Alginate-antacid (Gaviscon Double Action) chewable tablets reduce esophageal acid exposure in Chinese patients with gastroesophageal reflux disease and heartburn symptoms

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ABSTRACT

Aim
To assess efficacy of DA alginate-antacid chewable tablets for reducing esophageal acid exposure in Chinese patients with gastroesophageal reflux disease (GERD)

Methods
Forty-four patients reporting moderately severe heartburn symptoms underwent two pH monitoring visits. Treatment sequence was randomized: patients received DA alginate-antacid or placebo at one visit and the alternate treatment seven days later. After a standardized reflux-provoking meal, patients took four tablets of DA alginate-antacid or placebo. Esophageal pH was measured for 4h post-dosing, using an electrode positioned 5cm above the lower esophageal sphincter. Primary endpoint: percentage of 4-h post-dosing period with pH <4. Secondary endpoints: number of acid reflux episodes (pH <4), longest reflux time, and DeMeester scores.

Results
Forty-four patients completed the study and provided data for analysis. With DA alginate-antacid, mean percentage time with pH <4 was 5.1%, significantly less (p=0.0003) than with placebo (14.8%). DA alginate-antacid was statistically significantly superior (p≤0.0290) to placebo (at least 2–3-fold better) for all other endpoints. Two patients reported two mild adverse events (AEs) that resolved within a month of completing the study. No patients had serious and/or severe AEs; none withdrew due to AEs.

Conclusions
DA alginate-antacid was statistically significantly superior to placebo in reducing post-prandial acid exposure without serious clinically relevant health risks. These findings
suggest DA alginate-antacid tablets are appropriate for treating acid reflux in Chinese GERD patients with heartburn symptoms.

**Keywords:** sodium alginate, Gastroesophageal reflux disease, Esophagitis, Heartburn, Esophageal pH Monitoring

ClinicalTrials.gov: NCT01872897

**INTRODUCTION**

Patients with gastro-esophageal reflux disease (GERD) commonly experience troublesome symptoms such as heartburn and acid reflux, which adversely affect health-related quality of life and work productivity\(^1\)-\(^3\). Notably, almost half of symptomatic reflux episodes occur after meals\(^4\). Post-prandial accumulation of acidic, unbuffered gastric secretions in the proximal stomach gives rise to an ‘acid pocket’ that can persist for up to 2 h\(^5\),\(^6\). This acid pocket has been identified in both healthy individuals and patients with GERD as a source of post-prandial acid reflux\(^5\),\(^7\). In GERD patients, the acid pocket is often enlarged and extended towards the esophageal-gastric junction, features which are associated with increased acid reflux\(^7\),\(^8\). As the main source of acidic gastro-esophageal reflux, the acid pocket represents an important therapeutic target\(^9\).

Alginate-antacid formulations target the acid pocket directly via a unique non-systemic mechanism. On coming into contact with gastric acid, alginate-antacids rapidly form a buoyant gel-matrix ‘raft’ with a near-neutral pH within the proximal stomach\(^10\). This raft can remain in place above the stomach contents for up to 4 h\(^11\).
and is cleared by gastric emptying. Recent pH-impedance and imaging studies with Gaviscon alginate-antacid formulations have provided direct evidence that the alginate raft localizes to the acid pocket and displaces it away from the esophageal-gastric junction.

In clinical studies, alginate-antacid formulations significantly reduced acid reflux compared to antacids alone, suggesting that this mode of targeting the acid pocket can provide effective acid reflux suppression. Importantly, alginate-antacids are also fast-acting, with some patients reporting relief of symptoms as rapidly as 3–15 min after taking the medication. Consistent with their mode of action, alginate-antacid formulations have been shown to exert their greatest effects within the first hour after dosing, with effects that can last for up to 4 h.

Ambulatory pH monitoring provides direct and objective physiological measurements of esophageal acid exposure and is a standard method for evaluating acid-suppressive treatments for GERD. Gaviscon Double Action (Gaviscon DA; Reckitt Benckiser Healthcare [UK] Limited, Hull, United Kingdom) is an alginate-antacid formulation approved for treatment of acid-related symptoms of gastro-esophageal reflux such as acid regurgitation and heartburn. In pH-monitoring studies conducted in European GERD patients, the Gaviscon Double Action formulation (henceforth referred to as DA alginate-antacidor Gaviscon DA) decreased both the number of acid reflux events and overall acid exposure time over a 2–4-h post-meal period, compared to placebo. However, the physiological effects of the DA alginate-antacid tablet formulation have not been measured in Chinese patients with GERD.

