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Evaluation of the Efficacy and Safety of DA-9601 versus Its New Formulation, DA-5204, in Patients with Gastritis: Phase III, Randomized, Double-Blind, Non-Inferiority Study

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This study compared the efficacy of DA-9601 (Dong-A ST Co., Seoul, Korea) and its new formulation, DA-5204 (Dong-A ST Co.), for treating erosive gastritis. This phase III, randomized, multicenter, double-blind, non-inferiority trial randomly assigned 434 patients with endoscopically proven gastric mucosal erosions into two groups: DA-9601 3 times daily or DA-5,204 twice daily for 2 weeks. The final analysis included 421 patients (DA-5204, 209; DA-9601, 212). The primary endpoint (rate of effective gastric erosion healing) and secondary endpoints (cure rate of endoscopic erosion and gastrointestinal [GI] symptom relief) were assessed using endoscopy after the treatment. Drug-related adverse events (AEs), including GI symptoms, were also compared. At week 2, gastric healing rates with DA-5204 and DA-9601 were 42.1% (88/209) and 42.5% (90/212), respectively. The difference between the groups was −0.4% (95% confidence interval, −9.8% to 9.1%), which was above the non-inferiority margin of −14%. The cure rate of gastric erosion in both groups was 37.3%. The improvement rates of GI symptoms with DA-5204 and DA-9601 were 40.4% and 40.8%, respectively. There were no statistically significant differences between the two groups in both secondary endpoints. AEs were reported in 18 (8.4%) patients in the DA-5204 group and 19 (8.8%) in the DA-9601 group. Rates of AE were not different between the two groups. No serious AE or adverse drug reaction (ADR) occurred. These results demonstrate the non-inferiority of DA-5204 compared to DA-9601. DA-5204 is as effective as DA-9601 in the treatment of erosive gastritis. Registered randomized clinical trial at ClinicalTrials.gov (NCT02282670)

Keywords: Artemisia; Gastritis; Double-blind Study; Adverse Drug Event; Endoscopy

INTRODUCTION

DA-9601 (Stillen®; Dong-A ST Co., Seoul, Korea), an immediate release product which active ingredient is extracted from *Artemisia asiatica*, is used for treating chronic and acute gastritis (1). The recommended dosage regimen is usually thrice per day. DA-9601 is also approved for prophylactic use for potential gastritis in patients who have received nonsteroidal antiinflammatory drugs (NSAIDs); thus, most target consumers are those with chronic pain or those who need antiplatelet therapy. However, most medications prescribed for pain control or by physicians at cardiology clinics are administered once or twice per day; hence, the possibility of low compliance to the three times daily administration of DA-9601, thereby preventing optimal efficacy, has become a general concern. The DA-5204 (Stillen 2X®; Dong-A ST Co.) tablet, with 90 mg of *Artemisia asiatica* 95% ethanol extract per tablet, is a new formulation with longer intragastric retention of the active ingredient, and it is administered twice per day instead of three times per day.

DA-9601 is more beneficial as a gastro-retentive drug delivery system to allow continuous action in the stomach because of the local action of its main component (*Artemisia asiatica* extract) in the stomach. Generally, various systems are used in gastro-retentive technology, such as a high-density system, mucoadhesive or bioadhesive sys-

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tem, expandable system, and floating system. The floating system is the most applicable, but it is difficult to apply floating technology to tablet use because of its high density.

The DA-5204 tablet was developed using gastro-retentive floating technology, which combines controlled release with prolonged gastric-retention time of the *Artemisia asiatica* extract. The formulation and process for low-density microglobular granule were developed to apply the floating system.

The effectiveness and prolonged gastric retention of DA-5204 was confirmed in a study on beagle dogs (2). However, whether DA-5204 administration twice per day for gastritis improves lesions in humans remains unclear. Therefore, we conducted a study to compare DA-5204 (twice per day) and DA-9601 (three times per day) in terms of safety and improvements in endoscopic findings and gastrointestinal (GI) symptoms in patients with gastritis.

