CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022519Orig1s000

MEDICAL REVIEW(S)

Team Leader's Memorandum

Submission: NDA 22519
Product: Duexis (ibuprofen 800mg and famotidine 26.6 mg)
Sponsor: Horizon Therapeutics, Inc.
Indication: Risk reduction of ibuprofen-associated upper-gastrointestinal ulcer
Medical Div: DGP
Reviewer: M. Welch, DB3

The purpose of this memorandum is to document concurrence with the clinical trials section of the labeling as negotiated with the sponsor and to comment on some aspects of the review experience that were not addressed in the primary review. The primary reviewer noted that only Study HZ-CA-303 provides a persuasive level of evidence of efficacy in support of the intended indication and that Study HZ-CA-301 is not persuasive (on its own) since its conclusions depend on the assumed outcomes of early terminated subjects. I agree with this conclusion.

Prior SPA agreements with the sponsor in Nov. 06 centered on two features that were critical to the final analyses: how study drop-outs would be handled and the statistical methods to be used. The critical assumption was that patients who terminated the study early, without endoscopic evaluation, would not be considered treatment failures, that is, would not be considered to have developed an ulcer. The initial SPA agreement to the Cochran-Mantel-Haenszel (CMH) test of proportions as the primary analysis method was less of an issue, as this method is generally preferred, but because of drop-outs, results from both the CMH and Life Table (LT) methods depended on missing data patterns and assumptions.

During the course of the review, the sponsor was advised that the Agency's conservative analyses of proportions, assuming early terminators as treatment failures, would be considered a key sensitivity analysis, and the sponsor performed many sensitivity analyses, using different ITT populations and different early terminator assumptions which basically gave mixed results for Study 301; that is, statistical significance was not consistently shown. However, because of the robustness demonstrated in Study 303 (dependent in part on the larger sample size compared to Study 301) the directional (albeit weaker) effects from Study 301, could, at best, be considered marginally supportive. In particular, a conclusion that Study 301 was a failed study based primarily on a sensitivity analysis (assuming all drop-outs as treatment failures) seemed an unreasonable judgment.

One unusual aspect of the sponsor's analysis plan development however occurred when they submitted their SAP for review (Sep 2008). They had then proposed the use of the Kaplan Meier (KM) method to estimate treatment group proportions, a technique which adjusts for the "time on study" of early terminators. However this change to the analysis would not have been in compliance with the initial SPA agreement. It is not clear why the sponsor was changing the analysis at this point. The primary reviewer advised the sponsor that if they were to use the KM approach, the LT method would be preferable. However, for the final labeling negotiations, the sponsor reverted to use of the CMH results. (Both CMH and LT results for the primary endpoint were statistically significant given the assumption that early terminators remained ulcer free.)

Sponsors are usually advised to finalize their SAPs as early as possible, preferably prior to start of study; SPA agreements should not be made until the SAPs are finalized, or fully reflect all aspects of the planned statistical analysis that are critical to efficacy determination.

Another review issue relates to the sponsor's analysis population. Their so-called "primary population" was based on patients who were randomized, had study drug, and had at least the first scheduled endoscopy (week 8). The sponsor used the term modified ITT to describe this population if it included certain (few) subjects who terminated early but whose endoscopies were outside the scheduled windows. The Agency's usual preference for the primary analysis population has been the ITT based on all subjects randomized (or a modified ITT based on all randomized and treated) and it would be unlikely that an analysis population excluding subjects up to 8 weeks into the study would have been agreed to given current thinking. The point here is that the sponsor's sensitivity analyses should have included one based on all subjects randomized. In Study 301, for example, 35 subjects (8%) in the HZT group and 22 subjects (10%) in the Ibuprofen group terminated prior to endoscopy and were not analyzed for efficacy. In discussion with the clinical team, it was concluded that these exclusions would not necessarily be informative, and from a statistical view, the randomization would likely be preserved.

The clinical trials section of the label depicts two efficacy analyses. The sponsor's preferred version assumes all early drop-outs as not having ulcer, and the Agency's, more conservative, version is based on (some) early terminators as having an ulcer. To facilitate labeling presentation, it was agreed that both analyses reflect the sponsor's "primary population". These tables are reproduced below for completeness. The data for these tables were generated by the sponsor and were originally presented in the sponsor's submission dated Oct 21,2010. For Study 303, however, the data were modified by the sponsor to remove one site (site 389) from the analysis consistent with the presentation in the statistical review.

Table 3: Overall Incidence Rates of Patients Who Developed at Least One Upper Gastrointestinal or Gastric Ulcer - Study 301

	DUEXIS % (n/N)	Ibuprofen % (n/N)	*P*-value[a]
Primary endpoint			
Upper gastrointestinal ulcer*	10.5% (40/380)	20.0% (38/190)	0.002
Upper gastrointestinal ulcer**	22.9% (87/380)	32.1% (61/190)	0.020
Secondary endpoint			
Gastric ulcer*	9.7% (37/380)	17.9% (34/190)	0.005
Gastric ulcer**	22.4%% (85/380)	30.0% (57/190)	.0.052

Table 4: Overall Incidence Rate of Patients Who Developed at Least One Gastric or Upper Gastrointestinal Ulcer - Study 303

	DUEXIS % (n/N)	Ibuprofen % (n/N)	*P*-value[a]
Primary endpoint			
Gastric ulcer*	8.7% (39/447)	17.6% (38/216)	0.0004
Gastric ulcer**	17.4% (78/447)	31.0% (67/216)	<0.0001
Secondary endpoint			
Upper gastrointestinal ulcer*	10.1% (45/447)	21.3% (46/216)	<0.0001
Upper gastrointestinal ulcer**	18.6% (83/447)	34.3% (74/216)	<0.0001

[a] Cochran Mantel Haenszel test
* Classifying early terminated patients as NOT having an ulcer
** Classifying patients who early terminated due to an adverse event, were lost to follow up, discontinued due to the discretion of the sponsor or the investigator, or did not have an endoscopy performed within 14 days of their last dose of study drug, as having an ulcer

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL E WELCH
04/22/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22,519
Priority or Standard	Standard
Submit Date(s)	03-23-10
Received Date(s)	03-23-10
PDUFA Goal Date	04-23-11
Division / Office	DGIEP/ODE III
Reviewer Name(s)	Ali Niak, M.D.
Review Completion Date	04-22-11
Established Name	Ibuprofen (800mg)/Famotidine (26.6 mg)
(Proposed) Trade Name	Duexis
Therapeutic Class	H_2Blocker/NSAID Combination
Applicant	Horizon Therapeutics, Inc.
Formulation(s)	Oral tablet
Dosing Regimen	One tablet orally every 8 hours
Indication(s)	Risk reduction of development of ibuprofen-associated, upper gastro-intestinal ulcers when using ibuprofen
Intended Population(s)	Patients requiring use of ibuprofen

Table of Contents

Table of Tables

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of HZT-501 for risk reduction of ibuprofen-associated gastric ulcers in patients who require the use of ibuprofen for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis with limitations. Patients who have a history of ulcers, who are on oral anticoagulants or low-dose aspirin, or who are 65 years of age or older have not been studied sufficiently to assess efficacy and this should be reflected in product labeling.

1.2 Risk Benefit Assessment

Two pivotal studies (to be discussed fully in the following sections) were submitted by the applicant for supporting the claim of reduction of the risk of ibuprofen-associated gastrointestinal (both gastric and duodenal) ulcers in patients requiring ibuprofen treatment. Study HZ-CA-301 did not reach statistical significance when all the patients who terminated early were counted as treatment failures in the crude incident rate analysis. On the other hand, Study HZ-CA-303 obtained crude incidence rates for gastric ulcer development that were 15.4% lower in the group of patients receiving HZT-501 than in patients who received only ibuprofen treatment; this result was highly significant (p-value of 0.0001). Additionally, the difference in ulcer incidence between the two treatment groups is in the range as seen in proton pump inhibitors that have been approved for the reduction of gastric ulcers by non-steroidal anti-inflammatory drugs.

However, the applicant is seeking an indication for HZT-501 that would include all gastrointestinal ulcers (both gastric and duodenal ulcers). This reviewer disagrees with the applicant with regards of the indication for both duodenal and gastric ulcers. No H. pylori testing was performed in patients who developed duodenal ulcers and it is possible that some of these patients developed duodenal ulcers as a result of H. pylori infection. Additionally, the numbers of patients who developed duodenal ulcers were low in both studies. Therefore, this reviewer recommends that only the claim of risk reduction of gastric ulcers as a result of non-steroidal anti-inflammatory drug use be granted to the applicant.

In summary, one of the studies (study HZ-CA-301) failed to demonstrate a statistically significant difference in the reduction of gastrointestinal ulcers (the primary endpoint of the study) when the most conservative analysis was used to evaluate the data, while study HZ-CA-303 demonstrated a highly statistically significant difference in gastric ulcers (the primary endpoint of the study). Additionally, the statistical reviewer concluded that study HZ-CA-301 failed to provide persuasive evidence of effectiveness, but study HZ-CA-303 was highly persuasive.

1.3 Recommendations for Post-marketing Risk Evaluation and Mitigation Strategies

Routine surveillance for adverse events is recommended.

1.4 Recommendations for Post-marketing Requirements and Commitments

Given that HZT-501 is a combination of two previously approved medications (ibuprofen and famotidine) with a new indication and a new dosage form for both of its components and a new dosing regimen (famotidine), the Pediatric Research Equity Act (PREA) was triggered. Since substantial numbers of pediatric patients are prescribed ibuprofen, a recommendation has been made under PREA to evaluate the effect of HZT-501 in pediatric patients that may require ibuprofen chronically. The development of an age appropriate formulation of ibuprofen and famotidine to be used in pediatric patients has been negotiated during this review cycle. Additionally, a study to characterize the pharmacokinetic (PK) parameters of the ibuprofen and famotidine combination suspension following administration of a single dose is also to be included. Furthermore, the pharmacokinetics and safety of an age appropriate formulation of the ibuprofen and famotidine combination in the pediatric population ages 1 year and 11 months through 16 years and 11 months of age requiring chronic treatment of NSAIDS is also to be included. The pediatric study is to include a 24-week study to evaluate the safety of HZT-501 in the pediatric population ages 2 to 16 years and 11 months.

2 Introduction and Regulatory Background

2.1 NSAID induced gastric ulcers

Ibuprofen is the most commonly used non-steroidal anti-inflammatory drug (NSAID) in the U.S. It is used for the management of pain and inflammation and has been indicated for a wide range of chronic arthritic and nonarthritic conditions.[1] As in other NSAIDs, ibuprofen induces upper gastrointestinal (UGI) ulcers, and this may be complicated by the development of gastrointestinal (GI) bleeding, perforation, or obstruction.

UGI ulceration occurs as a result of NSAID inhibition of cyclooxygenase 1 and the subsequent inhibition of prostaglandin synthesis resulting in a series of effects that include the reduction of gastric mucus secretion, bicarbonate secretion, glutathione secretion reduction, mucosal blood flow reduction, and cellular tight junction reduction.[2] As a result of these effects, the gastric acid that is normally present in the stomach is more likely to reach the unprotected mucosal cellular

[1] Derry, C., Derry, S., Moore, R. A., & McQuay, H. J. (2009). Single dose oral ibuprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews (Online), (3), CD001548. doi:10.1002/14651858.CD001548.pub2.
[2] Elliott, G., Purmalis, A., VanderMeer, D., & Denlinger, R. (1988). The propionic acids. Gastrointestinal toxicity in various species. Toxicol.Pathol., 16(2), 245-250.

layer and induce irritation, erosions, and subsequent ulceration. This process can lead to further complications such as bleeding, perforation, obstruction, or death.

