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Open

Double-Blind Randomized Trials of Single-Tablet Ibuprofen/High-Dose Famotidine vs. Ibuprofen Alone for Reduction of Gastric and Duodenal Ulcers

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OBJECTIVES: **We performed two 24-week double-blind trials (REDUCE-1 and -2 (Registration Endoscopic Studies to Determine Ulcer Formation of HZT-501 Compared with Ibuprofen: Efficacy and Safety Studies)) to assess whether double-dose famotidine given in a single-tablet combination with ibuprofen (HZT-501) significantly reduces gastric and duodenal ulcers as compared with ibuprofen.**

METHODS: **Patients (40–80 years) requiring daily non-steroidal anti-inflammatory drugs (NSAIDs) for ≥6 months with no prior ulcer complications, negative *H. pylori* stool test, and baseline endoscopy showing no ulcers and <5 erosions were randomly assigned in a 2:1 ratio to HZT-501 or identical-appearing ibuprofen 800 mg tablets thrice daily. Study endoscopies were done at 8, 16, and 24 weeks. After unblinding and initial analyses, 12 patients were found to be misclassified as having gastric ulcers based on the adjudication of endoscopy reports, and analyses were re-run.**

RESULTS: **In REDUCE-1, the primary end point analysis of gastric ulcers at 24 weeks with HZT-501 vs. ibuprofen was 12.7% vs. 22.9% ($P=0.0044$) in the post-adjudication analysis. In REDUCE-2, the primary end point analysis of upper gastrointestinal (GI) ulcers was 13.0% vs. 20.5% ($P=0.0587$) in the post-adjudication analysis. Prespecified pooled analyses showed significantly fewer gastric (12.5% vs. 20.7%) and duodenal ulcers (1.1% vs. 5.1%) with HZT-501 vs. ibuprofen. Proportional hazards analysis of multiple potential risk factors showed the risk ratio of upper GI ulcers with HZT-501 vs. ibuprofen was 0.46, 95% confidence interval was 0.34–0.61.**

CONCLUSIONS: **Combined results of the REDUCE studies indicate that double-dose famotidine plus ibuprofen, given as a combination tablet, decreases endoscopic upper GI ulcers as compared with ibuprofen alone.**

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as analgesics (1,2). Ibuprofen is the most commonly used non-aspirin NSAID, with about one quarter of the US population aged 17 years or older reporting ibuprofen intake in the past month (2). The main factor that limits NSAID use is the development of upper gastrointestinal (GI) adverse effects including ulcers, complications such as bleeding, and dyspepsia. Strategies recommended (3–6) to decrease GI injury in NSAID users include co-therapy with misoprostol or proton-pump inhibitors and/or use of COX-2 selective inhibitors.

Histamine$_2$-receptor antagonists (H2RAs) have not been recommended for preventive therapy in NSAID users because, when given in standard doses, they significantly decrease duodenal but not gastric ulcers (3,7). However, a Cochrane systematic review of placebo-controlled randomized trials ≥3 months (7) identified one study showing a significant benefit of double-dose H2RAs in reducing both gastric ulcers (relative risk (RR)=0.42, 95% confidence interval, 0.18–0.97) and duodenal ulcers (RR=0.19, 0.04–0.85) (8). The RRs for proton-pump inhibitor vs. placebo co-therapy in the meta-analysis were 0.40 (0.32–0.51) for gastric ulcers and 0.19 (0.09–0.37) for duodenal ulcers (7).

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Although many national and international groups recommend protective therapy in NSAID users at increased risk of GI events (3–6), most such patients are not prescribed protective therapy (8,9). In addition, patients may not take their protective co-therapy along with their NSAID, especially if they are not experiencing any symptoms, and decreased adherence is associated with a significantly increased risk of developing upper GI ulcers or bleeding (10–13). For example, van Soest *et al.* (13) reported that the risk of an upper GI clinical event (bleeding, perforation, or symptomatic ulcer) in NSAID users at increased GI risk rose 16% for every 10% decrease in the proportion of time a proton-pump inhibitor or H2RA was prescribed. Mechanisms that ensure adherence to protective therapy, such as the combination of an NSAID and a protective agent in one pill, theoretically should decrease the GI risk associated with the NSAID therapy.