MATERIALS AND METHODS

Study subjects

This phase III, multicenter, double-blind, randomized, non-inferiority trial was conducted in Korea from April 2014 to October 2014. Patients were recruited from the following 21 Korean centers: Seoul National University Bundang Hospital (Seongnam), The Catholic University of Korea Seoul St. Mary's Hospital (Seoul), Kangwon National University Hospital (Chuncheon), Kyungpook National University Hospital (Daegu), Pusan National University Hospital (Busan), Samsung Medical Center (Seoul), Asan Medical Center (Seoul), Pusan National University Yangsan Hospital (Yangsan), Severance Hospital Yonsei University (Seoul), Youngnam University Medical Center (Daegu), Wonkwang University Hospital (Iksan), Ewha Womans University Medical Center (Seoul), Inje University Busan Paik Hospital (Busan), Inje University Seoul Paik Hospital (Seoul), Inha University Hospital (Incheon), Chonnam National University Hospital (Gwangju), Chonbuk Natinal University Hospital (Jeonju), Presbyterian Medical Center (Jeonju), Jeju National University Hospital (Jeju), Hanyang University Medical Center (Seoul), and Dong-A University Hospital (Busan).

Inclusion criteria were as follows: 1) patients aged 20 to 75 years with acute or chronic gastritis and 2) those with baseline endoscopic findings indicating ≥ 1 erosions. Exclusion criteria were as follows: 1) patients with a history of peptic ulcer or gastroesophageal reflux disease; 2) patients who had undergone a previous GI operation, such as an operation to inhibit gastric acid secretion or gastrectomy (simple stomach perforation operation was excluded); 3) patient who used any prokinetics, H_2 receptor antagonists, proton pump inhibitors, anticholinergic drugs (muscarinic receptor antagonists), gastrin receptor antagonists, protective factor enhancers, gastric mucosal protective agents, or NSAIDs within 2 weeks of the screening test; 4) women who were pregnant or lactating; 5) women of childbearing age not using contraception; and 6) patients with significant impairments in the hematologic, renal, cardiac, pulmonary, hematopoietic, and endocrine systems and those with known hypersensitivity to DA-9601.

Randomization

Subjects who participated in the clinical study were subjected to blood tests, urinalysis, and upper gastroendoscopy screening tests; and the eligible patients, based on the screening test results, were randomized (1:1 ratio) to the test group (DA-5204; Dong-A ST Co.) or the control group (DA-9601 Tab; Dong-A ST Co.) after a 1-week observation period. The random allocation table was generated by a computer program and distributed to each institution. This study was conducted in a double-blind manner.

Participants received either DA-5204 twice per day with a placebo once per day or DA-9601 three times per day for 2 weeks (Fig. 1). Patients visited each center for follow-up endoscopy 2 weeks after beginning the medication. Compliance was determined by the number of remaining tablets per drug type at the follow-up visit. Data of patients with ≥ 70% drug compliance were included in the per-protocol outcome measurements.

Outcome assessments: efficacy

Each patient underwent an upper GI endoscopy at baseline and 2 weeks after the treatment. Endoscopic erosion was scored and ranged from 1 to 4 (1, no visible erosion; 2, one or two erosions; 3, three to five erosions; 4, more than six erosions) (1) (Supplementary Table 1). Endoscopic results after treatment were assessed as follows: very much improved (4 to 1 or 3 to 1 erosion), much improved (4 to 2 or 2 to 1 erosion), minimally improved (4 to 3 or 3 to 2 erosions), no change (same score), or worse (any increase in score) (Supplementary Table 2). The primary endpoint was the improvement rate, defined as the percentage of patients classified as much improved or very much improved at the follow-up endoscopy 2 weeks after treatment. All principal investigators at each institution discussed how to assess endoscopic erosion before the clinical trial was initiated.

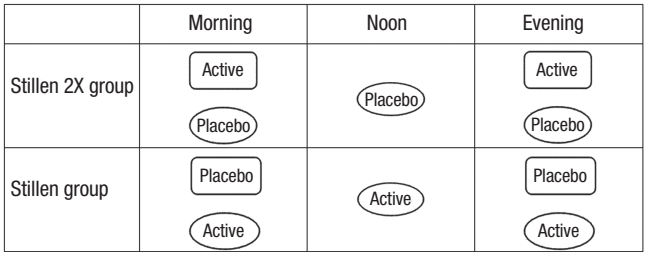

Fig. 1. Schematic illustration of the double-blind technique in the present study. Square and oval shapes indicate the active drugs of DA-5204 and DA-9601, respectively.

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For unification of the assessment, all gastric endoscopy was evaluated and recorded by the principal investigator, who reconfirmed the data if the sub-investigator conducted the gastroendoscopy in his absence.