The present study was designed to examine the effects of DA alginate-antacid chewable tablets on esophageal pH and post-prandial acid reflux in Chinese.
GERD patients, using a randomized, placebo-controlled two-way crossover design. In this study, esophageal pH monitoring over a 4-h period was used to compare the effects of DAalginate-antacid tablets with placebo on acid reflux provoked by a standardized ‘refluxogenic’ test meal.

METHODS

This was a randomized, open-label, placebo-controlled, two-period crossover study conducted at three hospitals in China between July 2013 and December 2013. The study was approved by the respective independent ethics committees of the three hospitals. Informed consent was obtained from all individual participants prior to their inclusion in the study. All procedures performed in this study that involved human participants were in accordance with the ethical standards of the institutional research committees and applicable regulatory requirements in China, and with the Helsinki declaration or comparable ethical standards. The study is registered in the ClinicalTrials.gov trial registry (NCT01872897).

Patients

Patients were recruited from among those treated at the hospitals or those who visited the hospitals to participate in the trial. The trial included adults (18 to 65 years inclusive) who had a primary diagnosis of GERD and met the diagnostic criteria for GERD (Montreal definition), with a history of frequent episodes of GERD-related symptoms in the two months prior to study screening. Patients had to have heartburn and/or acid reflux as the only or main symptom, and to have reported moderate to severe heartburn on three or more days per week in the three weeks prior to screening.
Patients were excluded if they had (i) participated in any other Gaviscon trials; (ii) taken any medications which might interfere with the action of the study medications prior to the start of the study or during the study; (iii) a clinical history or signs suggestive of seriouserosive GERD (Los Angeles [LA] classification grades C and D were excluded), Barrett’s esophagus, acute peptic ulcer and/or ulcer complications, indication for H. pylori eradication therapy, or any other gastrointestinal disease; (iv) a history of drug abuse, volatile solvents, or alcohol (≥140 g of alcohol per week); (v) any existing conditions that might compromise their safety or participation in the study. Details of the trial eligibility criteria are on the ClinicalTrials.gov trial registry website.25

Study medications
Study medications (DA alginate-antacid and placebo in chewable tablet form) were supplied by the Reckitt Benckiser (RB) Investigational Material Supply Unit (IMSU; Hull, United Kingdom). Each DAalginate-antacidchewable tablet contained 250 mg sodium alginate, 106.5 mg sodium bicarbonate, and 187.5 mg calcium carbonate as active ingredients. The standard dose is two to four DAalginate-antacidtablets, to be taken by mouth up to four times a day (after meals and before lying down for bed). While no blinding to the identity of study medications was intended in this study, the placebo tablets matched the DA tablets in appearance, odor, and flavor, while containing no active ingredients. The main constituents of the placebo tablets were mannitol and xylitol, plus standard excipients.

During the study, patients received DA alginate-antacid as a non-investigational medicinal product (NIMP) to take for symptom relief. The NIMP was supplied by the RB IMSU. Other than the NIMP, therapies that were not permitted
prior to or during the study included: PPIs (during the 10 days prior to screening and throughout the study); prokinetics or H$_2$-RAs (during the 5 days prior to screening and throughout the study); PPI-based triple or quadruple therapy for eradication of *Helicobacter pylori* (during the 28 days prior to screening and throughout the study); and any antacids (within 24 hours before randomization and throughout the remainder of the study). Patients who used any of the above medications during the study were to be withdrawn.

**Randomization and treatment schedule**

After providing written informed consent, patients underwent a screening period of up to 10 days. Those who satisfied the study entry requirements within 10 days of providing consent were randomly assigned to one of two treatment sequences (AB or BA), based on a computer-generated randomization code list prepared by RB. A randomization block size of 4 was used. Study medications were packaged by the RB IMSU and labeled according to the randomization code list, to be dispensed to patients with the corresponding codes.

Patients underwent two pH monitoring visits, with seven days in between visits. Each patient in the treatment sequence group AB received four tablets of DA alginate-antacid at the first visit and four tablets of placebo at the second visit. Patients in group BA received placebo at the first visit and DA alginate-antacid at the second visit (Figure 1A). The cross-over design ensured that each patient acted as his/her own control.