We performed the REDUCE trials (Registration Endoscopic Studies to Determine Ulcer Formation of HZT-501 Compared with Ibuprofen: Efficacy and Safety Studies) to assess whether double-dose famotidine given in a single-tablet combination with ibuprofen (HZT-501 (ibuprofen 800 mg plus famotidine 26.6 mg); Horizon Pharma, Northbrook, IL) significantly reduces the proportion of patients who develop gastric ulcers (REDUCE-1) or upper GI (gastric or duodenal) ulcers (REDUCE-2) during 24 weeks of treatment as compared with ibuprofen in adult NSAID users.

METHODS

Patients

Male and female patients aged 40–80 years expected to require daily NSAID therapy for at least 6 months for pain and/or inflammatory conditions were eligible. Exclusion criteria included history of erosive esophagitis; history of GI complications (bleeding, perforated ulcer, gastric outlet obstruction due to an ulcer); history of NSAID-associated asthma exacerbations, acute renal failure, interstitial nephritis, or hepatitis; history of GI malignancy; history of myocardial infarction, unstable cardiac arrhythmias, or stroke within 6 months of study entry; coronary artery bypass graft surgery within 14 days of study entry; uncontrolled congestive heart failure or hypertension at entry; acid-suppressive therapy or misoprostol within 14 days before study entry or investigational drug or NSAIDs (including aspirin >325 mg daily) within 30 days before study entry; ulcer or >5 erosions on screening upper GI tract endoscopy; or one of the following abnormalities on baseline laboratory testing: creatinine clearance <45 ml/min; aminotransferase >2.5 times upper limit of normal; fasting blood sugar >200 mg/dl; serum pregnancy test positive; serologic tests positive for human immunodeficiency virus, hepatitis B, or hepatitis C; or stool antigen for *H. pylori* positive.

Study design

Patients were randomly assigned, using a computer-generated randomization schedule, from a central location utilizing an interactive voice response system with blinded medication kit number allocation in a 2:1 ratio to identical-appearing tablets of HZT-501 (800 mg ibuprofen and 26.6 mg famotidine) or ibuprofen (800 mg) thrice daily for 24 weeks. Patients, care providers, and all study personnel were blinded to the treatment. Patients were stratified for two risk factors for ulcer development: concomitant use of low-dose aspirin (≤325 mg daily) and/or anticoagulant medication and history of gastric or duodenal ulcer. In addition to the screening upper endoscopy at baseline, patients had endoscopy at weeks 8, 16, and 24 (or earlier if premature study termination) of study therapy. The following medications were proscribed during the study: medications that may reduce ulcers (e.g., misoprostol, proton-pump inhibitors, and non-study H2RAs), non-study NSAIDs other than low-dose aspirin taken for cardiovascular prophylaxis. In addition, antacids could not be taken for >3 days in any 2-week period; patients requiring further antacid therapy were to be discontinued from the trial. The study medication was dispensed in an 8-week supply at 0, 8, and 16 weeks. Compliance was determined by pill count of returned bottles of study medication. Serum chemistries, complete blood count, and prothrombin time were performed at screening, week 8, week 16, and the final study visit (week 24 or earlier if early termination). Urinalysis was done at baseline and final visit.

End points and analysis

The primary end point for REDUCE-1 was gastric ulcers identified at endoscopy during the 24-week study period, with three secondary end points: upper GI ulcers (gastric and duodenal), duodenal ulcers, and GI complications (bleeding, ulcer perforation, and gastric outlet obstruction due to ulcer). The primary end point for REDUCE-2 was upper GI (gastric or duodenal) ulcers identified at endoscopy during the 24-week study period, with three secondary end points: gastric ulcers, duodenal ulcers, and GI complications. An endoscopic diagnosis of ulcer required unequivocal depth and diameter of ≥3 mm. The predefined primary population for analysis included all patients who were randomized, received a dose of study medication, and had at least one study-mandated follow-up endoscopy.

A sample size for REDUCE-1 of 875 was calculated based on a 90% power to detect a difference of 6% vs. 14% in the incidence of gastric ulcers with a two-sided α of 0.05 and assuming a 15% drop-out rate. A sample size for REDUCE-2 of 600 was calculated based on a 90% power to detect a difference of 6% vs. 16% in the incidence of upper GI ulcers with a two-sided α of 0.05 and assuming a 15% drop-out rate. Statistical comparisons were predefined to be done with a fixed testing sequence (hierarchical) in the following order of primary followed by secondary end points: REDUCE-1: gastric ulcers, upper GI ulcers, duodenal ulcers, GI complications; REDUCE-2: upper GI ulcers, gastric ulcers, duodenal ulcers, GI complications. With this approach, the first null hypothesis that is accepted (i.e., $P \geq 0.05$) will cause immediate acceptance of all subsequent null hypotheses in the sequence (subsequent comparisons will be considered not significantly different and no statistical comparison will be performed). This approach also requires no α adjustment for multiple comparisons (14).