Outcome assessments: symptoms

The secondary endpoints were the cure rate of erosions and gastric symptom improvement 2 weeks after treatment. Cure was defined as the disappearance of all erosions. The change in gastric symptoms was classified as very much improved (symptom reduction ≥ 75%), much improved (≥ 50% but < 75% symptom reduction), minimally improved (≥ 25% but < 50% symptom reduction), no change (< 25% symptom reduction), or worse (any case of increased score) (3). Effective improvement of gastric symptoms was defined as > 50% reduction of the initial gastric symptoms. The gastric symptoms of epigastric pain, epigastric burning, reflux, nausea, vomiting, abdominal bloating, and belching were self-reported and graded using a 6-point score: 0, none; 1, weak; 2, moderate; 3, severe; 4, very severe; 5, extremely severe. A symptom diary was maintained for 7 days before the baseline assessment and during the 2 weeks of treatment.

Outcome assessments: safety

Safety assessments included adverse events (AEs) and adverse drug reactions (ADRs), including any GI symptoms and abnormalities in laboratory findings or vital signs. Blood samples were obtained at the end of the therapy to determine the concentrations of glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, and bilirubin. Complaint questionnaires were administered to assess for any harmful or untoward reactions experienced by a patient.

Sample size and statistical analysis

We estimated the sample size to achieve a non-inferiority margin (i.e., 14%), assuming that the efficacy rate determined by endoscopy and the efficacy rate of placebos were 67% and 30%, respectively, based on a previous study (1). We expected a 15% dropout rate; thus, the study was designed to enroll 210 patients per group. Efficacy outcomes (or endpoints) were analyzed in the full-analysis set and per protocol set. For the primary efficacy analysis, a one-sided 97.5% lower limit of difference rate between the two groups was calculated. The gastric mucosa healing rate of DA-5204 was considered non-inferior to that of DA-9601 (control group) if the one-sided 97.5% (equivalent to two-