Patients were instructed to fast for at least 4 h before study visit procedures. High-resolution manometry was used to position a pH electrode 5 cm above the superior margin of the lower esophageal sphincter. After positioning of the pH electrode, patients consumed a standard reflux-provoking test meal (McDonalds Big
Mac, medium fries and medium-sized fruit-flavored carbonated soft drink). Thirty minutes after the end of the meal, patients received a single dose of study medication (four DA alginate-antacid tablets or four placebo tablets). Esophageal pH was then recorded for 4 h post-dosing (Figure 1B). The 4-tablet dose used in the two pH monitoring visits thus represents the higher dose used for single dosing.

Between pH monitoring visits, patients received DA alginate-antacid as an NIMP to take for symptom relief every day. Patients were instructed to take two tablets of the NIMP four times per day. The NIMP was provided after the first visit, but had to be stopped 24 hours prior to the second pH monitoring visit. The lower 2-tablet dose was used to minimize compliance issues with NIMP treatment over the period between visits. In between visits, patients were asked to follow their normal meal patterns and avoid food not normally consumed.

**Esophageal pH monitoring**

pH monitoring was performed using a Digitrapper 24-h pH monitoring system (Given Imaging, USA). Esophageal manometry (ManoScan 360 High Resolution Manometry System; Given Imaging, USA) was used at the first visit to position the pH electrode 5 cm above the superior margin of the lower esophageal sphincter.

Approximately 15 min after the pH electrode was in place, patients consumed the test meal. The study medication was given 30 min after the end of the meal. pH recording was started after the meal and continued until 4 h post-dosing. During the pH monitoring period, patients were instructed to remain upright (sitting or standing only). No eating or drinking was permitted.
**Efficacy and safety assessments**

The primary populations for evaluating efficacy and safety were the intention-to-treat (ITT) and safety populations, respectively. The ITT population included all eligible patients who took at least one dose of study medication and had evaluable pH monitoring data for at least 1 h post-dosing. The per-protocol (PP) population (all eligible patients who completed both pH monitoring visits and all study procedures without major protocol deviations), was used only for secondary evaluation of the primary endpoint. The safety population included all eligible patients who took at least one dose of study medication.

Acid reflux episodes were detected as occasions when esophageal pH fell below pH 4. Efficacy variables measured the overall duration and the number of episodes of acid reflux, as well as global esophageal acid exposure (DeMeester scores\(^{21}\)). The primary efficacy variable was the percentage of time during the 4-h post-dosing period that esophageal pH fell below pH 4. Secondary efficacy variables were: number of reflux episodes with pH <4; number of reflux episodes with pH <4 for at least 5 min; duration of the longest reflux episode with pH <4. Percentage time with pH <4 and number of reflux episodes with pH <4 were also separately analyzed for the first hour post-dosing. For patients with less than 4 h of post-dose pH monitoring data, pH parameters were adjusted according to the duration of the recording.

Safety assessments were based on records of AEs, as well as clinical laboratory investigations, vital signs and physical examinations performed at Visit 1 and Visit 3. Clinical laboratory investigations included hematology and biochemistry. The electrolytes monitored were sodium, potassium, and calcium. All AEs that occurred during the study period were documented. Reporting of AEs was based on patient recall. The incidence of AEs was summarized overall and by seriousness, severity, and relatedness to the study medication.
**Sample size determination**

Statistical justification for the sample size in this study could not be performed in the standard way because the variance of the response was not known for Gaviscon Double Action chewable tablets, the formulation of alginate-antacid investigated in this study. Assumptions for the sample size calculation for this study were derived using experience from an earlier study\(^{26}\) on Gaviscon Liquid, a formulation with the same dose of alginate (and therefore the same raft-forming capacity) as the tablet formulation in the present study. Based on the assumptions derived from the earlier pH monitoring study\(^{26}\), it was anticipated that evaluable data from 36 patients would be required. To achieve this, 44 patients were to be enrolled in this study.

**Data analysis**

The primary analysis tested the null hypothesis that there was no difference between DA alginate-antacid and placebo in percentage of time with pH $<4$. This was done by comparing the least-squares (LS) means for the two treatments and assessing the difference in least-square 95% confidence intervals (CIs), for the ITT population.