The two different primary end points in the individual studies were chosen to address both the more clinically relevant end point of upper GI ulcers (gastric and/or duodenal) and the traditional US FDA (Food and Drug Administration) end point of gastric ulcers. In clinical practice, physicians and patients are concerned about preventing ulcers, whether they are gastric or duodenal, and many clinical trials use this primary end point. However, the FDA generally has approved antisecretory medications for prevention of gastric ulcers (e.g., lansoprazole and esomeprazole). These two trials were designed to be used for registration, and, in pre-trial meetings, the FDA agreed to the use of the different end points in the two trials.

Comparison between treatment arms of the crude proportions of patients with ulcers at 24 weeks with a Cochran–Mantel–Haenszel test stratified by the two randomization risk factor strata (use of low-dose aspirin and other anticoagulants, prior ulcer history) was specified as the primary statistical analysis at the time of sample size calculation and study initiation. Before study termination and unblinding, the primary analysis was changed to a comparison between treatment arms of the life table estimates of the proportion of patients with ulcers at 24 weeks employing a modified χ^2 using the sum of squares from the life table in the error term, with the comparison of crude proportions using the Cochran–Mantel–Haenszel test maintained as a secondary analysis. Numbers-needed-to-treat (NNTs) and absolute risk reductions were calculated using crude proportions.

A pooled analysis of the patients in REDUCE-1 and -2 was prespecified, with the primary end point being upper GI ulcers, and the secondary end points being gastric ulcers and duodenal ulcers. The proportion of patients developing ulcers was also prespecified to be assessed in the following subgroups: use of low-dose aspirin and/or anticoagulants, prior ulcer history, age (≥65 vs. <65 years), gender, and race. In addition, *post hoc* subgroup analysis included use of low-dose aspirin alone, and presence or absence of erosions at screening endoscopy. For comparison of