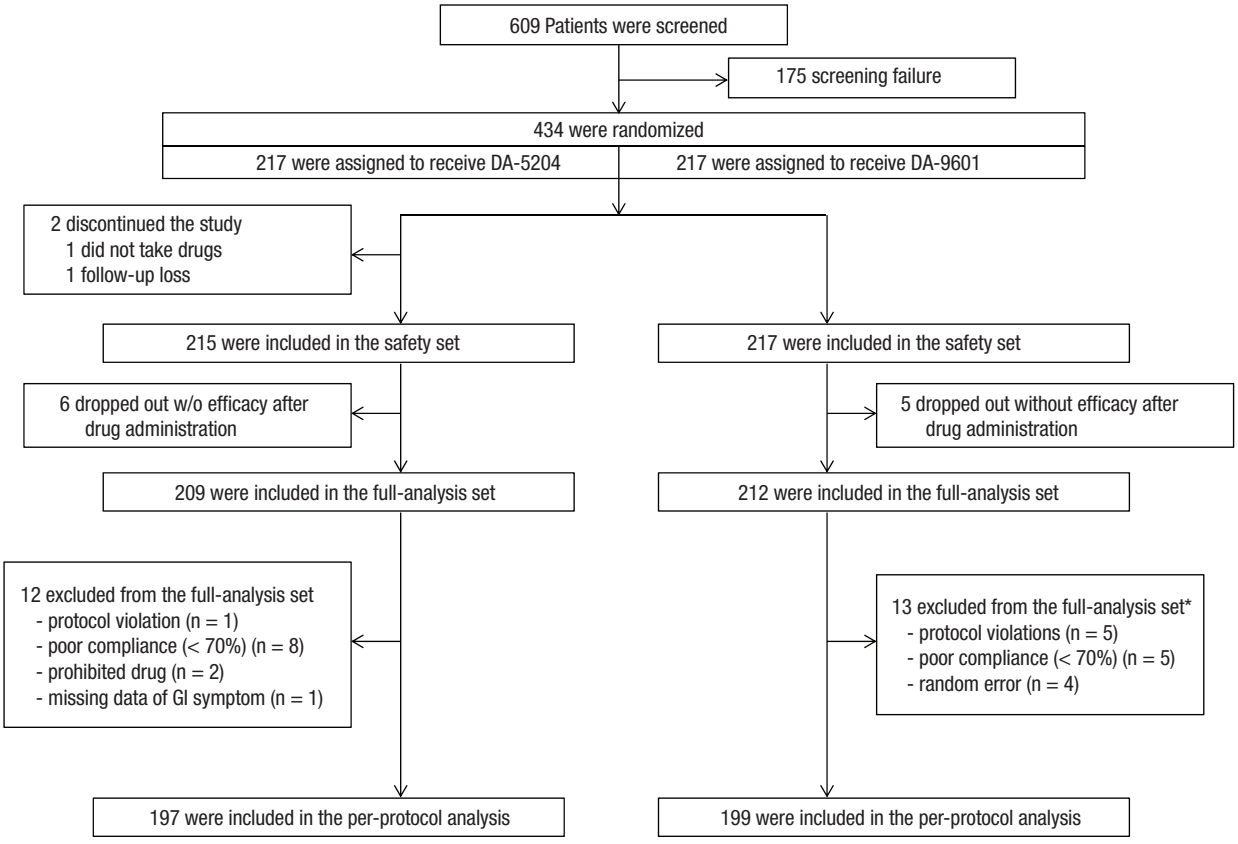

Fig. 2. Flow diagram of study patients.
GI = gastrointestinal.
*One subject was excluded for protocol violation and poor compliance.

sided 95%) lower limit was greater than –14, which was the prespecified non-inferiority margin (1). For AEs, the frequency and proportion (with 95% confidence interval [CI]) of patients who experienced one or more events were recorded and compared using the χ^2 test. Inter-group comparisons were conducted using a χ^2 test. Statistical analyses of the other variables were performed using a t-test or Wilcoxon rank-sum test for continuous data and the χ^2 or Fisher exact test for categorical data. All statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC, USA).

Ethics statement

This study was reviewed by the Institutional Review Board of each of the 21 participating institutions, including Seoul National University Bundang Hospital (B-1404-245-005). Informed consent was submitted by all subjects when they were enrolled. This trial was registered as a standard, randomized clinical trial (ClinicalTrials.gov: NCT02282670).

RESULTS

Allocation of patients

To evaluate the efficacy and safety of DA-5204 and to determine whether DA-5204 was non-inferior to DA-9601 in patients with acute and chronic gastritis, 609 patients were recruited from 21 tertiary hospitals in Korea from April 2014 to October 2014, of whom 434 were randomly assigned to either the DA-5204 (n = 217) or DA-9601 (n = 217) group. Twenty patients in the DA-5204 group and 18 in the DA-9601 group were excluded from the full analysis because of various non-compliance issues and contraindications. Consequently, data for 396 patients (DA-5204, n = 197; DA-9601, n = 199) were available for the per protocol analysis. Fig. 2 presents the flow of study patients with the reasons for premature discontinuation.

Demographic characteristics

Table 1 shows patients' demographic and baseline characteristics. There were no differences between the two groups in terms of age, sex, height, weight, body mass index, or alcohol consumption, except for smoking status. Patients' clinical status at baseline was also comparable in both groups, and the groups had similar GI symptom severity scores and presence of endoscopic gastritis.

Compliance

Drug compliance rates throughout the treatment period were 93.2% and 94.7% in the DA-5204 and DA-9601 groups, respectively. Although the difference between the two groups was statistically significant ($P = 0.008$), it is not important since both groups showed compliance > 90%.

Table 1. Demographic and baseline characteristics of the study patients

Characteristics	DA-5204 (n = 217)	DA-9601 (n = 217)	Total (n = 434)	*P* value
Age, yr	45.29 ± 12.95	46.02 ± 13.18	45.65 ± 13.05	0.464
Sex				0.278
Male	89 (41.0)	78 (35.9)	167 (38.5)	
Female	128 (59.0)	139 (64.1)	267 (61.5)	
Height, cm	164.2 ± 8.57	163.1 ± 8.67	163.7 ± 8.63	0.251
Weight, kg	63.18 ± 11.91	62.26 ± 10.90	62.72 ± 11.41	0.563
BMI, kg/m^2	23.23 ± 2.97	23.32 ± 3.12	23.30 ± 3.04	0.965
Smoking status				0.042
Smoker	43 (19.8)	28 (12.9)	71 (16.4)	
Ex-smoker	25 (11.5)	17 (7.8)	42 (9.7)	
Non-smoker	149 (68.7)	172 (79.3)	321 (74.0)	
Alcohol status				0.811
Drinker	113 (52.1)	109 (50.2)	222 (51.2)	
Ex-drinker	3 (1.4)	2 (0.9)	5 (1.2)	
Non-drinker	101 (46.5)	106 (48.8)	207 (47.7)	
No. of erosions	3.79 ± 3.97	4.53 ± 6.32		0.149
Gastric symptom score*				
Epigastric pain	1.65 ± 4.17	1.29 ± 3.04		0.301
Epigastric burning	5.41 ± 6.37	5.33 ± 6.06		0.886
Acid regurgitation	2.22 ± 4.17	1.85 ± 3.36		0.305
Nausea	3.61 ± 5.78	2.74 ± 4.17		0.073
Vomiting	0.34 ± 1.65	0.19 ± 0.86		0.247
Abdominal bloating	7.08 ± 6.96	6.16 ± 6.30		0.150
Belching	7.19 ± 7.18	7.03 ± 6.54		0.813