The primary endpoint was analyzed using an Analysis of Variance (ANOVA) model, with terms for treatment, dosing visit, and treatment sequence as fixed effects, and patient nested within treatment sequence as a random effect. This model assumed that the percentage of time with pH $<4$ within each treatment sequence group (AB or BA) would be normally distributed. As there was a major departure from the ANOVA assumptions for normality and/or homogeneity of residual variance, the analysis was repeated as specified in the analysis plan using
logarithmically-transformed percentage time values [natural logarithm of percentage time values +1, ln(%time+1)], in order to confirm the results.

Analyses of all secondary endpoints were conducted for the ITT population identically to those described for the primary endpoint. Sensitivity analyses of the primary and secondary endpoints were conducted using the PP population. Since the qualitative results for both ITT and PP populations were very similar, only the ITT results have been presented. Statistical analyses were conducted using two-tailed tests at the 5% significance level. All analyses were conducted using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient disposition and baseline characteristics

Figure 1A summarizes the flow of patients through the trial and their reasons for withdrawal from the trial. Forty-five patients were randomized to the two treatment sequence groups, AB and BA (Figure 1A). Of these, 44 patients took at least one dose of study medication and were included in the safety population. These 44 patients also comprised the efficacy evaluation (ITT) population: 21 in Group AB and 23 in Group BA (Figure 1A). All 44 patients completed the study and provided evaluable data.

Demographics and baseline characteristics of the study population are shown in Table 1. Over half of the patients were male (57.8%), mean age was 40.4 years, and mean BMI was 22.4 kg/m². Most patients (n=30; 66.7%) had non-erosive reflux disease; 33.3% had erosive reflux disease (LA grade A: 20.0%; grade B, 13.3%). In more than 90% of patients, the severity of heartburn was moderate or severe.
pH monitoring data was generally complete and of adequate quality. All patients had more than 2 h of recorded data, and only two out of 44 patients had less than 4 h (240 min) of post-dose pH monitoring data. For these two patients, pH parameters were adjusted based on the length of the available data recording (239 min and 234 min, respectively).

**Efficacy**

On average, esophageal pH was below pH 4 for 14.8% of the 4-h post-dosing period with placebo, and for 5.1% of the period with DA. The scatterplot in Figure 2 shows patient-level data for the percentage of time with pH < 4 with DA alginate-antacid and with placebo. The majority of the data points lie below the 45-degree reference line that represents equal percentage of time with pH < 4 under the two treatments (dotted line). Thus, for most patients, the percentage of time with pH < 4 was lower on DA alginate-antacid than on placebo over the 4-h post-dosing period. This is additionally illustrated in the box-and-whisker plots (Figure 2, left and bottom panels) showing the distributions of percentage time with pH < 4 on DA alginate-antacid and placebo, respectively.

On average, acid exposure was highest during the first hour of the 4-h post-dosing period. In the absence of active treatment (with placebo), pH was below pH 4 for 16.3% of the first hour, compared with 14.8% on average for the full 4-h period. Similarly, the average number of episodes with pH < 4 per unit time was larger within the first hour compared with the average for the entire 4-h period (Supplementary Table S1).

In the presence of DA alginate-antacid, acid exposure was reduced to a much lower level than on placebo, both within the first hour and over the full 4-h period. For the 4-h post-dosing period, the mean LS difference for the primary
endpoint was $-9.8\%$ (95% CI: $-14.9\%$ to $-4.7\%; p=0.0003$) in favor of DAalginate-antacid (Figure 3). This represents an approximately three-fold lower acid exposure time with DAalginate-antacid compared to placebo. For the first hour post-dosing, the difference in favor of DAalginate-antacid was even larger (LS mean difference $-14.4\%$ [95% CI: $-20.6\%$ to $-8.2\%$]; $p<0.0001$) (Figure 3). The treatment difference was highly statistically significant both for the first hour and the 4-h post-dosing period.

The primary endpoint analysis was repeated with the transformed endpoint values because of the departure from the ANOVA model assumptions. The transformation that was deemed appropriate for the observed data distribution was $\ln(\%\text{time}+1)$. The statistical significance of the between-treatment difference based on the transformed analysis ($p<0.0001$) was consistent with that in the non-transformed analysis ($p=0.0003$) (Supplementary Table S1). The magnitude of the treatment difference was likewise consistent with that seen in the non-transformed analysis: the back-transformed estimate of the difference between treatments corresponded to a 2.9-fold lower acid exposure with DAalginate-antacid than with placebo.