Famotidine is an H_2-receptor antagonist and it decreases the gastric acid secretion. The reduction in the gastric acid secretion by famotidine may provide some protection in the gastric mucosa and may reduce the incidence of UGI ulceration that is caused by ibuprofen. Horizon Therapeutics, Inc., has used the above statement to justify the combination of ibuprofen and famotidine. Additionally, the sponsor has stated that the combination of these two products into a single product enhances patient adherence by reducing the number of medications and pills that a patient has to take.

2.2 Product Information

DUEXIS is a combination of the NSAID ibuprofen and the histamine H_2-receptor antagonist famotidine.

Ibuprofen was approved for human use in the United States in 1974. It has been marketed for pain management and for the reduction of inflammation. Ibuprofen tablets and capsules containing up to 200 mg are approved for over-the-counter (OTC) sale, whereas 400, 600 and 800 mg tablets are approved for administration by prescription. Prescription Ibuprofen is indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis, for relief of mild to moderate pain, and for the treatment of primary dysmenorrhea; the suggested prescribed dosage is 1200 to 3200 mg daily (300 mg four times a day (qid); 400, 600 or 800 mg three times a day, tid, or qid).[3]

Famotidine (PEPCID) was approved in the U.S., in 1986, for the treatment of ulcers and other GI illnesses; the indication was expanded, in 1995, to include the treatment of heartburn for over the counter (OTC) use. It is approved for OTC use as 10 and 20 mg tablets, for prescription use as 20 and 40 mg tablets, as a powder for oral suspension (400 mg famotidine for reconstitution to a 40 mg/5 mL suspension), and as a solution for intravenous injection (10 mg/mL and 20 mg/50 mL). Prescription famotidine is indicated in adults for short-term treatment of active duodenal ulcer, maintenance therapy for duodenal ulcer patients, short-term treatment of active benign gastric ulcer, short-term treatment of GERD, treatment of patients with esophagitis, including erosions and ulcerations, and accompanying symptoms due to GERD, and treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas).[4]

[3] MOTRIN package insert 2007.
[4] PEPCID package insert 2007.

2.3 Table of Currently Available Treatments for Proposed Indications

As per the Sponsor, DEUXIS is indicated for the reduction of the risk of development of ibuprofen-associated, upper gastrointestinal ulcers in patients who require use of ibuprofen. Currently, several classes of medications are available for risk reduction of ibuprofen-associated, upper gastrointestinal ulcers in patients requiring ibuprofen.[5] Please refer to the table below.

Table 1 Gastro-protective Medications and their Indications

Medication	Class	Indication
Famotidine	H_2-Receptor Antagonist	"Short term treatment of active duodenal ulcer; safety not assessed for >8 weeks in uncomplicated active duodenal ulcers. Short-term treatment of active benign gastric ulcers; safety not assessed for >8 weeks in uncomplicated active benign gastric ulcers. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer; controlled studies in adults have not extended beyond one year."
Cimetidine	H_2-Receptor Antagonist	"Short-term treatment of active benign gastric ulcer. There is no information concerning usefulness of treatment periods of longer than 8 weeks. Short-term treatment of active duodenal ulcer."
Ranitidine	H_2-Receptor Antagonist	"Short-term treatment of active, benign gastric ulcer. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than 6 weeks. Maintenance therapy for gastric ulcer patients at reduced dosage after healing of acute ulcers; placebo-controlled studies have been carried out for 1 year. Short-term treatment of active duodenal ulcers. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks."
Nizatidine	H_2-Receptor Antagonist	"Indicated for up to 8 weeks for the treatment of active duodenal ulcers. Also indicated for up to 8 weeks for the treatment of active benign gastric ulcers. Indicated for maintenance therapy for duodenal ulcer patients;

[5] Chan FKL, Graham DY. Prevention of Non-steroidal anti-inflammatory drug: Gastrointestinal complications-review and recommendations based on risk assessment. Alimentary Pharmacology & Ther 2004; 19:1051-1061.

		unknown consequences with continuous therapy for longer than 1 year."
Esomeprazole	Proton Pump Inhibitor (PPI)	"Reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in participants at risk for developing gastric ulcers. Participants are considered to be at risk due to their age (> 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months."
Lansoprazole	PPI	"Reducing the risk of NSAID-associated gastric ulcers in participants with a history of a documented gastric ulcer that require the use of an NSAID. Controlled studies did not extend beyond 12 weeks."
Lansoprazole & Naproxen	PPI+NSAID (combination)	"Reducing the risk of NSAID-associated gastric ulcers in participants with a history of documented gastric ulcer who require the use of an NSAID for treatment of the signs & symptoms of RA, OA, and/or AS. Controlled studies did not extend beyond 12 weeks."
Esomeprazole & Naproxen	PPI+NSAID (combination)	"For relief of OA, RA, and AS and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. Controlled studies did not extend beyond 6 months."

RA-rheumatoid arthritis, OA-osteoarthritis, AS-ankylosing spondylitis
(Table taken from Table 1 of Dr. Erica Wynn's review of VIMOVO, NDA 022511, and the labels from famotidine, nizatidine, ranitidine)

2.4 Availability of Proposed Active Ingredient in the United States

As already discussed previously, the two active ingredients of Duexis are Ibuprofen and Famotidine. Ibuprofen has been available in the U.S. since 1974 and Famotidine has been available since 1986.

2.5 Important Safety Issues With Consideration to Related Drugs

Serious potentially life-threatening gastrointestinal (GI) bleeding and the potential for increased cardiovascular events are associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs). As a result, the labeling of all NSAIDs includes a Medication Guide and a Boxed Warning highlighting the above concerns.

A major factor that limits the use of NSAIDs is the potential for upper and lower GI tract mucosal injury, including inflammation, bleeding, ulceration, and perforation of the stomach,

small intestine, or large intestine, which can be fatal.[6] Ulcers are found on endoscopy in 15 to 30% of patients who use NSAIDs on a regular basis.[7] The annual incidence of upper GI complications (i.e. bleeding, perforation, and obstruction) is approximately 1.0% to 1.5%, whereas the annual rate of upper GI clinical events (complicated plus symptomatic uncomplicated ulcers) is approximately 2.5% to 4.5%.[5] Although any patient taking NSAIDs is at risk of developing GI toxicity, several risk factors have been identified that, when present, increase the risk for upper GI clinical events. By current American College of Gastroenterology guidelines, these risk factors are prior clinical event, older age (>65 years), concomitant use of anticoagulation, corticosteroids, and low-dose aspirin use.[5]

The administration of an NSAID may initiate a dose dependent reduction in prostaglandin synthesis and reduce the renal blood flow, precipitating renal decompensation. Additionally, there have been concerns regarding the potential cardiovascular hazards of NSAIDs especially in patients with serious coronary heart disease. Similar concerns were raised in cyclooxygenase (COX-2) inhibitors and one COX-2 inhibitor was withdrawn from the market after an association was found with an increased risk of heart attack and stroke. The mechanism of these adverse events may have been due to the increase in the ratio of thromboxane (causing vasoconstriction and promoting platelet aggregation) and prostacyclin (causing vasodilation and inhibiting platelet aggregation).

The famotidine component of DUEXIS has similar safety issues as with other histamine H_2-receptor antagonists, but of concern, are the central nervous system effects, namely, psychic disturbances, including hallucinations, confusion, agitation, depression, anxiety, decreased libido, paresthesia, insomnia, and somnolence.[8] Additionally, rare cases of prolonged QT interval have been reported in patients with impaired renal function.

2.6 Summary of Pre-submission Regulatory Activity Related to Submission

The major regulatory issues and meetings are as follows:

- June 13, 2005: A pre-IND meeting was held to discuss the development plan for the product. The Agency stated that adequate and well-controlled efficacy studies would be required to assess the effectiveness of HZT-501 in reduction and/or prevention of NSAID-induced ulcers.

- May 18, 2006: An end of phase 2 (EOP2) meeting was held to discuss the phase 3 clinical development program for HZT-501. The Agency recommended that the applicant conduct two 24-week clinical studies. Additionally, the Agency agreed that a statistically significant and clinically meaningful treatment effect in the cumulative incidence of endoscopically documented gastric and/or duodenal ulcers of unequivocal

[6] Ibuprofen label.
[7] Laine, L "GI Risk and Risk Factors of NSAID," Journal of Cardiovascular Pharmacology. 2006; 47(S1): S60-S66.
[8] Famotidine label.

depth and at least 3 mm in diameter would support demonstration of efficacy of HZT-501.

- December 14, 2006: SPA agreement reached for phase 3 clinical study protocols.

- May 22, 2007: Horizon submits request to increase sample sizes for the phase 3 clinical studies.

- August 31, 2007: The agency states that any changes to the sample sizes for the phase 3 clinical studies under the SPA agreement would constitute a change in the SPA and result in a nullification of the SPA agreement.

- September 15, 2007: The applicant formally submits a protocol amendment to increase the sample size of one of the phase 3 studies, HZ-CA-303.

- October 30, 2008: The Agency recommended that both the life table analysis and crude rate analysis be performed in accordance with the treatments to which they actually received. Furthermore, the Agency clarified that "in order to claim your study drug HZT-501 is effective for the proposed indication, the results for both the life table and crude rate analyses should show positive results in favor of HZT-501 for both randomized and treated populations."

- December 17, 2009: Pre-NDA meeting held (see meeting minutes under IND 72,116 dated January 19, 2010 and January 28, 2010 pre-NDA meeting minutes clarification). The Agency clarified that the crude rate + early termination (treated as treatment failures) analysis will be used for product labeling purposes. However, the determination of early terminations that were not treatment-related could be acceptable if the applicant was able to provide a reasonable explanation as to why these patients were not treatment related.

- March 23, 3010: NDA 22-519 submitted by the applicant.

- December 16, 2010: Additional information received from the applicant important to the review of the application received, thus triggering a Major Amendment and extending the review clock to April 22, 2011.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This was an electronic submission. Overall, the submission was well organized.

3.2 Compliance with Good Clinical Practices

According to the applicant, these trials were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. They were also conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) E6 guidelines.

Two sites in Study HZ-CA-303 were chosen for inspection by the Division of Scientific Investigations (DSI) based on their high number of enrolled patients. Of the two sites that were chosen, inspection at Site 389 failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60] and failed to maintain adequate and accurate case histories. Furthermore, additional good clinical practice deviations were noted, including but not limited to, the re-dispensing of study medication to 33 subjects at Week 8 and/or Week 16 in violation of the protocol. This allowed multiple patients to continue on the study at Week 4 without having assessed their compliance with dosing and the also allowing numerous out-of-window visits; additionally, it was discovered that a patient continued to take the study medication even after a gastric ulcer had been diagnosed. DSI recommended that the data generated by Site 389 to not be used in support of the respective indication. The results from a Life Table Analysis, which excluded site 389 with regards to gastric ulcers, was significant (p value < 0.01) pointing data in favor of HZT-501. Initially, 257 patients had been enrolled at this site, of which 167 patients were randomized, and 103 patients completed the study. For the purposes of accuracy, this reviewer has included incidence rates from the ITT population (906 patients) and an ITT population minus the patients from Site 389 (739 patients).