Most variables are presented as a mean ± standard deviation or number of patients (%).
BMI = body mass index.
*One patient was excluded in each group.

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Table 2. Endoscopic cure rate of gastric mucosa

Subjects	DA-5204	DA-9601	95% CI	*P* value
Full analysis set				
No. of patients	209	212		
Gastric mucosa improvement rate	88 (42.1)	90 (42.5)	–9.8, –9.1	
Endoscopic cure rate	78 (37.3)	79 (37.3)	–9.2, –9.3	0.990
Ameliorative rates of GI symptoms*	84 (40.4)	86 (40.8)	–9.8, –9.0	0.938
Per protocol set				
No. of patients	197	199		
Gastric mucosa improvement rate	82 (41.6)	86 (43.2)	–11.3, –8.1	
Endoscopic cure rate	73 (37.1)	75 (37.7)	–10.2, –8.9	0.990
Ameliorative rates of GI symptoms*	79 (40.1)	80 (40.2)	–9.8, –9.6	0.984

Data are presented as number of patients (%).
CI = confidence interval, GI = gastrointestinal.
*One patient in each group was excluded from the assessment of symptom change because the symptom diary was lost.

Table 3. Incidence of ADR of the two medications

ADRs	DA-5204 (n = 215)	DA-9601 (n = 217)	*P* value
GI disorder			0.283
Belching	4 (1.9) [4]	1 (0.5) [1]	
Abdominal distension	1 (0.5) [1]	0	
Constipation	0	1 (0.5) [1]	
Dyspepsia	1 (0.5) [1]	0	
Nausea	1 (0.5) [1]	0	
Retching	1 (0.5) [1]	0	
Parameter investigated			0.499
Alanine aminotransferase level	0	1 (0.5) [1]	
Aspartate aminotransferase level	0	1 (0.5) [1]	
Blood alkaline phosphatase level	0	1 (0.5) [1]	
Abnormal liver function test results	0	1 (0.5) [1]	
Total	5 (2.3) [8]	4 (1.8) [6]	

Data are presented as number of patients (%) and [number of cases].
ADR = adverse drug reaction, GI = gastrointestinal.

Primary efficacy endpoint

Gastric mucosa healing rates 2 weeks after drug administration were 42.1% (88/209) and 42.5% (90/212) in the DA-5204 and DA-9601 groups, respectively. The one-sided 97.5% lower limit for the healing rate difference between the two groups was –9.8%, which was greater than the non-inferiority margin of –14.0%. Thus, DA-5204 was not inferior to DA-9601 (Table 2).

Secondary efficacy endpoints

Endoscopic cure rates of the gastric mucosa were 37.3% (78/209) and 37.3% (79/212) in the DA-5204 and DA-9601 groups, respectively. No statistically significant difference in the endoscopic cure rate of the mucosa was observed between the groups (P = 0.990). Improvement rates of GI symptoms (reduction rate of symptoms) were 40.4% (84/208) and 40.8% (86/211) in the DA-5204 and DA-9601 groups, respectively (P = 0.938). The 95% CI for the difference between the groups was –9.8 to 9.0 (Table 2).

Additionally, crude number of gastric erosions were evaluated (Supplementary Table 3). The change in number of gastric erosion after medication were –1.92 ± 3.54 and –2.54 ± 5.63 in the DA-5204 and DA-9601 groups, respectively (P = 0.180). No statistically significant differences in initial and change of number of erosions were observed between the groups (Supplementary Table 3).