Patients also experienced highly statistically significantly fewer acid reflux episodes (occasions when pH <4) with DAalginate-antacid than with placebo, both during the first hour post-dosing and over the entire 4-h period ($p\leq0.0004$). In the 4-h post-dosing period, the mean (standard deviation, SD) number of episodes was 11.4 (16.4) for DAalginate-antacid vs. 30.9 (34.2) occasions for placebo; the LS mean difference was $-19.4$ (95% CI: $-29.6$ to $-9.2$; $p=0.0004$). For the first hour post-dosing, the mean (SD) number of episodes was 1.7 (3.6) for DAalginate-antacid and
9.0 (10.2) for placebo, with LS mean difference of -7.3 (95% CI: -10.0, -4.6; p≤0.0001) (Figure 3; Supplementary Table S1).

DA alginate-antacid performed significantly better than placebo in all other secondary efficacy analyses over the 4-h post-dosing period (Supplementary Table S2). The longest acid reflux episode was three times shorter on average with DA alginate-antacid than with placebo [mean (SD): 3.3 (6.8) min vs. 9.6 (20.1) min]. The treatment difference for this endpoint (LS mean difference) was -6.3 min (95% CI: -10.9 to -1.8 min) and was also statistically significant (p=0.0075). DeMeester scores, which measure global acid exposure, were statistically significantly lower with DA alginate-antacid than with placebo over the 4-h post-dosing period [LS mean difference -24.2 (95% CI: -37.4 to -10.9); p=0.0007].

Safety

Adverse events reported during the study are summarized in Table 2. The incidence of AEs was low, with only two patients (4.5%) who reported two mild AEs at the second pH monitoring visit, after receiving placebo one week earlier and after self-administering NIMP (Gaviscon DA) tablets to relieve GERD symptoms over the previous week. Each of these AEs was a transient decrease in white blood cell counts that resolved within a month of the patient completing the study. Other than these two mild AEs, no clinically significant quantitative laboratory findings or changes in vital signs were recorded. No patients experienced serious and/or severe AEs, and there were no withdrawals from study treatment due to AEs.
DISCUSSION

Post-prandial acid reflux and heartburn are among the most prominent manifestations of GERD. The severity of GERD symptoms and complications such as esophagitis are known to be related to the amount of acid reflux and esophageal acid exposure. Various anti-reflux medications have therefore been developed to suppress acid secretion, including proton pump inhibitors (PPIs) and histamine H₂-receptor antagonists (H₂-RAs). Unlike other anti-reflux medications, raft-forming alginate-antacid works by neutralizing and displacing the acid pocket, which is the main source of acidic gastro-esophageal reflux.

The present study is the first to measure the effect of Gaviscon Double Action (alginate-antacid) chewable tablets on esophageal acid exposure in Chinese GERD patients using a randomized, placebo-controlled, two-period crossover design. The study results indicate the nature and degree of benefit in a patient population likely to use this anti-reflux medication, namely GERD patients with moderate to severe heartburn symptoms who may be taking over-the-counter medications for short-term relief.

Post-prandial esophageal pH monitoring was performed in Chinese patients with a clinical diagnosis of GERD, whose main or only symptom was heartburn of at least moderate severity. Except for one patient who withdrew consent before undergoing any study procedures, all patients were able to complete the study (n=44). Most patients (n=42) had evaluable pH data for the full 4-h monitoring period. In this cohort, pH was below pH 4 for approximately 15% of the monitoring period in the absence of active treatment (placebo), similar to levels previously reported for a group of patients with endoscopically confirmed low-grade esophagitis²⁷.
Compared with placebo, DA alginate-antacid significantly decreased the overall acid reflux time (percentage of time with pH < 4) and the number of acid reflux episodes (occasions when pH < 4) following a reflux-provoking meal. Over a 4-h period, patients experienced approximately threefold lower acid reflux with DA alginate-antacid than with placebo. DA alginate-antacid was statistically significantly superior to placebo (at least two- to three-fold better) for the primary endpoint and all secondary endpoints (p ≤ 0.0290 for all) (Figure 3; Supplementary Tables S1 and S2).

