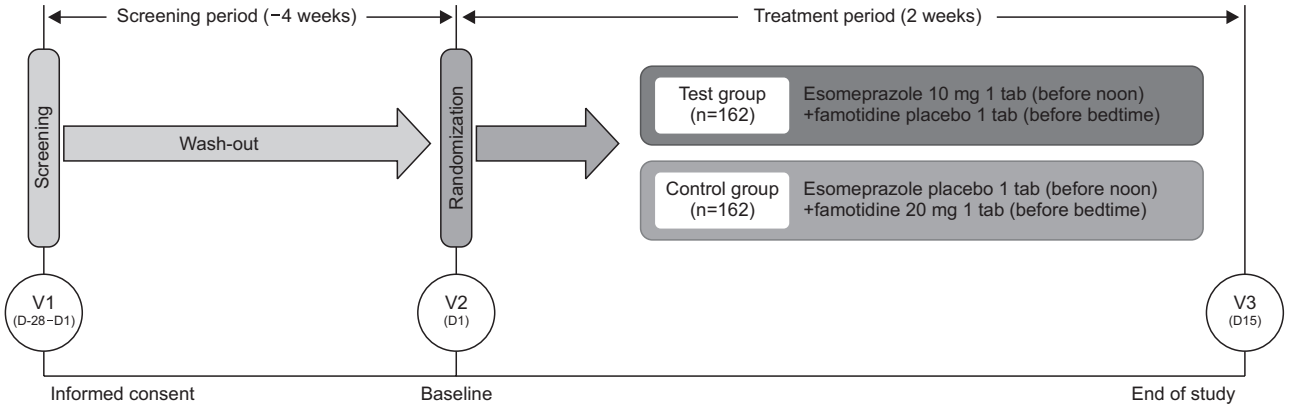

Fig. 1. Schematic study design in the present study.

Patients underwent follow-up endoscopy at 2 weeks after initiating the treatment. Compliance was assessed by the number of remaining tablets per drug type at the follow-up visit. If the drug compliance was ≥80%, but ≤120%, the participants' data were analyzed in the per-protocol (PP) manner.

3. Efficacy assessment

All principal investigators had a consensus meeting to assess endoscopic features, including erosion, edema, erythema, and hemorrhage, in this study using reference figures before the clinical study started. Based on endoscopic findings, gastric erosion was scored from 1 to 4 (1, no visible erosion; 2, one or two erosions; 3, three to five erosions; 4, more than six erosions) (Supplementary Table 1).[6] Edema, erythema, and hemorrhage were scored from 1 to 2, 1 to 4, and 1 to 5, respectively (Supplementary Table 1).[7] Cure rate of erosions was defined as the portion of disappearance of all erosions. Improvement of endoscopic findings was defined as ≥50% reduction of initial scores at the follow-up endoscopy.

GI symptoms including epigastric pain, epigastric burning, nausea/vomiting, anorexia, abdominal bloating, and belching were self-reported. They were evaluated by severity and frequency. Severity was scored from 0 to 5 (0, none; 1, very weak; 2, weak; 3, moderate; 4, severe; 5, very severe). Frequency was scored from 0 to 4 (0, absent; 1, one or two times a week; 2, three or four times a week; 3, five or six times a week; 4, daily). Symptom scores were measured by the sum of severity and frequency scores. Improvement of GI symptoms was defined as ≥50% reduction of initial scores.[8]

The primary efficacy endpoint was measured as the improvement rate of erosions at the follow-up endoscopy. Secondary efficacy endpoints included the following items: (1) cure rate of erosions, (2) cure rate of edema, (3) improvement rate of erythema, (4) improvement rate of hemorrhage, and (5) improvement rate of GI symptoms.

4. Safety assessment

Safety assessments included adverse events (AEs) and adverse drug reactions. It was assessed by any GI symptoms and abnormalities in the electrocardiography, laboratory findings, and vital signs. All AEs were recorded, including the onset date, stop date, severity, relationship with study drugs, treatment modification, and outcomes.

5. Sample size calculation and Statistical analysis

The sample size was estimated to achieve a noninferiority margin, which was assuming the efficacy rate of treatment and that of placebos were 80% and 30%, respectively, based on the previous studies.[6,8] Considering a 20% dropout rate, this study was designed to enroll 162 patients for each group. Efficacy was measured by the full-analysis set (FAS) and the PP manner. For primary efficacy outcome analysis, a one-sided 97.5% lower limit of difference rate between the two groups was calculated. The erosion improvement rate of DW1903 (test group) was considered noninferior to that of DW1903R1 (control group) if the one-sided 97.5% (equivalent to two-sided 95%) lower limit was greater than −14%, which was the pre-specified noninferiority margin.[4,6] Statistical analyses used a two-sample t-test for continuous variables and a chi-square test or Fisher exact test for categorical variables. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used.