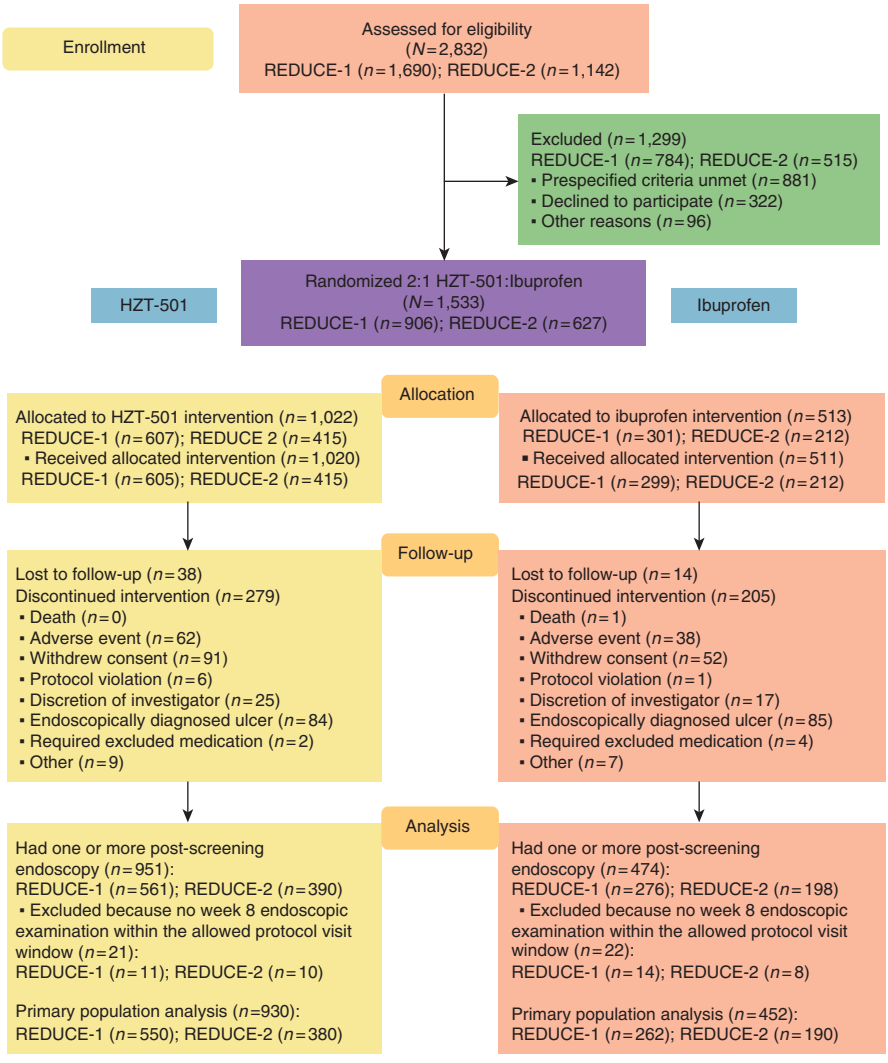

Figure 1. Trial flow and patient disposition.

subgroups with <100 patients across the combined treatment arms, a Fisher's exact test was used. The independent variables prior ulcer history, gender, age, low-dose aspirin use, baseline erosions, and therapy also were included in a proportional hazards model to determine the effect on the dependent variable of development of upper GI ulcer. Treatment-by-subgroup interaction was also assessed among these subgroups in the model. A *post hoc* fixed effect meta-analysis of the results of the two studies for end points of upper GI, gastric, and duodenal ulcers was also performed (Review Manager 5.1, Cochrane Collaboration, Copenhagen, Denmark).

Statistical comparison between the study groups in the population of all patients randomized was also prespecified for common adverse events (occurring in >5% of patients) with a Cochran–Mantel–Haenszel test. In addition, we prespecified comparison of the proportion of patients who reported any symptom consistent with dyspepsia (e.g., dyspepsia, upper abdominal pain or discomfort, epigastric pain or discomfort, stomach pain or discomfort; with and without nausea).

All study patients provided written informed consent and the study was approved by institutional review boards for all participating centers.

RESULTS

The progress of the studies from enrollment through analysis is shown in the CONSORT diagrams in **Figure 1**. The REDUCE-1 trial took place from March 2007 through August 2008 at 68 centers in the United States and REDUCE-2 took place from March 2007 through September 2008 at 68 centers in the United States. The trials continued until their planned completion based on the prespecified sample sizes. Selected baseline characteristics of the primary population analyzed in the two study groups for each trial are shown in **Table 1**. Reason for NSAID use across both trials included pain (37.9%), osteoarthritis (50.6%), rheumatoid arthritis (3.5%), and other (7.8%).

The initial results after data lock and unblinding in REDUCE-1 for the primary end point of proportion of patients with gastric ulcers at 24 weeks was 12.9% for HZT-501 and 25.3% for ibuprofen ($P=0.0009$; NNT = 11). The initial results for the primary end point in REDUCE-2 showed the proportions of patients with upper GI ulcers of 13.8% for HZT-501 and 22.6% for ibuprofen ($P=0.0304$; NNT = 11).

After unblinding and performance of the statistical analyses, a review of endoscopy reports revealed that some patients with esophageal ulcers had been incorrectly assigned as having gastric

Table 1. Baseline characteristics of patients randomly assigned to HZT-501 or ibuprofen

Characteristic	Group					
	REDUCE-1 trial		REDUCE-2 trial		Pooled data	
	HZT-501 (*N*=550)	Ibuprofen (*N*=262)	HZT-501 (*N*=380)	Ibuprofen (*N*=190)	HZT-501 (*N*=930)	Ibuprofen (*N*=452)
Age (years)						
Median	55.0	55.0	54.0	54.0	55.0	55.0
Range	40–80	40–78	39–79	40–78	39–80	40–78
Age class % (n)						
<65 years	81.5% (448)	82.1% (215)	82.6% (314)	82.1% (156)	81.6% (762)	82.1% (371)
≥65 years	18.5% (102)	17.9% (47)	17.4% (66)	17.9% (34)	18.1% (168)	17.9% (81)
Gender % (n)						
Male	32.0% (176)	31.3% (82)	34.2% (130)	28.4% (54)	32.9% (306)	30.1% (136)
Female	68.0% (374)	68.7% (180)	65.8% (250)	71.6% (136)	67.1% (624)	69.9% (316)
Race % (n)						
White	77.1% (424)	77.5% (203)	81.6% (310)	84.7% (161)	78.9% (734)	80.5% (364)
Black	19.5% (107)	20.2% (53)	15.0% (57)	10.5% (20)	17.6% (164)	16.2% (73)
Other	3.5% (19)	2.3% (6)	3.4% (13)	4.7% (9)	3.4% (32)	3.3% (15)
Potential risk factors % (n)						
Prior ulcer history	7.6% (42)	5.7% (15)	4.7% (18)	5.8% (11)	6.5% (60)	5.8% (26)
Use of low-dose aspirin and/or anticoagulants	17.1% (94)	13.4% (35)	15.5% (59)	13.2% (25)	16.5% (153)	13.3% (60)
Use of low-dose aspirin	16.7% (92)	12.6% (33)	15.0% (57)	13.2% (25)	16.0% (149)	12.8% (58)
Use of corticosteroids	0	0	0.3% (1)	0	0.11% (1)	0
Erosions at baseline	23.8% (131)	17.2% (45)	21.3% (81)	19.5% (37)	22.8% (212)	18.1% (82)