Given the above findings at Site 389, two additional sites were submitted to DSI for further inspections. Sites 340 and 363 were chosen given the large number of patients with early terminations not related to ulcers. Site 340 has been cleared by DSI. However, the DSI inspection at site 363 uncovered additional deficiencies that called the validity of the data in four patients into question (patient 005,021,050, and 100). The DSI reviewer recommended that these four patients also be excluded from all efficacy analyses.

3.3 Financial Disclosures

Horizon Therapeutics, Inc., has disclosed financial agreements with clinical investigators, as recommended in the FDA guidance for industry. Of the 894 investigators that participated in the phase 3 trials, the applicant received financial information on all except for 3 investigators. Each of these 3 investigators was at different sites (b) (6)) and they were removed as investigators from the clinical trials. Horizon Therapeutics, Inc., provided a signed copy of FDA

Form 3454 certifying that they have not entered into any financial agreement with the remainder of the clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Additionally, no documentation showing any proprietary interest in DUEXIS or any significant equity interest in Horizon Therapeutics, Inc., was disclosed by the investigators as defined in 21 CFR 54.2(b). Furthermore, no investigator received any significant payments as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

For complete information, please refer to the Chemistry Review by G. Holbert and the Manufacturing Process Review by Y. Tang dated March 3, 2011.

HZT-501 is a (b) (4) combination product containing ibuprofen USP (800 mg) and famotidine USP (26.6 mg). It is an immediate release tablet available for oral use. (b) (4) The information submitted by the applicant was reviewed and the chemistry reviewer concluded that the information was adequate to support the quality, strength, identity, and purity of the drug product.

The manufacture of the (b) (4) was found to be deficient initially; additionally, it was determined that about 1.5% to 2.0% of the lots with tablets (b) (4) The chemistry reviewer reached a conclusion that the corrective actions that were taken by the applicant did result in process controls that were consistent and reliable in rejecting the defective tablets. No other substantive issues were noted by the chemistry reviewer. It appears that the application provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

A prior approval inspection was conducted at Pharmaceutics International Inc. (Pii) encompassing the period from November 29, 2010, to December 7, 2010. Several deficiencies were noted as a result of the inspection and a Form 483 was issued. A classification of Official Action Indicated (OAI) was designated to the Pii facility as a result of the deficiencies. As a result of this classification, the Office of Compliance recommended withholding an approval action. However, these deficiencies have been adequately addressed by the facility and the Office of Compliance has changed the classification to Voluntary Action Indicated (VAI) and an approval action for this NDA has been recommended by the Office of Compliance.

4.2 Clinical Microbiology

Since HZT-501 is not intended as an antimicrobial product, clinical microbiology considerations do not apply to this application.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the Agency's pharmacology toxicology officer (Dr. D. Gautam) review from December 6, 2010, for full details.

The components of HZT-501 (ibuprofen and famotidine) have been well documented from the pharmaco-toxicologic standpoint; literature has been cited by the applicant regarding various studies for ibuprofen and famotidine in dogs, rats, mice, and cynomolgus monkeys. In this 505(b)2 submission, the applicant has relied upon this extensive previously determined information. After a review of the information submitted by the applicant, Dr. Gautam did not uncover any new concerns.

4.4 Clinical Pharmacology

The clinical pharmacology data were reviewed by PeiFan Bai, Ph.D. For a full description regarding the clinical pharmacology of DUEXIS, please refer to Dr. Bai's review in DAARTS under the same NDA number

4.4.1 Mechanism of Action

DUEXIS is a combination of ibuprofen and famotidine. Ibuprofen exhibits analgesic and antipyretic properties, and its mode of action is not completely understood (similar to other NSAIDS), but it may be related to prostaglandin synthetase inhibition. The second component of DUEXIS is famotidine which is an H_2-receptor antagonist. The important pharmacologic activities of famotidine include suppression of the gastric acid concentration and volume.

4.4.2 Pharmacodynamics

None.

4.4.3 Pharmacokinetics

HZT-501 is a combination of famotidine and ibuprofen for oral use. The application provided by Horizon Therapeutics, Inc., included an evaluation of the efficacy of famotidine in reducing the risk of NSAID-associated gastric ulcers in a phase 3 trial. The efficacy of ibuprofen relied on previously established claims of efficacy for ibuprofen (Motrin) which was based on the bioequivalence of the applicant's formulation of ibuprofen (HZT-405) to the comparator. Several bioequivalence studies were performed and reviewed in this application:

1. Bioequivalence of HZT-405 to ibuprofen
2. Bioequivalence of the ibuprofen component of HZT-501 in phase 3 to the commercial formulation of ibuprofen
3. Bioequivalence of the ibuprofen component of the commercial formulation of HZT-501 to ibuprofen
4. Bioequivalence of the ibuprofen component of HZT-501 in phase 3 to the ibuprofen component of the commercial formulation of HZT-501
5. Bioequivalence of the famotidine component of HZT-501 in phase 3 to the famotidine component of the commercial formulation of HZT-501

It is of note that there were no bioequivalence studies in the application between famotidine administered at 26.6 mg orally tid compared to a previously approved famotidine administered at a dose of 40 mg orally bid because the clinical efficacy and safety data for the new famotidine dosing regimen were included in the present NDA.

Co-administration of Pepcid and Motrin increased ibuprofen C_{max} by 15.6%, but did not change its AUC, and caused famotidine AUC and C_{max} to increase 16% and 22%, respectively.[9] These differences were not considered to be statistically significant because of the wide variability in the samples and appear to be driven by one patients. Therefore, the pharmacology reviwer concluded that further drug-drug interaction studies were not required.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

In total, nine clinical studies have been completed as part of the development plan for HZT-501, six were Phase 1 pharmacokinetic studies (Table 2) and three were Phase 3 studies (Table 3). Of these studies, two were pivotal Phase 3, multicenter, randomized, double blind, parallel group, comparator controlled studies of HZT-501 (Studies HZ-CA-301 and HZ-CA-303), which examined the safety and efficacy of HZT-501 (800 mg ibuprofen and 26.6 mg famotidine) versus 800 mg ibuprofen alone for up to 24 weeks for the reduction of the risk of development of ibuprofen-associated UGI ulcers in patients who require use of ibuprofen.

[9] Please refer to Dr. PeiFan Bai's clinical pharmacology review in DAARTS under the same NDA.

Table 2 Summary of Phase 1 Studies

Study No.	Regimen	Objective
HZ-CA-001	Commercial 800 mg ibuprofen tablet (Motrin) vs. commercial 40 mg famotidine tablet (Pepcid) vs. combination of 800 mg ibuprofen tablet (Motrin) and 40 mg famotidine tablet (Pepcid) in healthy subjects*	Single dose drug interaction Single dose bioavailability
HZ-CA-005	Prototype HZT-501 Phase 1 combination tablet vs. combination of commercial 800 mg ibuprofen tablet (Motrin) and 26.6 mg famotidine suspension (Pepcid) in healthy subjects	Single dose bioavailability
HZ-CA-010	HZT-405 (800 mg ibuprofen) tablet vs. commercial 800 mg ibuprofen tablet	Single dose bioequivalence
HZ-CA-015	HZT-501 Phase 3 combination tablet vs. HZT-501 tablet-in-tablet vs. commercial 800 mg ibuprofen tablet	Single dose bioequivalence
HZ-CA-016	HZT-501 tablet-in-tablet fasting vs. HZT-501 tablet-in-tablet fed	Food - drug interaction
HZ-CA-006	HZT-501 Phase 3 combination tablet vs. combination of commercial 800 mg ibuprofen tablet (Motrin) and 26.6 mg famotidine suspension (Pepcid) in subjects with renal insufficiency	Single dose bioavailability in a special population

*The dose of HZT-501 that was used during the investigative studies was based on the labeling recommendations of each component of HZT-501 (ibuprofen and famotidine). Ibuprofen is indicated at doses of 800 mg three times daily for relief of the signs and symptoms of rheumatoid arthritis, osteoarthritis. Doses less than 800 mg, tid are used for other ibuprofen indications (i.e., relief of mild to moderate pain, and for treatment of primary dysmenorrhea). Famotidine is indicated for the treatment of active duodenal ulcers, and for the treatment of heartburn. The total daily dose for over the counter (OTC) use is 80 mg per day. The applicant has divided the 80 mg maximum recommended dose for famotidine into three equal doses (26.6 mg x 3 79.8 mg) to be combined with the ibuprofen component.

Table 3 Summary of Phase 3 Studies

Study No.	Regimen	Objective
HZ-CA-301	HZT-501 Phase 3 combination tablet [(ibuprofen 800 mg/famotidine 26.6 mg) vs. HZT-405 (ibuprofen 800 mg)]	Safety and Efficacy
HZ-CA-303	HZT-501 Phase 3 combination tablet [(ibuprofen 800 mg/famotidine 26.6 mg) vs. HZT-405 (ibuprofen 800 mg)]	Safety and Efficacy
HZ-CA-304	HZT-501 Phase 3 combination tablet (ibuprofen 800 mg/famotidine 26.6 mg) vs. HZT-405 (ibuprofen 800 mg)	Safety

For the purposes of efficacy, the two pivotal Phase 3 studies (HZ-CA-301 and HZ-CA-303) will be reviewed in detail.

5.2 Review Strategy

The development program for HZT-501 was reviewed as best possible by this medical officer. Close attention was made to the two pivotal trials in this study. The MITT population for endoscopy endpoint trials was defined as patients who were randomized, received at least one dose of study drug, and had at least one on-study endoscopy (International Conference on Harmonization, E9 1998, Full Analysis Set). This reviewer used the MITT population for all analyses unless otherwise specified. The statistical reviewer used the primary population, defined as all randomized subjects who received at least one dose of study medication who underwent a baseline endoscopic examination and at least the Week 8 endoscopic examination within the protocol allowed visit window (i.e., ≥6.7 weeks to ≤26.7 weeks).. Despite the different populations used for the analysis between this review and the statistical review, there were no substantive differences in the results.

It is of note that in Study HZ-CA-303, the efficacy data obtained from one of the sites (Site 389) was excluded by this reviewer given that Site 389 received a site classification of Official Action Indicated (OAI) by the Division of Scientific Investigations (DSI). Additionally, results of the DSI inspection at site 363 uncovered additional deficiencies that called the validity of the data in four patients into question (patient 005,021,050, and 100). The DSI reviewer recommended that these four patients also be excluded from all efficacy analyses. These findings are discussed fully in section 6.1.4 and above in section 3.2.

With regards to the safety, the data from both pivotal studies were pooled to evaluate for the safety signals. This was possible given the similarities of the two pivotal studies with regards to the safety parameters and the protocol of each pivotal study. Additionally, safety data from the extension study (HZ-CA-304) were also reviewed separately.

5.3 Discussion of Individual Studies/Clinical Trials

Each study (HZ-CA-301 and HZ-CA-303) was a Phase 3, multicenter, randomized, double blind, and parallel group study designed to evaluate the efficacy, as measured by endoscopically-diagnosed gastrointestinal ulcers, and safety of HZT-501 compared with ibuprofen.