RESULTS

1. Participant demographics and baseline characteristics

A total of 332 patients were enrolled and randomized (Fig. 2). Three patients did not take any study drugs. Ten patients dropped out without efficacy after drug administration, resulting in a population of 319 patients. All patients (159 in the DW1903 group and 160 in the

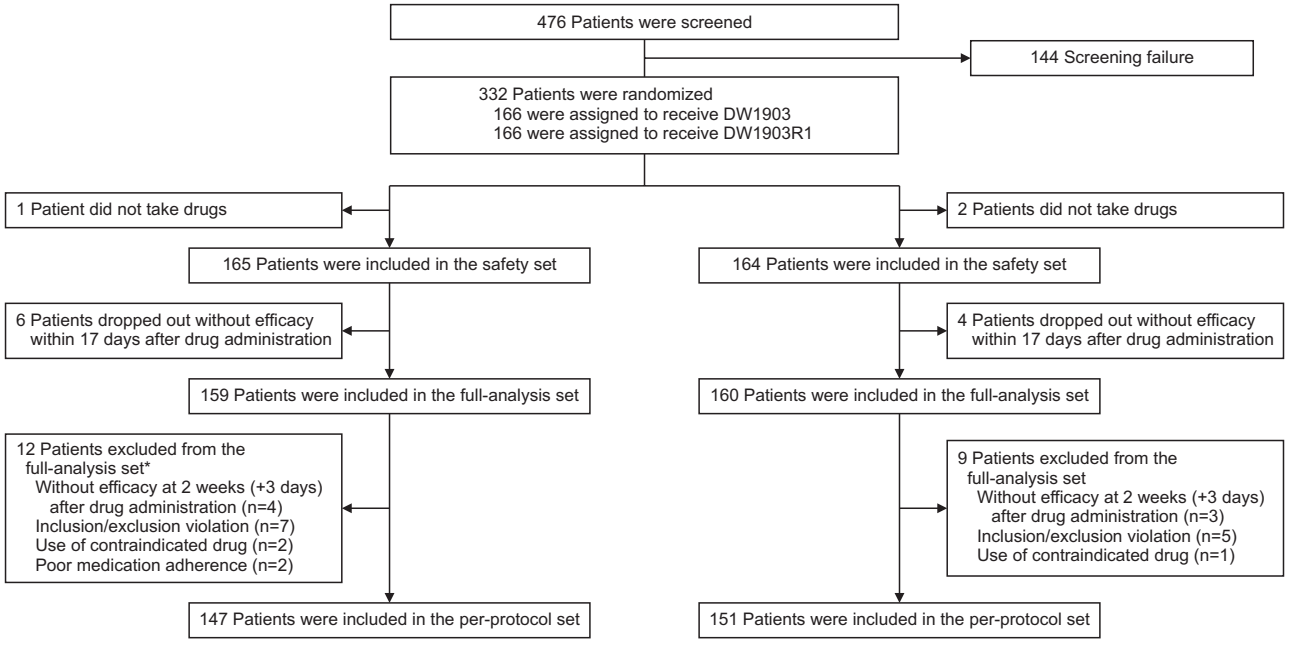

Fig. 2. The CONSORT flow diagram. DW1903, test group (low-dose esomeprazole 10 mg); DW1903R1, control group (famotidine at 20 mg). *Patients may be excluded from the analysis populations due to more than one reason.

Table 1. Baseline Patient Characteristics

Characteristic	DW1903 (n=166)	DW1903R1 (n=166)	p-value
Age, yr	44.86±12.85	45.06±12.47	0.886
Sex			0.113
Male	70 (42.2)	56 (33.7)	
Female	96 (57.8)	110 (66.3)	
Height, cm	165.21±8.99	164.20±8.47	0.293
Weight, kg	65.41±13.60	64.84±12.63	0.692
Body mass index, kg/m^2	23.81±3.69	23.90±3.32	0.803
Smoking status			0.435
Non-smoker	129 (77.7)	131 (78.9)	
Smoker	20 (12.1)	24 (14.5)	
Ex-smoker	17 (10.2)	11 (6.6)	
Alcohol consumption			0.964
Non-drinker	53 (31.9)	55 (33.1)	
Drinker	96 (57.8)	95 (57.2)	
Ex-drinker	17 (10.3)	16 (9.7)	
Classification of gastritis			0.583
Acute gastritis	84 (50.6)	79 (47.6)	
Chronic gastritis	82 (49.4)	87 (52.4)	
Helicobacter pylori infection	46 (27.7)	47 (28.3)	0.903
In acute gastritis	24 (52.2)	20 (42.6)	
In chronic gastritis	22 (47.8)	27 (57.4)	
Gastrointestinal symptoms	148 (89.2)	150 (90.4)	0.717
Erosion grade			0.379
1	0	0	
2	80 (48.2)	80 (48.2)	
3	46 (27.7)	55 (33.1)	
4	40 (24.1)	31 (18.7)	

Data are presented as mean±SD or number (%).
DW1903, test group (low-dose esomeprazole 10 mg); DW1903R1, control group (famotidine at 20 mg).