REDUCE, Registration Endoscopic Studies to Determine Ulcer Formation of HZT-501 Compared with Ibuprofen: Efficacy and Safety Studies.

ulcers. An adjudication committee of two independent gastroenterologists then reviewed all positive endoscopy reports to determine how many ulcers had been misclassified. In the primary population, five patients in REDUCE-1 (one HZT-501 (no ulcer), four ibuprofen (four esophageal ulcers)) and seven patients in REDUCE-2 (three HZT-501 (two no ulcer, one esophageal ulcer), four ibuprofen (one no ulcer, three esophageal ulcers)) had esophageal ulcers misclassified as gastric ulcers or had no gastric ulcer present; duodenal ulcers were not affected. The results for the analyses were then re-run with these patients no longer listed as having gastric ulcers. These post-adjudication results are presented in **Table 2**. In REDUCE-1, the primary end point of proportion of patients with gastric ulcers at 24 weeks was 12.7% for HZT-501 and 22.9% for ibuprofen ($P=0.0044$; NNT = 12). The results for the primary end point in REDUCE-2 showed the proportions of patients with upper GI ulcers of 13.0% for HZT-501 and 20.5% for ibuprofen ($P=0.0587$).

Assessment of the secondary ulcer end points in REDUCE-1 revealed that significantly fewer patients receiving HZT-501 developed upper GI ulcers in both the initial (NNT = 9) and post-adjudication analysis (NNT = 10), and significantly fewer patients developed duodenal ulcers (NNT = 25). Assessment of secondary end points in REDUCE-2 showed that the 6.7% reduction in life table estimate of gastric ulcers was not significant in the initial comparison ($P=0.0795$) and the 5.3% reduction in the post-adjudication analysis was not formally tested based on the predefined hierarchical testing sequence for the analysis. The combined trial cumulative incidence for crude rate of ulcers by visit is shown in **Figure 2**.

Results of the pooled analysis of the two studies are also shown in **Table 2**. When a fixed effect meta-analysis of the two studies was performed, the differences and 95% confidence intervals were identical to those shown in **Table 2** for the pooled analyses of upper GI, gastric, and duodenal ulcers without evidence of heterogeneity ($I^2=0$ for upper GI, gastric, and duodenal ulcer analyses). In addition, when the Cochran–Mantel–Haenszel analysis was re-run with study (REDUCE-1 or -2) included in the model, the P values for comparisons of all three end points remained <0.0001.

The combined trial data of the primary population was used in a proportional hazards analysis to examine multiple risk factors in relation to development of upper GI ulcers. Treatment with HZT-501 (vs. ibuprofen) was associated with a significantly lower risk ratio (RR) for upper GI ulcer formation in the initial (RR = 0.44, 0.33–0.58) and post-adjudication analyses (RR = 0.46, 0.34–0.61). Patients ≥65 years had a significantly higher risk ratio of upper GI ulcer formation (initial: 1.47, 1.06–2.05; post-adjudication: 1.54, 1.10–2.17) than those <65 years. RRs of upper GI ulcer formation for low-dose aspirin use were 1.40 (0.97–2.02) for initial and 1.46 (1.004–2.11) for post-adjudication analyses and for prior ulcer history they were 1.55 (0.95–2.53) for initial and 1.65 (1.01–2.69) for post-adjudication analyses. Baseline erosions did not show a significant association with upper GI ulcer formation (initial: 1.20, 0.86–1.67; post-adjudication: 1.15, 0.82–1.62).