5.3.1 Study HZ-CA-301

Study Design

The protocol was designed to evaluate the efficacy of HZT-501 in reducing the proportion of patients who developed at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer (of unequivocal depth and at least 3mm in diameter) during a 24-week treatment period, as compared to ibuprofen, in patients at risk for non-steroidal anti-inflammatory drug (NSAID)-induced ulcers. In Study HZ-CA-301, 627 patients between the ages of 40 to 80 years, inclusively, who had not used a non-steroidal anti-inflammatory drug (NSAID) within 30 days prior to the study entry, and who were expected to require daily administration of an NSAID for at least the coming six months, were enrolled. Patients were assigned randomly, in approximately a 2:1 ratio, to treatment with either HZT-501 or ibuprofen for 24 consecutive weeks or until the patient developed either an endoscopically-diagnosed upper gastrointestinal ulcer and/or terminated early for other reasons (i.e., adverse event, withdrawal of consent, lost to follow-up, or other specified reasons). Randomization was stratified based on the following two risk factors for ulcer development:

(1) Concomitant use of low-dose aspirin and/or other anticoagulant medication;

(2) History of an upper gastrointestinal ulcer. Patients who completed the 24-week treatment period without developing an endoscopically-diagnosed upper gastrointestinal ulcer were eligible to participate in a follow-on study with HZT-501 (Study HZ-CA-304).

All randomized patients who received at least one dose of study drug and who underwent a baseline and at least the Week 8 (visit window allowance ≥ 6.7 weeks) endoscopic examination were included in the primary population for all primary and secondary efficacy analyses. The 24-week Treatment Period, due to visit window allowance, was defined as up to and including Week 26.7.

Experimental Controls

Patients who received the HZT-501 were compared to patients who received only ibuprofen.

Dosage Schedule

HZT-501 (ibuprofen 800 mg/famotidine 26.6 mg) tablet or ibuprofen (800 mg) tablet was self-administered orally, on a double-blind basis, three times a day (TID) for up to 24 consecutive

weeks. Patients were prohibited from taking any NSAIDs other than study drug, and other than low-dose aspirin taken for cardiovascular prophylaxis, during the 24-week treatment period. Patients were prohibited from taking any drugs or interventions that neutralize gastric acid for more than three days during any two-week period during the 24-week treatment period. Patients were prohibited from taking any H2-receptor antagonists and/or any proton pump inhibitors other than study drug during the 24-week treatment period. Patients taking low-dose aspirin and/or other anticoagulant medication could continue to use these medications, on their usual regimen, during the treatment period.

Clinical Procedures

Endoscopic examinations were performed during Screening (baseline) and at Weeks 8, 16, and 24, with a four-day window prior to the actual clinic visit day (the clinic visit day had a plus/minus five-day window around the target clinic visit day). Patients were deemed a treatment failure and terminated early from the study in the event they developed an endoscopically-diagnosed upper gastrointestinal ulcer of unequivocal depth and at least 3 mm in diameter. Patients who terminated early for reasons other than development of an endoscopically-diagnosed upper gastrointestinal ulcer underwent an endoscopic examination at a Termination Visit that was conducted as soon as possible after administration of their final dose of the study medication.

Safety Monitoring

Safety was assessed by monitoring AEs, changes in clinical laboratory values, changes in vital signs, and changes in physical examination findings over the 24-week treatment period as well as during the four-week follow-up period.

Adverse events (AEs) were collected from all patients beginning at the time of administration of the first dose of study drug and continuing through completion of the four-week follow-up period. Cardiovascular safety was monitored on a quarterly basis by an independent data monitoring committee (IDMC). A written charter defined the makeup and conduct of the IDMC. Unblinded reports of deaths and serious cardiovascular events, including myocardial infarctions, were provided on a quarterly basis to the IDMC for review.

Inclusion Criteria for Study HZ-CA-301

(1) Male and female subjects between 40 and 80 years of age, inclusively
(2) Patient had not used an NSAI within the 30 days prior to study entry
(3) Patient was expected to require daily administration of an NSAID for at least the coming 6 months for conditions such as the following: osteoarthritis, rheumatoid arthritis, chronic low back pain, chronic regional pain syndrome, chronic soft tissue pain.
(4) Female subjects of childbearing potential, and male subjects with partners of childbearing potential, must have agreed to use medically acceptable methods of contraception throughout the entire study period.

Exclusion Criteria for Study HZ-CA-301

(1) Patient had a history of erosive esophagitis.
(2) Patient had a prior history of any of the following NSAID-associated and/or primary peptic ulcer disease-associated serious gastrointestinal complications: perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding.
(3) Patient had a history of any of the following NSAID-associated serious events: NSAID-induced asthma exacerbation, acute renal failure, interstitial nephritis, hepatitis.
(4) Patient had current or past evidence of malignant disease of the gastrointestinal tract.
(5) Five or more erosions of the upper gastrointestinal tract were observed during the screening endoscopy.
(6) Patient had a documented current Helicobacter pylori (H. pylori) infection. Patients with a prior history of H. pylori infection were eligible for study participation after adequate treatment and provision of a current negative test result.
(7) Patient used an acid suppressant agent within the 14 days prior to study entry.
(8) Patient had active cardiac, renal, and/or hepatic disease, as evidenced by:
    - Creatinine clearance < 45 mL/min at Screening
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal at Screening
    - History of acute myocardial infarction, unstable cardiac arrhythmias, and/or stroke within the six months prior to study entry
    - Uncontrolled congestive heart failure
(9) Patient had uncontrolled diabetes mellitus, as evidenced by fasting blood glucose > 200 mg/dL.
(10) Patient was on high-dose aspirin therapy (> 325 mg/day) or misoprostol within the 14 days prior to study entry.
(11) Patient had coronary artery bypass graft surgery within the 14 days prior to study entry.
(12) Patient had uncontrolled hypertension.
(13) Female patient had a positive serum pregnancy test at Screening.
(14) Patient tested positive at Screening for human immunodeficiency virus (HIV), hepatitis B, and/or hepatitis C.
(15) Patients could not have used an NSAID within the 30 days prior to study entry, but were expected to require daily administration of an NSAID for at least the coming six months for conditions such as the following: osteoarthritis, rheumatoid arthritis, chronic low back pain, chronic regional pain syndrome, and chronic soft tissue pain.
(16) Patients could not have a history of erosive esophagitis or of NSAID-associated serious gastrointestinal complications, a creatinine clearance < 45 mL/min, or the presence of five or more erosions observed on endoscopy at Screening.

Primary Efficacy Endpoint for Study HZ-CA-301

The primary efficacy endpoint for Study HZ-CA-301 was to evaluate the efficacy of HZT-501 in reducing the proportion of patients who develop at least one endoscopically-diagnosed upper

gastrointestinal ulcer (defined as either a gastric or duodenal ulcer of unequivocal depth and at least 3mm in diameter) during the 24-week treatment period as compared to ibuprofen, in patients at risk for NSAID-induced ulcers.

For all analyses involving the safety population, including the incidence rate of NSAID-associated serious gastrointestinal complications, patients were grouped in accordance with the treatment each patient initially received. In the event that a patient received both study treatments, the patient was to be grouped for the safety analyses in accordance with the treatment he or she initially received.

5.3.2 Study HZ-CA-303

Study Design

The protocol was designed to evaluate the efficacy of HZT-501 in reducing the proportion of patients who developed at least one endoscopically-diagnosed gastric ulcer (of unequivocal depth and at least 3mm in diameter) during a 24-week treatment period, as compared to ibuprofen, in patients at risk for non-steroidal anti-inflammatory drug (NSAID)-induced ulcers. In Study HZ-CA-303, 906 patients between the ages of 40 to 80 years, inclusively, who had not used a non-steroidal anti-inflammatory drug (NSAID) within 30 days prior to the study entry, and who were expected to require daily administration of an NSAID for at least the coming six months, were enrolled. Patients were assigned randomly, in approximately a 2:1 ratio, to treatment with either HZT-501 or ibuprofen for 24 consecutive weeks or until they developed either an endoscopically-diagnosed upper gastrointestinal ulcer and/or terminated early for other reasons (i.e., adverse event, withdrawal of consent, lost to follow-up, or other specified reasons). Randomization was stratified based on the following two risk factors for ulcer development:

(1) Concomitant use of low-dose aspirin and/or other anticoagulant medication;

(2) History of an upper gastrointestinal ulcer. Subjects who completed the 24-week Treatment Period without developing an endoscopically-diagnosed upper gastrointestinal ulcer were eligible to participate in a follow-on study with HZT-501 (Study HZ-CA-304).

All randomized patients who received at least one dose of study drug and who underwent a baseline and at least the Week 8 (visit window allowance ≥ 6.7 weeks) endoscopic examination were included in the primary population for all primary and secondary efficacy analyses. The 24-week treatment period, due to visit window allowance, was defined as up to and including Week 26.7.

Experimental Controls

Patients who received HZT-501 were compared to patients who received only ibuprofen.

Dosage Schedule

HZT-501 (ibuprofen 800 mg/famotidine 26.6 mg) tablet or ibuprofen (800 mg) tablet was self-administered orally, on a double-blind basis, three times a day (TID) for up to 24 consecutive weeks. Patients were prohibited from taking any NSAIDs other than study drug, and other than low-dose aspirin taken for cardiovascular prophylaxis, during the 24-week treatment period. Patients were prohibited from taking any drugs or interventions that neutralize gastric acid for more than three days during any two-week period during the 24-week Treatment Period. Patients were prohibited from taking any H_2-receptor antagonists and/or any proton pump inhibitors other than study drug during the 24-week Treatment Period. Patients taking low-dose aspirin and/or other anticoagulant medication could continue to use these medications, on their usual regimen, during the treatment period.

Clinical Procedures

Endoscopic examinations were performed during Screening (baseline) and at Weeks 8, 16, and 24, with a four-day window prior to the actual clinic visit day (the clinic visit day had a plus/minus five-day window around the target clinic visit day). Patients were deemed a treatment failure and terminated early from the study in the event they developed an endoscopically-diagnosed upper gastrointestinal ulcer of unequivocal depth and at least 3 mm in diameter. Patients who terminated early for reasons other than development of an endoscopically-diagnosed upper gastrointestinal ulcer underwent an endoscopic examination at a Termination Visit that was conducted as soon as possible after administration of their final dose of the study medication.

Safety Monitoring

Safety was assessed by monitoring AEs, changes in clinical laboratory values, changes in vital signs, and changes in physical examination findings over the 24-week treatment period as well as during the four-week follow-up period.

Adverse events (AEs) were collected from all patients beginning at the time of administration of the first dose of study drug and continuing through completion of the four-week follow-up period. Cardiovascular safety was monitored on a quarterly basis by an independent data monitoring committee (IDMC). A written charter defined the makeup and conduct of the IDMC. Unblinded reports of deaths and serious cardiovascular events, including myocardial infarctions, were provided on a quarterly basis to the IDMC for review.

Inclusion Criteria for Study HZ-CA-303

(1) Male and female subjects between 40 and 80 years of age, inclusively
(2) Patient had not used an NSAI within the 30 days prior to study entry
(3) Patient was expected to require daily administration of an NSAID for at least the coming 6 months for conditions such as the following: osteoarthritis, rheumatoid arthritis, chronic low back pain, chronic regional pain syndrome, chronic soft tissue pain.

(4) Female subjects of childbearing potential, and male subjects with partners of childbearing potential, must have agreed to use medically acceptable methods of contraception throughout the entire study period.