DW1903R1 group) reported some efficacy data. Their outcomes were analyzed (FAS analysis). Table 1 summarizes the baseline characteristics of subjects in the two groups.

2. Primary efficacy analysis

Table 2 shows results of primary efficacy analysis. Improvement rates of erosions at follow-up endoscopy in DW1903 and DW1903R1 groups were 59.8% (95/159) and 58.8% (94/160), respectively, based on FAS analysis. The one-sided 97.5% lower limit for the healing rate difference between the two groups was −9.8%, which was greater than the noninferiority margin of −14.0%. Therefore, DW1903 was not inferior to DW1903R1. PP analysis showed similar results. The improvement rates of erosions at the follow-up endoscopy in DW1903 and DW1903R1 groups were 61.9% (91/147) and 59.6% (90/151), respectively. The one-sided 97.5% lower limit for the healing rate difference between the two groups was −8.8%, which was greater than the noninferiority margin of −14.0%. Thus, DW1903 was not inferior to DW1903R1. Supplementary Table 2 shows improvement rates of erosions according to the erosion grade. Differences in improvement rates were more prominent for those with grade 4 (≥6 of erosions) than in those with other grades, although such differences were statistically insignificant. Supplementary Table 3 shows improvement rates of erosions according to gastritis. Erosion improvement rates were not statistically different in acute and chronic gastritis.

Table 2. Primary Efficacy Analysis: The Erosion Improvement Rate

Analysis	DW1903	DW1903R1	Difference (95% CI)*	p-value
Full analysis set				
No. of patients	159	160		
Erosion improvement rate, No. (%)	95 (59.8)	94 (58.8)	1.0 (–9.8 to 11.8)	0.856
Per protocol set				
No. of patients	147	151		
Erosion improvement rate, No. (%)	91 (61.9)	90 (59.6)	2.3 (–8.8 to13.4)	0.684

DW1903, test group (low-dose esomeprazole 10 mg); DW1903R1, control group (famotidine at 20 mg); CI, confidence interval.
*The difference is expressed as a one-sided 97.5% lower limit of the difference rate between two groups.

Table 3. Secondary Efficacy Analysis

Analysis	DW1903	DW1903R1	p-value
Full analysis set, No. (%)			
No. of patients	159	160	
Erosion cure rate	89 (56.0)	87 (54.4)	0.774
Edema cure rate	20/53 (37.7)	16/49 (32.7)	0.592
Erythema improvement rate	35/94 (37.2)	36/102 (35.3)	0.778
Hemorrhage improvement rate	47/57 (82.5)	34/50 (68.0)	0.082
GI symptoms improvement rate	97/158 (61.4)	95/158 (60.1)	0.818
Per protocol set, No. (%)			
No. of patients	147	151	
Erosion cure rate	85 (57.8)	84 (55.6)	0.702
Edema cure rate	19/51 (37.3)	15/46 (32.6)	0.632
Erythema improvement rate	32/89 (36.0)	34/96 (35.4)	0.939
Hemorrhage improvement rate	42/52 (80.8)	33/47 (70.2)	0.221
GI symptoms improvement rate	92/146 (63.0)	92/149 (61.7)	0.822

DW1903, test group (low-dose esomeprazole 10 mg); DW1903R1, control group (famotidine at 20 mg); GI, gastrointestinal.

3. Secondary efficacy analysis

Erosion cure rates in DW1903 and DW1903R1 groups based on FAS analysis were 56.0% and 54.4%, respectively, showing no statistically significant difference between the two groups (Table 3). PP analysis showed similar results (Table 3). Edema cure rates and erythema improvement rates between DW1903 and DW1903R1 groups were not significantly different either according to FAS or PP analysis (Table 3). However, hemorrhage improvement rates were higher in the DW1903 than in the DW1903R1 group in FAS analysis, showing a statistical tendency (p=0.082) (Table 3). Improvement rates of GI symptoms were not significantly different between DW1903 and DW1903R1 groups in the FAS or PP analysis (Table 3). However, the rate with ≥75% reduction of initial GI symptom scores was higher in the DW1903 group than in the DW1903R1 group (43.2% vs 39.6% in PP analysis, p=0.54), different from rates with 50% to 74% reduction of initial scores in DW 1903 and DW 1903R1 groups (19.9% vs 22.2% in PP analysis, p=0.63).