The effect of treatment was also examined within subgroups for the combined studies. The forest plot of these is shown in **Figure 3**.

Table 2. The proportions of patients (life table and crude rate) in the primary population developing an upper GI, gastric, or duodenal ulcer in the post-adjudication analysis (excluding esophageal or no ulcers previously labeled as gastric ulcers) over 24 weeks of treatment

	REDUCE-1 trial		REDUCE-2 trial		Pooled results	
	HZT-501 *N* =550	Ibuprofen *N* =262	HZT-501 *N* =380	Ibuprofen *N* =190	HZT-501 *N* =930	Ibuprofen *N* =452
Upper gastrointestinal (gastric or duodenal) ulcers						
Life table %	14.5%*	26.9%	13.0%	20.5%	13.9%**	24.3%
Crude rate % (*n*)	11.1% (61)***	21.8% (57)	9.7% (37)*	17.9% (34)	10.5% (98)***	20.1% (91)
Absolute risk reduction (95% CI)	10.7% (5.0, 16.3%)		8.2% (1.9, 14.4%)		9.6% (5.4, 13.8%)	
Gastric ulcers						
Life table %	12.7%*	22.9%	12.2%	17.5%	12.5%**	20.7%
Crude rate % (*n*)	9.8% (54)**	18.3% (48)	8.9% (34)*	15.8% (30)	9.5% (88)***	17.3% (78)
Absolute risk reduction (95% CI)	8.5% (3.2, 13.8%)		6.8% (0.9, 12.8%)		7.8% (3.8, 11.8%)	
Duodenal ulcers						
Life table %	2.1%*	7.1%	0.9%	6.6%	1.6%*	6.9%
Crude rate % (*n*)	1.3% (7)*	5.3% (14)	0.8% (3)*	4.7% (9)	1.1% (10)***	5.1% (23)
Absolute risk reduction (95% CI)	4.1 (1.2, 7.0%)		3.9% (0.8, 7.1%)		4.0% (1.9, 6.1%)	

CI, confidence interval; GI, gastrointestinal; REDUCE, Registration Endoscopic Studies to Determine Ulcer Formation of HZT-501 Compared with Ibuprofen: Efficacy and Safety Studies.

*$P<0.05$; **$P<0.001$; ***$P<0.0001$.

No significant treatment-by-subgroup interactions were identified for the subgroups assessed (all *P* values >0.10).

Only two adverse event terms were reported in either study at a rate of ≥5%: dyspepsia and nausea. The rates for HZT-501 vs. ibuprofen in the pooled results were 4.7% vs. 8.0% for dyspepsia and 5.8% vs. 4.7% for nausea. However, the proportion of patients with one or more predefined symptoms consistent with dyspepsia was not significantly different between HZT-501 and ibuprofen (12.3% vs. 14.9%).

GI complications were reported by investigators for three patients (0.6%) given HZT-501 and zero given ibuprofen in REDUCE-1. These were GI bleeding episodes in which hemoglobin dropped 1.6, 2.1, and 3.1 g/dl without clinical evidence of overt GI bleeding, transfusions, or hospitalizations. Gastric erosions were noted at endoscopy in all three patients. No GI complications were reported in REDUCE-2. One death occurred in the two studies: a 48-year-old female in the ibuprofen group died of cardiorespiratory arrest and multiorgan system failure attributed to acetaminophen toxicity.