Safety

During the study period, AEs were reported in 18 patients (8.4%, 29 cases) in the DA-5204 group and 19 patients (8.8%, 28 cases) in the DA-9601 group. Among those reported AEs, 5 patients (2.3%, 8 cases) from the DA-5204 group and 4 patients (1.8%, 6 cases) from the DA-9601 group were confirmed to have an ADR (Table 3). Belching was the most common event, and AEs and ADR were not statistically significantly different between the two groups (AE, P = 0.890; ADR, P = 0.750). No serious AE or ADR was reported.

DISCUSSION

DA-9601, a phytopharmaceutical medicine derived from *Artemisia asiatica*, has been reported to have antioxidative and cytoprotective actions in various models of gastric mucosal damage (4-6). Eupatilin, a major component of DA-9601, has been shown to inhibit $FeSO_4$-induced reactive oxygen species production and reduce oxidative-driven gene expression, resulting in the prevention of H_2O_2-induced gastric epithelial damage (7) and the production of tumor necrosis factor-α through modulation of p38 kinase and nuclear factor (NF)-κB-dependent pathways (8). Cytoprotective effects of DA-9601 have been reported in several animal and human studies. DA-9601 reduced the alcohol-induced hemorrhagic injury to the gastric mucosa in rats by inhibiting alcohol-induced xanthine oxidase (9) and treated gastric mucosa in patients with erosive gastritis (1).

Although DA-9601 comprises 60 mg of *Artemisia asiatica* 95% ethanol extract, one tablet of DA-5204 has a 1.5-fold greater amount of the active ingredient. Moreover, the DA-5204 tablet was developed using gastro-retentive floating technology, which combines controlled continuous release with a prolonged gas-

tric retention time of the active ingredient. Generally, various systems are involved in gastro-retentive technology, such as a high-density system (10), a mucoadhesive or bioadhesive formula (11), expandable (12), and floating methods (13). Although the floating system is the most applicable among all the systems, a tablet's high density makes the application of floating methods challenging. Thus, to apply the floating system, a process for making low-density microglobular granules was developed. Therefore, DA-5204 readily floats in water because of its low density.

Adverse reactions were observed in 2.3% (5/215) of the patients in the DA-5204 group and 1.8% (4/217) in the DA-9601 group. In both groups, the main adverse reactions were belching and liver enzyme level elevation. No serious adverse reactions were observed.

Simplifying the medication regimen by reducing the number of daily doses is an essential factor to improve adherence to treatment (14). Although gastritis and epigastric pain are not serious illnesses in which drug omission results in mortality, simple and less frequent dosing regimens can lead to better compliance across various therapeutic classes (15).

This study demonstrated that DA-5204 administered twice daily is not inferior to DA-9601 administered three times daily for treating erosive gastritis and improving GI symptoms. DA-5204 has an excellent efficacy and safety profile, and it is a promising option for treating erosive gastritis, and facilitating convenience and adherence through a reduction in the administration frequency.

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DISCLOSURE

Min-hee Oh is a biostatistician of Dong-A ST Co., but she made no influence on this work in relation with the company or its products. Other authors declare that they have no potential conflicts of interest.

AUTHOR CONTRIBUTION

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Supplementary Table 1. Endoscopic scoring of gastric erosions

Scores	No. of gastric erosions
1	No erosions
2	1 or 2 erosions
3	Numerous (3–5) areas of erosions
4	Large number (> 6) of erosions

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Supplementary Table 2. Endoscopic evaluation based on the number of erosions

Evaluations	Change of endoscopy score
Very much improved	4 → 1, 3 → 1
Much improved	4 → 2, 2 → 1
Minimally improved	4 → 3, 3 → 2
No change	4 → 4, 3 → 3, 2 → 2, 1 → 1
Worse	In case of worse

Supplementary Table 3. Crude number of gastric erosions

Subjects	DA-5204	DA-9601	*P* value*
Full analysis set			
No. of patients	209	212	
Baseline	3.68 ± 3.78	4.51 ± 6.37	0.389
Visit3	1.76 ± 2.23	1.97 ± 2.76	0.106
Change from baseline	–1.92 ± 3.54	–2.54 ± 5.63	0.180
Per protocol set			
No. of patients	197	199	
Baseline	3.69 ± 3.84	4.60 ± 6.54	0.089
Visit3	1.70 ± 2.13	1.94 ± 2.76	0.315
Change from baseline	–1.99 ± 3.62	–2.66 ± 5.76	0.167

Data are presented as a mean ± standard deviation.
*Two sample t-test.

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