4. Safety

The incidence of AEs was investigated. Five patients (3.0%, 6 cases) in the DW1903 group and 12 patients (7.3%, 14 cases) in the DW1903R1 group reported AEs without statistical difference between the two groups. Among patients who reported AEs, four patients (2.4%, 4 cases) from the DW1903R1 group had an adverse drug reaction (1 diarrhea, 1 headache, 1 constipation, 1 dizziness). No adverse drug reaction was reported in the DW1903 group.

DISCUSSION

This study was the first one to investigate the efficacy and safety of a low-dose PPI for treating gastritis. Until now, H2RAs among acid suppressants have been used to treat gastritis, whereas PPIs have not been permitted as a therapy for gastritis. According to the present study, DW1903 (Escorten®; Daewon Pharm Co. Ltd.) of low-dose PPI was not inferior to DW1903R1 of H2RA. Therefore, low-dose PPI can be a novel option for treating gastritis.

PPI is a well-documented, effective, and reliable treatment for GI symptom relief and mucosal healing of acid-related disorders such as gastroesophageal reflux disease.[9] The treatment goal of gastritis is to achieve mucosal healing and relief of GI symptoms. Generally, more robust treatment is necessary for successful mucosal healing.[9-13] Thus, we can hypothesize that low-dose PPI is sufficient to treat gastritis compared with erosive esophagitis or peptic ulcer disease. In addition, the dose of PPI is important when considering safety issues of PPI.[14,15] Complications of a drug should be related to a biological gradient, including the dose and duration of drug use.[14,15] Thus, reducing the PPI dose is important for safe use of PPI.

When considering the efficacy and safety of PPIs for treating gastritis, 10 mg esomeprazole (one-quarter of the standard dose) was planned for treating gastritis. First, a phase 1 clinical trial of DW1903 was performed before the present study. That study had a randomized, open-label, three-treatment, six-sequence, and three-way crossover

design. A total of 30 healthy volunteers underwent 24-hour pH monitoring after taking DW1903 (esomeprazole 10 mg, low-dose PPI), DW1903R1 (famotidine, H2RA), or DW1903R2 (esomeprazole 20 mg, half dose PPI) for 5 days. Low-dose PPI was a more potent acid suppressant than H2RA, which was the current treatment for gastritis according to the PK/PD result of phase 1 clinical trial. Thus, the present phase 3 trial was conducted based on results of that phase 1 trial.

The present phase 3 trial showed that low-dose PPI was not inferior to H2RA in terms of erosion improvement rate. However, improvement rates of erosions were more prominent in grade 4 (≥6 of erosions) than in other grades. In addition, hemorrhage improvement rates were higher in the DW1903 group than in the DW1903R1 group, showing a statistical tendency ($p<0.15$). Regarding improvement rates of GI symptoms, excellent reduction rates (rates with ≥75% reduction of initial GI symptom scores) were higher in the DW1903 group than in the DW1903R1 group. These results showed that low-dose PPI could be more potent in gastritis combined with a severe mucosal injury such as many numbers of erosions or hemorrhage than H2RA. In addition, low-dose PPI can be more effective when expecting dramatic symptom relief than H2RA.

Our study designed the 2-week therapeutic regimens; however, longer therapeutic regimens exceeding 2 weeks might yield more representative results.

In conclusion, the efficacy and safety of DW1903 (Escorten®; Daewon Pharm Co. Ltd.) low-dose PPI were not inferior to those of DW1903R1 H2RA in treating gastritis. Thus, low-dose PPI can be a novel option for treating gastritis.

CONFLICTS OF INTEREST

This study was supported by Daewon Pharm Co. Ltd, Seoul, Korea.

J.H.K., G.H.K., and Y.C.L. are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Study concept and design: S.W.L. Data acquisition: S.W.L., J.H.K., H.Y.J., I.K.Y., S.Y.P., J.G.K., J.K.S., J.S.J., G.J.C., K.O.K., T.O.K., S.T.L., K.B.C., H.J.C., J.J.P., M.I.P., J.Y.J., S.W.J., J.W.C., D.H.K., G.H.K., J.J.K., S.G.K., N.K., Y.C.L., S.J.H., H.S.K. Data analysis and interpretation: J.H.K. Drafting of the manuscript: J.H.K. Critical revision of the manuscript for important intellectual content: S.W.L. Statistical analysis: S.L. Obtained funding: S.L. Administrative, technical, or material support: S.L. Study supervision: S.W.L. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl220446.

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