These data objectively demonstrate the efficacy of DA alginate-antacid tablets in controlling post-prandial acid exposure for at least 4 h after a single dose of medication. Both acid reflux time and the number of acid reflux episodes were significantly reduced with DA alginate-antacid versus placebo. The results are in good agreement with those from pH monitoring studies in European GERD patients. In these studies, post-prandial acid reflux was significantly reduced following treatment with a liquid formulation of alginate-antacid (Gaviscon DA)\textsuperscript{14, 16}.

Importantly, the present study also shows that, like other Gaviscon alginate-antacid formulations that have been studied, DA alginate-antacid chewable tablets exert their effects relatively rapidly. Esophageal acid exposure was significantly reduced within the first hour post-dosing, as well as over the full 4-h period. In fact, the treatment difference for acid reflux time was larger for the first hour compared to the overall 4-h period. These observations are consistent with results from a study comparing time to onset of action for another alginate-antacid formulation (Liquid Gaviscon) with ranitidine (H\textsubscript{2}-RA) and omeprazole (PPI), versus a water control\textsuperscript{20}. While both Liquid Gaviscon and ranitidine significantly reduced esophageal acid exposure over a 4-h period, time to onset of action was much
shorter with Liquid Gaviscon. Esophageal pH increased almost immediately after dosing with Liquid Gaviscon and the greatest effects were seen over the first hour\textsuperscript{20}. Similarly, studies investigating the onset of perceived symptom relief with Gaviscon alginate-antacid formulations indicate that patients can experience relief within 5–15 minutes of taking these medications\textsuperscript{17-19}.

This mechanistic study was designed to quantify the effects of DA alginate-antacid treatment over a 4-h post-prandial period. Unlike PPIs and other anti-reflux medications, alginate-based formulations act non-systemically within the proximal stomach and esophagus, and are cleared by gastric emptying within a few hours after a meal\textsuperscript{11, 12}. Therefore the 2–4 h post-meal period is the most relevant period of observation in this experimental setting. Indeed, within the present study, pH measurements showed that acid exposure was most pronounced within the first hour of the post-prandial monitoring period.

Although acid exposure is the main cause of esophageal damage and an important source of heartburn symptoms in GERD, non-acidic or weakly acidic reflux has also been linked to troublesome symptoms in patients with non-erosive GERD\textsuperscript{28, 29}. A recent pH-impedance monitoring study indicated that, although the overall number of reflux events (acidic or non-acidic) was not reduced after administration of DA alginate-antacid, the pH of these reflux events was less acidic\textsuperscript{16}. In the context of the present study, performing combined pH-impedance monitoring could have yielded additional information on the occurrence of non-acidic or weakly acidic reflux events during the post-prandial monitoring period. This could have been helpful in interpreting the results for the substantial proportion (66.6%) of patients with heartburn symptoms but without evidence of erosive esophagitis at baseline.
The present study did not attempt to analyze associations between esophageal pH changes and patient-reported symptoms over the post-prandial monitoring period. Esophageal pH monitoring is a standard procedure used to evaluate the effects of anti-reflux medications on acid exposure. However, the experimental setup, particularly nasal intubation for pH probe placement, results in a level of discomfort and relative immobility during pH monitoring. This limits the ability to assess the effects of the medication on esophageal pH and symptoms at the same time under real-life conditions. This study therefore focused on measuring the effects of DA alginate-antacid treatment on acid exposure in Chinese GERD patients.

These objective pH data are complemented by those from recent studies based on patient-reported GERD symptom scores, including one study conducted in a similar Chinese GERD cohort. This was a randomized double-blind placebo-controlled study that used a validated patient-reported outcome instrument, the Reflux Disease Questionnaire (RDQ), as the primary endpoint. Chinese GERD patients receiving DA alginate-antacid tablets reported statistically significantly greater improvement in GERD symptoms (heartburn, regurgitation, and dyspepsia) after 7 days of treatment. Taken together, findings from the pH monitoring and symptom relief studies support the efficacy of DA alginate-antacid tablets for treating post-prandial acid reflux and heartburn, and for short-term symptom relief in GERD.

The present study compared the effect of DA alginate-antacid tablets on post-prandial esophageal acid exposure with that of placebo in Chinese GERD patients with moderately severe heartburn symptoms. DA alginate-antacid was superior to placebo for reducing acid exposure provoked by a refluxogenic meal, with a favorable benefit/risk balance. Treatment with DA alginate-antacid was well-tolerated in this study; only two mild AEs were reported and there were no withdrawals due to
AEs. Analysis of safety variables indicated no serious safety issues. With this direct, objective evidence of mechanistic benefit without serious clinically relevant health risks, DA alginate-antacid (Gaviscon DA) chewable tablets may be appropriate for the treatment of heartburn symptoms in Chinese GERD patients.