Exclusion Criteria for Study HZ-CA-303

(1) Patient had a history of erosive esophagitis.
(2) Patient had a prior history of any of the following NSAID-associated and/or primary peptic ulcer disease-associated serious gastrointestinal complications: perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding.
(3) Patient had a history of any of the following NSAID-associated serious events: NSAID-induced asthma exacerbation, acute renal failure, interstitial nephritis, hepatitis.
(4) Patient had current or past evidence of malignant disease of the gastrointestinal tract.
(5) Five or more erosions of the upper gastrointestinal tract were observed during the screening endoscopy.
(6) Patient had a documented current Helicobacter pylori (H. pylori) infection. Patients with a prior history of H. pylori infection were eligible for study participation after adequate treatment and provision of a current negative test result.
(7) Patient used an acid suppressant agent within the 14 days prior to study entry.
(8) Patient had active cardiac, renal, and/or hepatic disease, as evidenced by:
    - Creatinine clearance < 45 mL/min at Screening
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal at Screening
    - History of acute myocardial infarction, unstable cardiac arrhythmias, and/or stroke within the six months prior to study entry
    - Uncontrolled congestive heart failure
(9) Patient had uncontrolled diabetes mellitus, as evidenced by fasting blood glucose > 200 mg/dL.
(10) Patient was on high-dose aspirin therapy (> 325 mg/day) or misoprostol within the 14 days prior to study entry.
(11) Patient had coronary artery bypass graft surgery within the 14 days prior to study entry.
(12) Patient had uncontrolled hypertension.
(13) Female patient had a positive serum pregnancy test at Screening.
(14) Patient tested positive at Screening for human immunodeficiency virus (HIV), hepatitis B, and/or hepatitis C.
(15) Patients could not have used an NSAID within the 30 days prior to study entry, but were expected to require daily administration of an NSAID for at least the coming six months for conditions such as the following: osteoarthritis, rheumatoid arthritis, chronic low back pain, chronic regional pain syndrome, and chronic soft tissue pain.
(16) Patients could not have a history of erosive esophagitis or of NSAID-associated serious gastrointestinal complications, a creatinine clearance < 45 mL/min, or the presence of five or more erosions observed on endoscopy at Screening.

Primary Efficacy Endpoint for Study HZ-CA-303

The primary efficacy endpoint for Study HZ-CA-303 was to evaluate the efficacy of HZT-501 in reducing the proportion of patients who develop at least one endoscopically-diagnosed gastric ulcer (of unequivocal depth and at least 3mm in diameter) during the 24-week treatment period as compared to ibuprofen, in patients at risk for NSAID-induced ulcers.

For all efficacy analyses, including the incidence rate of NSAID-associated serious gastrointestinal complications, patients were grouped in accordance with the treatment each patient initially received. In the event that a patient received both study treatments, the patient was to be grouped for the safety analyses in accordance with the treatment he or she initially received.

6 Review of Efficacy

Efficacy Summary

The applicant provided 2 pivotal phase 3 studies (Studies HZ-CA-301 and HZ-CA-303) for the evaluation of the proportion of patients requiring long term ibuprofen therapy who develop upper gastrointestinal ulcer (either gastric or duodenal ulcers) while on HZT-501 treatment or only on ibuprofen treatment. The applicant had provided life table analyses for the demonstration of efficacy (reduction of gastric and upper gastrointestinal ulcer incidences), however, the Division of Gastroenterology Products noted in two communications with the applicant (October 2008 and December 2009) that crude incidence rate analyses would also be required in order to claim that the study drug HZT-501 is effective for the proposed indication. Furthermore, the communications stated that the results for both the life table and crude rate analyses should show positive results in favor of HZT-501 for both randomized and treated populations. It should be noted that for both studies, the life table analyses and the crude incident rate analyses were generally consistent within the studies.

Study HZ-CA-301 does not provide persuasive efficacy for the primary endpoints, upper gastrointestinal ulcers, if the patients who terminated early are counted as treatment failures for both the life table and the crude incident rate analyses. In Study HZ-CA-301, a p-value of 0.0304 was obtained in the applicant's pre-specified life table analysis using the primary population, but a p-value of 0.1228 was obtained when the early terminations were counted as treatment failures and the results were re-analyzed.

On the other hand, Study HZ-CA-303 does provide statistically significant efficacy results for the primary endpoint, gastric ulcers, for both life table and crude incident rate analyses whether or not the patients who terminated early are considered treatment failures. In Study HZ-CA-303, a p-value of 0.0009 was obtained in the applicant's pre-specified life table analysis using the primary population, and a p-value of 0.0001 was obtained when the early terminations were counted as treatment failures and the results were re-analyzed.

In Study HZ-CA-301, there was a decreased incidence of upper gastrointestinal (UGI) ulcers in patients receiving HZT-501 as compared to patients receiving ibuprofen [(30.3% vs. 36.8%, respectively, with p-value of 0.1290) values taken from Dr. Wen Jen Chen's review of NDA 22,519, Division of Biometrics, FDA, and Horizon Therapeutics, Inc.]. This finding was also consistent with regards to the duodenal ulcers; patients receiving the study medication showed decreased incidence of duodenal ulcers as compared to patients receiving ibuprofen (28.4% vs. 36.3%, respectively, with a p-value of 0.0679). The findings were not statistically significant with the crude rate analyses.

In patients greater than or equal to 65 years old, the gastric ulcer incidences based on the modified intent to treat population (MITT) in patients who received HZT-501 compared to patients who received ibuprofen were 14.1% vs. 16.7%, respectively. In patients, greater than or equal to age 65, the duodenal ulcer incidence in patients who received the treatment medication was 0% and the incidence in patients receiving only ibuprofen treatment was 2.8%.

With regards to race in Study HZ-CA-301, HZT-501 showed efficacy in Caucasian (white) and African-American (black) patient populations. The non-white populations were too small to reach an accurate conclusion regarding the efficacy of the study medication.

There were also imbalances noted by both the statistical reviewer and the clinical reviewer regarding the incidence of ulcers in women compared to men in the ibuprofen treated group. Using life table analyses, there were a higher proportion of men in the HZT-501 treatment group who developed upper gastrointestinal ulcers compared to the ibuprofen group (-15.5%; p 0.065); however, this finding was not statistically significant. It is not clear why men in this study would have had a worse outcome.

Gastric ulcer incidences in patients on anticoagulants and/or on low-dose aspirin (Study HZ-CA-301) who received HZT-501 were lower as compared to patients on anticoagulants and/or low-dose aspirin who received ibuprofen based on the MITT; patients on anticoagulants and aspirin (low-dose aspirin) showed a 13.1% incidence of gastric ulcers in patients who were on the study medication as opposed to a 18.5% gastric ulcer incidence in patients who only received the ibuprofen. In patients who were only on low-dose aspirin, there was a 13.6% gastric ulcer incidence in patients receiving the study medication and there was a 17.2% gastric ulcer incidence in patients on the ibuprofen treatment. In patients with a prior history of upper gastrointestinal ulcer based on the MITT, HZT-501 did not provide protection against gastric ulcer incidence in patients enrolled in Study HZ-CA-301; in fact, the gastric ulcer incidence in patients receiving the study medication was 15.0% and it was 8.3% in patients receiving only ibuprofen. However, it is difficult to reach a conclusion regarding the efficacy of the study medication in patients on anticoagulants and/or aspirin given that the numbers of patients on anticoagulants and/or aspirin were small.

In Study HZ-CA-303, there was a decreased incidence of upper gastrointestinal (UGI) ulcers in patients receiving HZT-501 as compared to patients receiving ibuprofen [(23.5% vs. 37.4%,

respectively, with p-value of <0.0001) values taken from Dr. Wen Jen Chen's review of NDA 22,519, Division of Biometrics, FDA, and Horizon Therapeutics, Inc.]. In this study, there was a decreased incidence of gastric ulcers in patients receiving HZT-501 as compared to patients receiving ibuprofen (12.9% vs. 25.3%, respectively, with a p-value of 0.0009, primary population, using a life-table analysis). This finding was also consistent with regards to the duodenal ulcers; patients receiving the study medication showed a decreased incidence of duodenal ulcers as compared to patients receiving ibuprofen (2.1% vs. 7.1%, respectively, p-value of 0.0226, using a life-table analysis). Even with exclusion of the patients from site 389 in Study HZ-CA-303, HZT-501 continued to show efficacy with regards to UGI ulcers; the crude incident rate analysis in patients who developed at least one UGI ulcer using the primary population with the exclusion of patients from site 389 showed an UGI ulcer incidence of 22.0% in patients with the treatment medication and an UGI ulcer incidence of 37.5% in patients with only the ibuprofen treatment (p-value of <0.0001). It appears that even with the exclusion of site 389, HZT-501 showed efficacy in both UGI and gastric ulcers as compared to ibuprofen-only treatment.

With regards to age in Study HZ-CA-303, there was a decreased gastric ulcer incidence (using the MITT) in patients less than 65 years of age in patients who received HZT-501 (6.8% vs. 16.5%, respectively); the incidence of duodenal ulcers in patients less than 65 years of age who received the study medication was also less than the incidence in patients who received ibuprofen (1.4% vs. 3.4%, respectively). However, in patients ≥ 65 years of age, the differences between the incidences of gastric ulcers amongst the two treatment groups were negligible (18.5% in study medication treatment patients vs. 18.4% in ibuprofen treatment patients). In the patients ≥ 65 years of age, the duodenal ulcer incidence in patients receiving HZT-501 was 1.1% and it was 4.1% in patients receiving only the ibuprofen treatment. Similar findings with regards to age were noted in Study HZ-CA-303 when the patients from site 389 were not included. Again, as stated above, clear conclusions regarding the effect of age cannot be drawn because the study was not powered appropriately to detect a difference in this subgroup analysis.

With regards to race in Study HZ-CA-303, HZT-501 showed efficacy in the incidence of gastric ulcers across all three racial groups. With regards to duodenal ulcers, the Caucasian and African-American racial groups showed slightly decreased incidences of ulcers, but there were no patients in the racial group termed "other" with a diagnosis of duodenal ulcer. It is of note that the non-white populations were too small to reach an accurate conclusion regarding the efficacy of the study medication. When the patients from site 389 are excluded, the efficacy results with regards to race stayed the same as the results from all the sites for Study HZ-CA-303.

Regarding gender, female patients receiving HZT-501 showed a decreased incidence of gastric ulcers as compared to female patients on ibuprofen treatment (10.4% vs. 15.7%, respectively). This decreased incidence was also noted in female patients with regards to duodenal ulcers (0.3% in study medication treatment patients vs. 3.3% ibuprofen treatment patients). In male patients, a similar effect was noted; male patients showed gastric ulcer incidences of 6.6% in the group that received HZT-501 and 19.4% in the group receiving ibuprofen only; duodenal ulcers

were noted in 3.3% of male patients receiving the study medication vs. 4.2% of male patients receiving ibuprofen. Similar findings with regards to gender were noted in Study HZ-CA-303 when patients from site 389 were excluded.