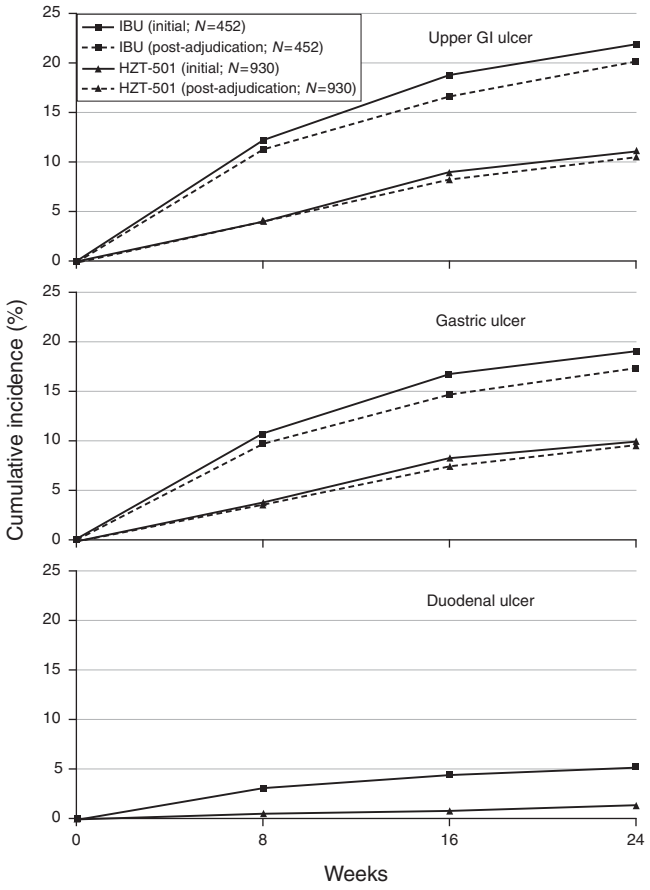

Figure 2. The cumulative incidence (crude rate (%)) of ulcers at 8, 16, and 24 weeks in patients taking HZT-501 or ibuprofen (IBU) for the initial and post-adjudication analysis of the pooled data for the primary population of REDUCE-1 and REDUCE-2 trials. GI, gastrointestinal; REDUCE, Registration Endoscopic Studies to Determine Ulcer Formation of HZT-501 Compared with Ibuprofen: Efficacy and Safety Studies.

DISCUSSION

The goal of the REDUCE trials was to confirm the results of a single smaller study by Taha *et al.* (15), and demonstrate a significant decrease in NSAID-associated gastric and duodenal ulcers with double-dose famotidine, using a combination tablet of ibuprofen and famotidine.

Two studies of identical design were performed, as is generally required when phase 3 trials are used to apply for regulatory approval. The trials differed only in their sample size and their primary vs. secondary end point (gastric ulcers followed by upper GI ulcers in REDUCE-1 and upper GI ulcers followed by gastric ulcers in REDUCE-2). After unblinding and initial analyses were performed, it was discovered on adjudication of endoscopy reports that 12 patients listed as having gastric ulcers actually had esophageal ulcers or no ulcers. Therefore, analyses were re-run using the post-adjudication data, with these 12 patients no longer listed as having gastric ulcers.

The larger REDUCE-1 trial demonstrated a significant decrease in the primary end point of gastric ulcers ($P=0.0044$) as well as in duodenal ulcers. The smaller REDUCE-2 trial did not show a significant difference in the post-adjudication primary analysis of life table estimates of upper GI ulcers, with a *P* value of 0.0587; the secondary statistical comparison of crude proportions of upper GI ulcers revealed a *P* value of 0.0070. Pooled analysis of the trials showed a significant decrease in upper GI ulcers with an NNT of 11, as well as significant decreases in both components, gastric ulcers and duodenal ulcers.

Multivariable analysis revealed a significant RR reduction in ulcers of ~55% with HZT-501 after adjustment for risk factors that may influence the development of ulcers, such as age, ulcer history, aspirin use, and baseline erosions. Furthermore, the treatment

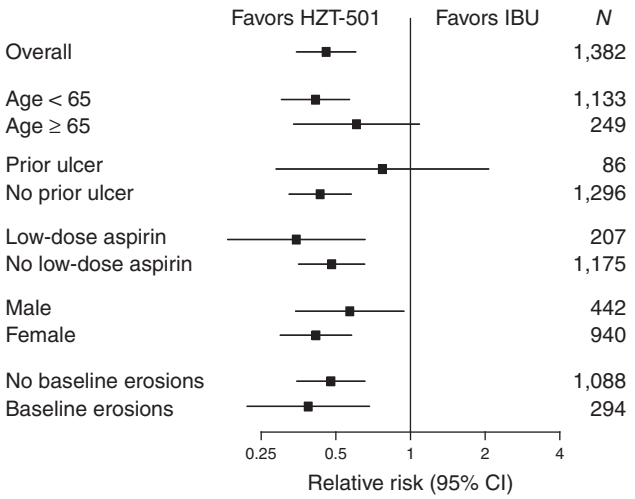

Figure 3. Forest plots of the relative risks (95% confidence interval (CI)) for upper gastrointestinal ulcers for HZT-501 vs. ibuprofen (IBU) in subgroup analyses of the pooled data for the primary population of REDUCE-1 and REDUCE-2 trials. The sample sizes for each of the subgroups are shown at the right side. REDUCE, Registration Endoscopic Studies to Determine Ulcer Formation of HZT-501 Compared with Ibuprofen: Efficacy and Safety Studies.

effect of HZT-501 was not significantly different in subgroups of patients with or without these characteristics. Of interest, there was no decrement in treatment effect noted among patients taking low-dose aspirin.