Authors’ contributions
Yao Zong YUAN, Jing Yuan FANG and Duo Wu ZOU were responsible for data acquisition and revision of the article for important intellectual content. Bartosz JENNER was responsible for interpretation of statistical and methodological aspects of the study, and revision of the article for important intellectual content. Nigel LEVINSON and Joanne WILKINSON were responsible for conception and design of the trial, data interpretation and revision of the article for important intellectual content. All authors approved the final version of the manuscript.

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Conflict of interest: Yao Zong YUAN, Jing Yuan FANG and Duo Wu ZOU have no relevant interests to disclose. Nigel LEVINSON, Bartosz JENNER and Joanne WILKINSON are employees of Reckitt Benckiser (UK). This study was funded in full.
REFERENCES


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<table>
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<th>Characteristic</th>
<th>All patients (n=45)</th>
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<td>Male, n (%)</td>
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<td>Severity of heartburn, n (%)‡</td>
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<td>Level 1</td>
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<td>Level 3</td>
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<tr>
<td>Average frequency of heartburn (days per week), mean (SD)</td>
<td>5.3 (1.25)</td>
</tr>
</tbody>
</table>

†Los Angeles (LA) classification grade A or B only. Patients with severe erosive reflux disease (grade C or D) were excluded from this study.

‡Heartburn severity level:

- Level 0: No heartburn.

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• Level 1: Heartburn is mild in severity and is not obvious.

• Level 2: Heartburn is moderate or obvious when it occurs, and the patient experiences discomfort.

• Level 3: Heartburn is severe and significant, seriously interfering with daily activities.

BMI, body mass index; SD, standard deviation
### Table 2. Incidence of adverse events (safety population)

<table>
<thead>
<tr>
<th>Adverse events (AEs)</th>
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<tr>
<td>Any severe¶ AE</td>
<td>0</td>
</tr>
<tr>
<td>Any AE leading to discontinuation of study medication</td>
<td>0</td>
</tr>
</tbody>
</table>

AE, adverse event

†Both AEs were transient decreases in white blood cell counts that resolved within a month of the patient completing the study.

‡Adverse events that were at least possibly related to the study medication.

§ Serious AEs were defined as any AEs that resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or were otherwise considered to be medically significant.

¶ Severe AEs were defined as AEs that resulted in an inability to carry out usual activities, for example, the patient may have experienced intolerable discomfort or pain.
Figure 1. Patient disposition (A) and study treatments (B). ITT, intent-to-treat; PP, per-protocol; DA, Double Action (alginate-antacid; Gaviscon Double Action)
Figure 2. Patient-level data for percentage of time with pH <4 in the 4 h post-dosing period (ITT population, n=44). Scatterplot showing percentage of time in the 4-h post-dosing period with pH <4 on DA (alginate-antacid; Gaviscon Double Action) vs. placebo (ITT population; n=44). Each point represents data for an individual patient. Points that lie below the 45-degree reference line (dotted) indicate a lower percentage of time with pH <4 on DA vs. placebo. Box-and-whisker plots along the horizontal axis (“Placebo”) and the vertical axis (“DA”) of the scatterplot show the distributions of percentage time with pH <4 on DA and placebo, respectively. Boxes: 25th, median (50th) and 75th percentiles of distributions; whisker ends: minimum and maximum values.
Figure 3. Post-prandial acid reflux time and number of acid reflux episodes with DA (alginate-antacid) vs. placebo over the post-dosing period (ITT population, n=44). Treatment difference (least-squares mean difference and 95% confidence interval) for percentage of time with pH <4 (A) and number of acid reflux episodes (pH <4) (B) for DA (alginate-antacid; Gaviscon Double Action) compared with placebo, for the first hour and for the overall 4-h post-dosing period. **** denotes a highly statistically significant (p ≤ 0.001) difference. DA, Double Action (alginate-antacid; Gaviscon Double Action); CI, confidence interval; LS, least-squares; ITT, intent-to-treat; p, p-value for the comparison between DA and placebo to test the null hypothesis of no difference in LS means.
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