Gastric ulcer incidences in patients on anticoagulants and/or on low-dose aspirin (Study HZ-CA-303) who received HZT-501 were lower as compared to patients on anticoagulants and/or low-dose aspirin who received ibuprofen (using the MITT even when excluding site 389); patients on anticoagulants and aspirin (low-dose aspirin) showed a 14.5% incidence of gastric ulcers in patients who were on the study medication as opposed to a 23.1% gastric ulcer incidence in patients who only received the ibuprofen. In patients who were only on low-dose aspirin, there was an 11.9% gastric ulcer incidence in patients receiving the study medication and there was a 24.0% gastric ulcer incidence in patients on the ibuprofen treatment. In patients who were on anticoagulants alone, the gastric ulcer incidence in patients receiving the study medication was 40.0% (total of 2 patients) and the incidence in patients receiving ibuprofen only was 66.7% (total of 2 patients). However, it is difficult to reach a conclusion regarding the efficacy of the study medication in patients on anticoagulants and/or aspirin given that the numbers of patients on anticoagulants and/or aspirin were small. In patients with an ulcer history, HZT-501 did not provide protection against gastric ulcer incidence in patients enrolled in Study HZ-CA-303 or in the same study with the patients from site 389 excluded; in fact, the gastric ulcer incidence in patients receiving the study medication was 20.6% and it was 15.4% in patients receiving only ibuprofen.

One combination product, VIMOVO (Naproxen and Esomeprazole combination) has been approved for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers.[10] In two pivotal studies over a 6 month course, VIMOVO showed 19.0% and 17.2% decreased incidence of gastric ulcers as compared to Naproxen. Table 4 displays the treatment effects on gastric ulcers in approved gastroprotective products as compared to placebo in endoscopy trials of patients who were treated with NSAIDs. Additionally, it also displays the results of a published study that evaluated esomeprazole for the risk reduction of GUs in low-dose aspirin-treated patients13 and a comparison of the risk factors for NSAID-associated UGI toxicity across the endoscopy trials. The difference in the incidence of ulcers between the gastroprotective products and control groups (observed risk difference) ranged from 7% to 29%.

[10] VIMOVO Label 2010.

Table 4 Risk difference and relative risk of gastric ulcers for gastroprotective products compared to placebo control in 3-6 month endoscopy trials

	Incidence of GUs	Risk Difference[2]	Relative Risk (95% CI)[3]	Risk Factors	NSAIDs Used
Misoprostol ± NSAIDs					
Misoprostol Endoscopy Study 1 (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Misoprostol 200 µg QID (n=74)	1 %	24%	0.1 (<0.1, 0.4)	Mean age = 74 years old Hx of ulcer = 18%	ibuprofen, piroxicam, naproxen
Placebo (n=76)	25%				
Misoprostol Endoscopy Study 2 (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Misoprostol 200 µg QID (n=65)	3%	15%	0.2 (<0.1, 0.8)	Mean age = 60 years old Hx of ulcer = 7%	ibuprofen, piroxicam, naproxen
Placebo (n=62)	18%				
PPIs ± NSAIDs					
Lansoprazole Study (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Lansoprazole 15 mg/day (n=136)	20%	29%	0.4 (0.3, 0.6)	Mean age 60 years Hx of GU = 99% Hx of DU = 50% Low dose aspirin use = 19%	ibuprofen, piroxicam, naproxen, diclofenac
Placebo (n=133)	49%				
Esomeprazole Study 1 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole 20 mg/day (n=191)	5%	7%	0.4 (0.2, 0.9)	Mean age = 64 Hx of PUB 26% Hx of POB = 1% Low dose aspirin use = 10%	COX-2 = 14% Non-selective = 85%
Placebo (n=184)	12%				
Esomeprazole Study 2 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole 20 mg/day (n=267)	5%	12%	0.3 (0.1, 0.5)	Mean age = 66 Hx of PUB = 10% Hx of POB = 1% Low dose aspirin use = 12%	COX-2 = 39% Non-selective = 61%
Placebo (n=257)	17%				
Esomeprazole/Naproxen Study 1 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole/naproxen (20/500 mg) BID (n=218)	4%	19%	0.2	Mean age = 60 Hx of PUB =5% Low dose aspirin use = 24%	Naproxen
Naproxen 500 mg BID (n=216)	23%				
Esomeprazole/Naproxen Study 2 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole/naproxen (20/500 mg) BID (n=210)	7%	17%	0.3	Mean age = 60 Hx of PUB = 11% Low dose aspirin use = 23%	Naproxen
Naproxen 500 mg BID (n=210)	24%				
Esomeprazole ± Low-Dose Aspirin (75 to 325 mg) – 26 week study[13] EGD at Weeks 0, 8, and 26					
Esomeprazole 20 mg (n=493)	1%	3%	0.3	Mean age = 69	Low dose aspirin
Placebo (n=498)	4%				

[1] The primary endpoint for some of these endoscopy trials was the proportion of patients without GUs during the treatment period. Although in other trials, the primary endpoint was the proportion of patients free from GUs, the data are presented as the proportion of patients without GUs for consistency.
[2] The risk difference was the difference between the incidence of GUs in the control group and the gastroprotective product group.

(Taken from GIDAC advisory briefing document, "Outcome Measures for Claims to Reduce NSAID-Associated Upper Gastrointestinal (UGI) Toxicity," November 4, 2010, available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/ucm195280.htm)

The findings with regards to HZT-501 are similar to the gastroprotective products; the difference in the incidence of gastric ulcers between patients receiving HZT-501 and patients receiving ibuprofen treatment in Study HZ-CA-303 was 15.4% which is in the range seen with proton pump inhibitors approved for the reduction of NSAID-associated gastric ulcers.

6.1 Indication

HZT-501 is a combination product of ibuprofen and famotidine that has been developed by Horizon Therapeutics, Inc., for the reduction of the risk of development of ibuprofen-associated upper gastrointestinal (UGI) ulcers in patients who require use of ibuprofen.

6.1.1 Methods

For the purposes of this review, Study HZ-CA-301 will be referred to as "Study 301," and Study HZ-CA-303 will be referred to as "Study 303."

Site 389 was one of the sites chosen for audit by the Agency given the high number of patients that were enrolled in the study at that site. The inspection found that the investigator failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60] and failed to maintain adequate and accurate case histories. Furthermore, additional good clinical practice deviations were noted including but not limited to the re-dispensing of the study medication to 33 patients at Week 8 and/or Week 16 in violation of the protocol, allowing multiple patients to continue on the study at Week 4 without having assessed their compliance with dosing, numerous out-of-window visits and a patient's continuing to take the study medication after the discovery of a gastric ulcer. Given the above issues, the patients from Site 389 have been excluded when discussing the efficacy outcome of the study in this review.

Additionally, Site 363 was another site that was chosen for a random audit by the Agency and some violations were noted by the field investigator for the Division of Scientific Investigations (DSI). After assessing the data integrity, a recommendation was made by DSI to exclude 4 patients from Site 363 (patient numbers: 005, 021, 050, and 100). The remaining patients from this site were deemed acceptable for data inclusion. Throughout this review, two sets of data will be presented, one including the 4 patients and one set with exclusion of these 4 patients.

Demographics

Demographic information for study 301 is shown in Table 5 (modified intent to treat, MITT, population) and Table 6 (primary population), and for study 303, the demographic information is shown in Table 7 (MITT population) and Table 8 (primary population) (see the patient disposition section for definitions). The patient demographics for studies 301 and 303 were

similar, and additionally, their MITT and primary populations were similar. The mean age for patients enrolled both studies was about 55 years old. In both studies the majority of the patients were less than 65 years old (about 82% of the patients in each treatment of each study were less than 65 years old and about 18% of the patients in each treatment of each study were 65 years old or older).

Table 5 Patient Demographics from Study HZ-CA-301 (MITT Population)

	Statistic	HZ-CA-301		
		HZT-501 (N=390)	Ibuprofen (198)	Total (N=588)
Age (years)				
	Mean (SD)	55.4 (9.0)	55.5 (9.5)	55.4 (9.1)
	Median	55.0	54.0	54.5
	Min, Max	39, 79	40, 78	39, 79
Age class				
< 65 years	**% (n)**	81.8% (319)	81.8% (162)	81.8% (481)
≥ 65 years	**% (n)**	18.2% (71)	18.2% (36)	18.2% (107)
Gender				
Male	**% (n)**	34.9% (136)	27.8% (55)	32.5% (191)
Female	**% (n)**	65.1% (254)	72.2% (143)	67.5% (397)
Race				
White	**% (n)**	82.1% (320)	83.8% (166)	82.7% (486)
Black	**% (n)**	14.6% (57)	10.6% (21)	13.3% (78)
Other*	**% (n)**	3.3% (13)	5.6% (11)	4.1% (24)

*Other: composed of Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native
(Data taken from Table 2 of page 16 of HZ CA 301 Clinical Study Report Addendum from Horizon Therapeutics, **Inc.)**

Table 6 Patient Demographics from Study HZ-CA-301 (Primary Population)

	Statistic	HZ-CA-301		
		HZT-501 (N=380)	Ibuprofen (190)	Total (N=570)
Age (years)				
	Mean (SD)	55.2 (9.0)	55.7 (9.4)	55.4 (9.1)
	Median	54.0	54.0	54.0
	Min, Max	39, 79	40, 78	39, 79
Age class				
< 65 years	**% (n)**	82.6% (314)	82.16% (156)	82.5% (470)
≥ 65 years	**% (n)**	17.4% (66)	17.9% (34)	17.5% (100)
Gender				
Male	**% (n)**	34.2% (130)	28.4% (54)	32.3% (184)
Female	**% (n)**	65.8% (250)	71.6% (136)	67.7% (386)
Race				
White	**% (n)**	81.6% (310)	84.7% (161)	82.6% (471)
Black	**% (n)**	15.0% (57)	10.5% (20)	13.5% (77)
Other*	**% (n)**	3.4% (13)	4.7% (9)	3.9% (22)

*Other: composed of Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native
(Data taken from Table 4 of page 60 of Horizon Therapeutics, Inc., Protocol HZ CA 301)

With regards to gender in Study 301 (MITT population), there was a predominance of female patients enrolled (67.5% female vs. 32.4% male). Similarly, in Study 303 (MITT population), 31.7% of the patients were male and 68.3% of the patients were female. The percentages of male patients in each treatment group within this Study (303, MITT population) were similar; 32.1% of the patients who received HZT-501 were male and 30.8% of the patients who received ibuprofen were male. The percentages of female patients in each treatment group within this study were also similar; 67.9% of the patients who received HZT-501 were female and 69.2% of the patients who received ibuprofen were female. However, in Study 301 (MITT population), the percentage of male patients receiving the study medication (34.9%) was slightly more than the percentage of male patients receiving ibuprofen (27.8%). Additionally, the percentage of female patients receiving the study medication (65.1%) was slightly less than the percentage of female patients receiving ibuprofen (72.2%) in the same study (see Tables 5, 6, 7, and 8).

Regarding race, there was a predominance of Caucasian (white) patients in both studies. Study 301 (MITT population) was comprised of 82.7% Caucasians; Caucasian patients comprised 82.1% of the patients receiving HZT-501 and 83.8% of the patients receiving ibuprofen. African-American (black) patients comprised 13.3% of the population in Study 301; 14.6% of the patients receiving the study medication were African-American and 10.6% of the patients receiving ibuprofen were African-American. The population listed as "Other" (composed of Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native) was only 4.1% of the population of Study 301. Of the total patients receiving HZT-501, only 3.3% were

listed as "Other;" the percentage of "Other" patients receiving ibuprofen was slightly larger (5.6%).