Ibuprofen was chosen as the NSAID studied because it is the most widely used non-aspirin NSAID in the United States (2). Although famotidine is generally given twice daily, ibuprofen at full doses for arthritis is typically given thrice daily. The double-dose famotidine was therefore given as three daily doses of 26.6 mg in the combination tablet. A preliminary study suggested that 26.6 mg thrice daily produces gastric acid suppression similar to 40 mg twice daily after 1 day (16). Also, oral administration of HZT-501 is bioequivalent to concurrent oral administration of equivalent separate doses of ibuprofen and famotidine (17).

Previous trials have suggested that H2RAs may decrease upper GI symptoms in patients taking NSAIDs (18,19). We did not find a significant decrease in the proportion of patients spontaneously reporting a composite of symptoms consistent with dyspepsia. Future studies should formally assess NSAID users with a patient-reported outcome instrument validated for NSAID-associated dyspepsia.

Upper GI complications such as bleeding are more important clinically than ulcers identified at a scheduled endoscopy, although results of endoscopic ulcer trials in NSAID users generally correlate with results in outcome trials assessing upper GI complications (7,20). Nevertheless, our study was insufficient in size and duration to reasonably assess complications, and the results do not demonstrate a benefit in complications. No patients had overt bleeding, obstruction, or perforation. Two patients in the HZT-501 arms (and none in the ibuprofen arms) had asymptomatic hemoglobin decreases >2.0 g/dl, the level typically used in outcome trials as a clinically relevant hemoglobin drop (21,22), and a third had a 1.6 g/dl decrease. Chan *et al.* (22) recently showed that such hemoglobin drops are much more common than overt complications in patients taking an NSAID plus antisecretory therapy, and that a majority are probably of small intestinal origin. Our patients with hemoglobin drops had gastric erosions noted, although no examination was performed to assess potential small intestinal injury.

Very few patients were on antiplatelet agents other than low-dose aspirin so our study is unable to assess any potential interactions of famotidine with clopidogrel. Famotidine, like ranitidine and unlike cimetidine, shows little or no interaction with the hepatic cytochrome P450 system (23).

In summary, the combined results of two studies indicate that double-dose famotidine plus ibuprofen, given as a combination tablet, decreases endoscopic upper GI ulcers as compared with ibuprofen alone. Use of a combination tablet theoretically should improve adherence to antisecretory therapy as compared with use of separate individual NSAID and antisecretory agents, but future studies will be necessary to prospectively study adherence and the effect on endoscopic or clinical outcomes.

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CONFLICT OF INTEREST

Guarantor of the article: Loren Laine, MD.

Specific author contributions: Planning and conducting study, analysis/interpretation of data, drafting and revision of the manuscript, approved the final draft submitted: Loren Laine; planning and conducting study, collecting data, interpretation of data, critical review of the manuscript, approved the final draft submitted: Alan J. Kivitz, Alfonso E. Bello, and Michael H. Schiff; analysis/interpretation of data, critical review of the manuscript, approved the final draft submitted: Amy Y. Grahn; analysis/interpretation of data; drafting and critical review of the manuscript, approved the final draft submitted: Ali S. Taha.

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Potential competing interests: Loren Laine is a consultant for Horizon Pharma, AstraZeneca, Eisai, and Logical Therapeutics; is on the Data Safety Monitoring Board for Merck, Bayer, and BMS. Alfonso E. Bello is a consultant for Horizon Pharma and Pfizer; is a speaker for Abbott and Amgen. Amy Y. Grahn is an employee of Horizon Pharma. Michael H. Schiff is a consultant for Horizon Pharma. Ali S. Taha is a consultant for Horizon Pharma and Astellas Pharma.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Histamine$_2$-receptor antagonists (H2RAs) are not generally recommended to decrease gastrointestinal risk in non-steroidal anti-inflammatory drug (NSAID) users.
- ✓ H2RAs in standard doses do not significantly decrease gastric ulcers in NSAID users.

WHAT IS NEW HERE

- ✓ A single-tablet combination of double-dose famotidine plus ibuprofen reduced gastric and duodenal ulcers as compared with NSAIDs alone.

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