Study 303 (MITT population) was comprised of 77.7% Caucasians; Caucasian patients comprised 77.4% of the patients receiving HZT-501 and 78.3% of the patients receiving ibuprofen. African-American (black) patients comprised 19.2% of the population in Study 303; 19.3% of the patients receiving the study medication was African-American and 19.2% of the patients receiving ibuprofen was African-American. The population listed as "Other" (composed of Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native) was only 3.1% of the population of Study 303. Of the total patients receiving HZT-501, only 3.4% were listed as "Other;" the percentage of "Other" patients receiving ibuprofen was slightly smaller (2.5%).

Table 7 Patient Demographics from Study HZ-CA-303 (MITT Population)

	Statistic	HZ-CA-303		
		HZT-501 (N=561)	Ibuprofen (276)	Total (N=837)
Age (years)				
	Mean (SD)	55.7 (9.3)	55.8 (9.5)	55.7 (9.4)
	Median	55.0	55.0	55.0
	Min, Max	40, 80	40, 78	40, 80
Age class				
< 65 years	**% (n)**	81.5% (457)	80.8% (223)	81.2% (681)
≥ 65 years	**% (n)**	18.5% (104)	19.2% (53)	18.8% (157)
Gender				
Male	**% (n)**	32.1% (180)	30.8% (85)	31.7% (265)
Female	**% (n)**	67.9% (381)	69.2% (191)	68.3% (572)
Race				
White	**% (n)**	77.4% (434)	78.3% (216)	77.7% (650)
Black	**% (n)**	19.3% (108)	19.2% (53)	19.2% (161)
Other*	**% (n)**	3.4% (19)	2.5% (7)	3.1% (26)

*Other: composed of Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native
(Data taken from Table 2 of page 16 of HZ-CA-301 Clinical Study Report Addendum from Horizon Therapeutics, Inc.)

Table 8 Patient Demographics from Study HZ-CA-303 (Primary Population)

	Statistic	HZ-CA-303		
		HZT-501 (N=550)	Ibuprofen (262)	Total (N=812)
Age (years)				
	Mean (SD)	55.7 (9.3)	55.7 (9.4)	55.7 (9.3)
	Median	55.0	55.0	55.0
	Min, Max	40, 80	40, 78	40, 80
Age class				
< 65 years	**% (n)**	81.5% (448)	82.1% (215)	81.7% (663)
≥ 65 years	**% (n)**	18.5% (102)	17.9% (47)	18.3% (149)
Gender				
Male	**% (n)**	32.0% (176)	31.3% (82)	31.8% (258)
Female	**% (n)**	68.0% (374)	68.7% (180)	68.2% (554)
Race				
White	**% (n)**	77.1% (424)	77.5% (203)	77.2% (627)
Black	**% (n)**	19.5% (107)	20.2% (53)	19.7% (160)
Other*	**% (n)**	3.5% (19)	2.3% (6)	3.1% (25)

*Other: composed of Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native
(Data taken from Table 14.1.2.2 of page 137 of Horizon Therapeutics, Inc., Protocol HZ CA 303)

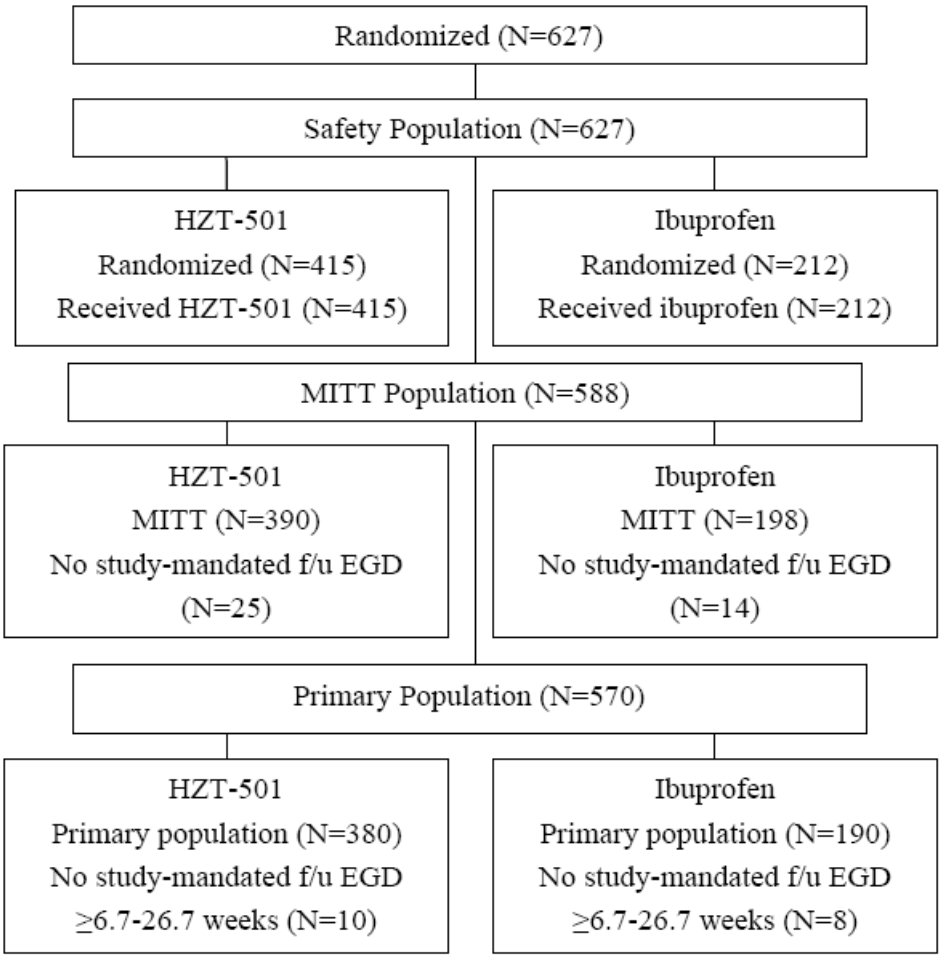
Patient Disposition

The population of interest for the primary efficacy outcome was termed the primary population by the applicant. The primary population was defined as subjects in the safety population (i.e., all randomized subjects who received at least one dose of study medication) who underwent a baseline endoscopic examination and at least the Week 8 endoscopic examination within the protocol allowed visit window (i.e., ≥6.7 weeks to ≤26.7 weeks). The modified intent to treat (MITT) population, not specifically pre-defined in the two pivotal study statistical analysis plans, was included as an important sensitivity analysis. The MITT population for endoscopy endpoint trials was defined as patients who were randomized, received at least one dose of study drug, and had at least one on-study endoscopy (International Conference on Harmonization, E9 1998, Full Analysis Set). This reviewer employed the MITT populations in Studies 301 and 303 for efficacy assessment; therefore, any patient who received at least one dose of the study medication was included in the final efficacy results regardless of when the follow-up endoscopy was performed (during the protocol visiting window or outside that window). By choosing this population, a more conservative estimate of the efficacy of the study medication would be obtained in both pivotal studies as compared to the primary population that the applicant had chosen which would be a less conservative measure of the efficacy data; in the primary population, only the patients who had received at least one dose of the study medication and who had undergone endoscopic examinations at baseline and only during the protocol visiting window were included.

Figure 1 and Table 9 (MITT population) and Table 10 (primary population) present the patient disposition in Study 301. 627 patients were randomized and received at least one dose of HZT-501. All 627 patients comprised the safety population, of which 415 patients received the study medication and 212 patients received ibuprofen. The MITT population was comprised of 588 patients, of which, 390 patients received HZT-501 and 198 patients received ibuprofen. The primary population was composed of 570 patients, of which, 380 patients received the study medication and 190 patients received ibuprofen. Figure 1 illustrates the breakdown of the populations in Study HZ-CA-301 as chosen by the applicant.

In Study 301 (MITT population), 66.1% of the patients received HZT-501 and 33.8% of the patients receiving ibuprofen. 69.7% of the patients completed the study in the group receiving the study medication and 61.6% of the patients receiving ibuprofen completed the study. 30.3% of the study medication patients were terminated early as compared to 38.4% of the patients that received ibuprofen. The reasons for early termination were listed as death, adverse events, consent withdrawal, protocol violations, being lost to follow-up, investigator/sponsor discretion, endoscopically-diagnosed UGI ulcer, the requirement of an excluded medication and "other". The listing of "other" as a reason for early termination included, noncompliance, a patient's refusal to undergo one or more endoscopies as dictated by the protocol, and incarceration.

Figure 1 Patient Disposition in Study HZ-CA-301



EGD esophagogastroduodenoscopy; f/u follow up; MITT modified intent to treat
Taken from page 35 of Section 2.7.3 of Summary of Clinical Efficacy submitted by Horizon

Table 9 Patient Disposition in Study HZ-CA-301 (MITT Population)

	HZT-501 % (n)	Ibuprofen % (n)	Total % (n)
All Pts.			
Number of Patients	66.1 (390)	33.8 (198)	100.0 (588)
Completed Study	69.7 (272)	61.6 (122)	62.8 (394)
Early Termination	30.3 (143)	38.4 (76)	37.2 (233)
Reasons for Early Termination			
Death	0.0 (0)	0.0 (0)	0.0 (0)
Adverse Events	4.9 (19)	5.6 (11)	5.1 (30)
Patient Withdrawing Consent	8.7 (34)	9.6 (19)	9.0 (53)
Protocol Violations	1.3 (5)	0.0 (0)	0.9 (5)
Patient Lost to Follow-up	3.3 (13)	1.5 (3)	2.7 (16)
Discretion of Investigator/Sponsor	2.3 (9)	4.0 (8)	2.9 (17)
Endoscopically-Diagnosed UGI Ulcer	8.5 (33)	17.2 (34)	11.4 (67)
Patient Required Excluded Medication	0.3 (1)	0.5 (1)	0.3 (2)
Other	1.0 (4)	0.0 (0)	0.7 (4)

(Taken from Table 1 on page 13 of Section 2 of HZ CA 301 Clinical Study Report Addendum from Horizon Therapeutics, Inc.)

Table 10 Patient Disposition in Study HZ-CA-301 (Primary Population)

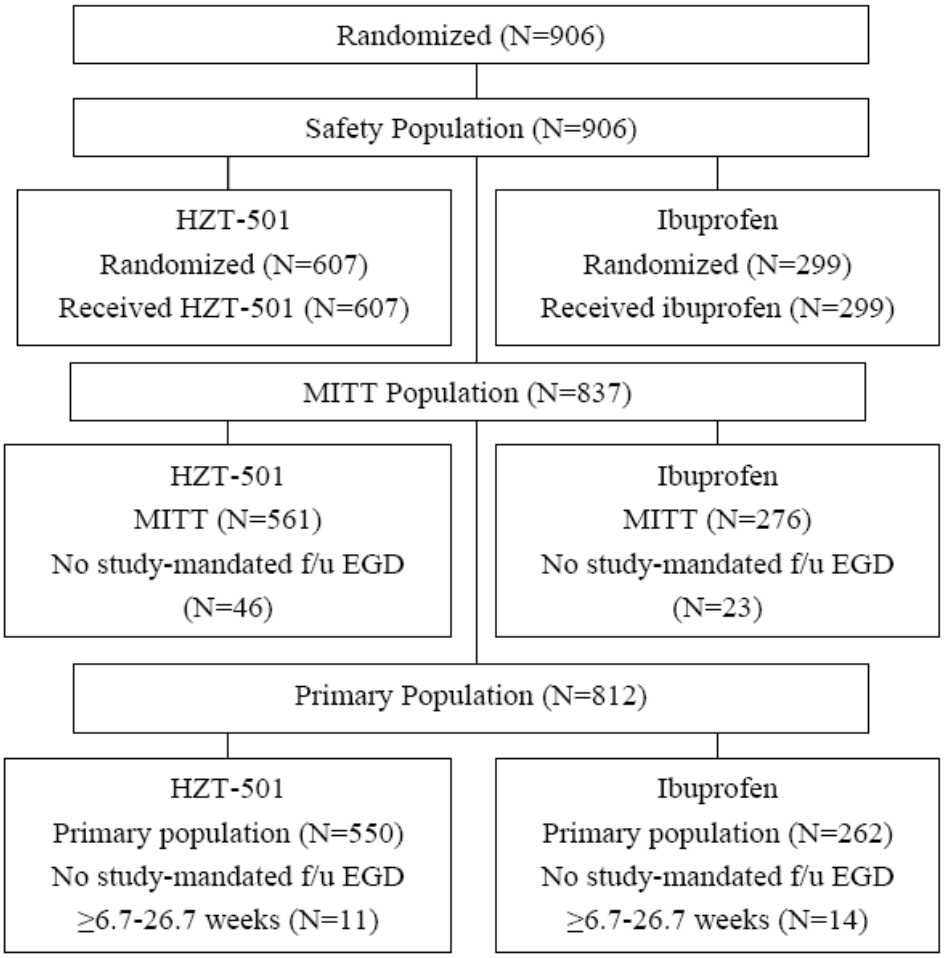
	HZT-501 % (n)	Ibuprofen % (n)	Total % (n)
All Pts.			
Number of Patients	66.7 (380)	33.3 (190)	100.0 (570)
Completed Study	71.6 (272)	64.2 (122)	69.1 (394)
Early Termination	28.4 (108)	35.8 (68)	30.9 (176)
Reasons for Early Termination			
Death	0.0 (0)	0.0 (0)	0.0 (0)
Adverse Events	3.9 (15)	3.7 (7)	3.9 (22)
Patient Withdrawing Consent	8.2 (31)	8.4 (16)	8.2 (47)
Protocol Violations	1.1 (4)	0.0 (0)	0.7 (4)
Patient Lost to Follow-up	3.4 (13)	1.6 (3)	2.8 (16)
Discretion of Investigator/Sponsor	2.1 (8)	3.7 (7)	2.6 (15)
Endoscopically-Diagnosed UGI Ulcer	8.4 (32)	17.9 (34)	11.6 (66)
Patient Required Excluded Medication	0.3 (1)	0.5 (1)	0.4 (2)
Other	1.1 (4)	0.0 (0)	0.7 (4)

(Taken from Table 14.1.1.2 on page 107 of Section 14 of Study HZ CA 301 from Horizon Therapeutics, Inc.)

Figure 2 and Table 11 (MITT population) and Table 12 (primary population) present the patient disposition in Study 303. 906 patients were randomized and received at least one dose of HZT-501. All 906 patients comprised the safety population, of which 607 patients received the study medication and 299 patients received ibuprofen. The MITT population was comprised of 837 patients, of which, 561 patients received HZT-501 and 276 patients received ibuprofen. The primary population was composed of 812 patients, of which, 550 patients received the study medication and 262 patients received ibuprofen. In Study 303 (MITT population) , 67.0% of the

patients received HZT-501 and 33.0% of the patients receiving ibuprofen. 77.0% of the patients completed the study in the group receiving the study medication and 62.0% of the patients receiving ibuprofen completed the study. 23.0% of the study medication patients were terminated early as compared to 38.0% of the patients that received ibuprofen. The reasons for early termination were listed as death, adverse events, consent withdrawal, protocol violations, being lost to follow-up, investigator/sponsor discretion, endoscopically-diagnosed UGI ulcer, the requirement of an excluded medication and “other". The listing of “other” as a reason for early termination included, noncompliance, a patient leaving the country, error in scheduling of endoscopies, patient losing contact with the research facility secondary to change of location of the research site. One death was noted in the group of patients receiving ibuprofen (to be discussed in detail in section 7.3.1).

Figure 2 Patient Disposition in Study HZ-CA-303



EGD esophagogastroduodenoscopy; f/u follow up; MITT modified intent to treat
Taken from page 35 of Section 2.7.3 of Summary of Clinical Efficacy submitted by Horizon

Table 11 Patient Disposition in Study HZ-CA-303 (MITT Population)

	HZT-501 % (n)	Ibuprofen % (n)	Total % (n)
All Pts.			
Number of Patient	67.0 (561)	33.0 (276)	100.0 (837)
Completed Study	77.0 (432)	62.0 (171)	72.0 (603)
Early Termination	23.0 (129)	38.0 (105)	28.0 (234)
Reasons for Early Termination			
Death	0.0 (0)	0.4 (1)	0.1 (1)
Adverse Events	5.2 (29)	6.9 (19)	5.7 (48)
Patient Withdrawing Consent	5.3 (30)	5.4 (15)	5.4 (45)
Protocol Violations	0.2 (1)	0.4 (1)	0.2 (2)
Patient Lost to Follow-up	0.9 (5)	1.4 (4)	1.1 (95)
Discretion of Investigator/Sponsor	1.8 (10)	2.2 (6)	1.9 (16)
Endoscopically-Diagnosed UGI Ulcer	8.9 (50)	18.8 (52)	12.2 (102)
Patient Required Excluded Medication	0.2 (1)	0.7 (2)	0.4 (3)
Other	0.5 (3)	1.8 (5)	1.0 (8)

(Taken from Table 1 on page 13 of Section 2 of HZ CA 303 Clinical Study Report Addendum from Horizon Therapeutics, Inc.)

Table 12 Patient Disposition in Study HZ-CA-303 (Primary Population)

	HZT-501 % (n)	Ibuprofen % (n)	Total % (n)
All Pts.			
Number of Patient	67.7 (550)	32.3 (262)	100.0 (812)
Completed Study	78.5 (432)	65.3 (171)	74.3 (603)
Early Termination	21.5 (118)	34.7 (91)	25.7 (209)
Reasons for Early Termination			
Death	0.0 (0)	0.4 (1)	0.1 (1)
Adverse Events	3.6 (20)	4.2 (11)	3.8 (31)
Patient Withdrawing Consent	5.3 (29)	5.3 (14)	5.3 (43)
Protocol Violations	0.2 (1)	0.0 (0)	0.1 (1)
Patient Lost to Follow-up	0.9 (5)	1.5 (4)	1.1 (9)
Discretion of Investigator/Sponsor	1.8 (10)	1.9 (5)	1.8 (15)
Endoscopically-Diagnosed UGI Ulcer	8.9 (49)	19.1 (50)	12.2 (99)
Patient Required Excluded Medication	0.2 (1)	0.4 (1)	0.2 (2)
Other	0.5 (3)	1.9 (5)	1.0 (8)

(Taken from Table 14.1.1.2 on page 114 of Section 14 of Study HZ CA 303 from Horizon Therapeutics, Inc.)

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint of Study 301 was the incidence of an endoscopic upper gastrointestinal (UGI) ulcer (ulcer described as having an unequivocal depth and at least 3 mm in

diameter) during the 24-week treatment period compared to ibuprofen in patients at risk for NSAID-induced ulcers. In the original NDA study report, the applicant had submitted Table 13 showing the proportion of patients who developed at least one upper gastrointestinal (UGI) ulcer using the primary population of 570 patients in Study 301.

Table 13: Study 301: Proportion of patients who developed at least one UGI ulcer (primary population)

	HZT-501 (N=380)			Ibuprofen (N=190)			Difference			
	Proportion[a]	SE[b]	95% CI	Proportion[a]	SE[b]	95% CI	Proportion	SE[c]	95% CI	p-value
All Subjects (N=570)	13.8%	0.022	10.1%, 18.8%	22.6%	0.034	16.7%, 30.1%	8.8%	0.040	0.8%, 16.7%	0.0304[c]

a: Week 24 proportions are estimated from a life table analysis that included a covariate for treatment.
b: Standard errors are Greenwood estimates of the standard errors for the life table estimated Week 24 proportions.
c: p value and standard error are for the difference of the Week 24 estimated proportions of subjects developing at least one UGI ulcer.
CI Confidence Interval, SE Standard Error

An information request (IR) letter was sent to the applicant to clarify whether all patients who terminated early were counted as treatment failures. On page 22 of the footnote of Table 3 in section 2.7.3.2.1.4.3 of the applicant's clinical summary, it was noted that early terminations were "based on subjects imputed as treatment failures who early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug (or end of treatment date)."

Table 14: Study 301: Proportion of patients who developed at least one UGI ulcer based upon IR letter request (primary population)

HZT-501 (H) (N=380)		Ibuprofen (I) (N= 190)		Difference (H- I)			
Proportion[a]	**SE[b]**	**Proportion**	**SE**	**Proportion**	**SE**	**95%CI**	**p-value[c]**
21.3%	**0.025**	**28.0%**	**0.036**	**-6.7%**	**0.043**	**(-15.2%, 1.8%)**	**0.1228**

a: Week 24 proportions are estimated from a life table analysis that included a covariate for treatment.
b: Standard errors are Greenwood estimates of the standard errors for the life table estimated Week 24 proportions.
c: standard error are for the difference of the Week 24 estimated proportions of subjects developing at least one duodenal ulcer.
CI Confidence Interval, SE Standard Error

Based upon this reanalysis, a treatment effect of 6.7% for HZT-501 was obtained (Table 14) which is not statistically significant (p 0.1228). As requested by the Agency, a crude analysis was also performed by the applicant (Table 15). The results of the crude rate analysis show a statistically significant treatment effect for HZT-501 of 9.5% if patients who terminated early were not counted as treatment failures. The treatment effect of the study medication decreases to 7.1% if patients who terminated early were counted as treatment failures; this is not statistically significant by the significance testing methods employed by the statistical reviewer.

Table 15 Re-analysis of Results with all Early Terminations Counted as Treatment Failures

HZT-501 (H) (N=380)		Ibuprofen (I) (N= 190)		Difference (H- I)			
Proportion[a]	SE[b]	Proportion	SE	Proportion	SE	95%CI	p-value[c]
21.3%	0.025	28.0%	0.036	-6.7%	0.043	(-15.2%, 1.8%)	0.1228

a: Week 24 proportions are estimated from a life table analysis that included a covariate for treatment.
b: Standard errors are Greenwood estimates of the standard errors for the life table estimated Week 24 proportions.
c: standard error are for the difference of the Week 24 estimated proportions of subjects developing at least one duodenal ulcer.
CI Confidence Interval, SE Standard Error

However, based upon the efficacy results shown in the following sections, some protection against UGI ulcers was shown in patients who were receiving HZT-501. A discussion of the populations used to obtain the efficacy results by this reviewer for both studies is warranted.

The applicant initially started with a randomized population (or termed safety population by the sponsor) of 627 patients in Study HZ-CA-301, but 57 patients were considered early termination who did not have a negative endoscopy for ulcers within 14 days of the last dose of the medication. A final population of 570 patients (termed primary population by the sponsor) was considered for the evaluation of ulcer incidence in Study HZ-CA-301. This reviewer has chosen to consider the 588 patients in Study HZ-CA-301 for calculation of the incidence of ulcers [modified intent to treat (ITT) Population] in this NDA. However, the statistical reviewer analyzed the data using the applicant's per-protocol or "primary population" for all statistical analyses.

Review of Gastric Ulcer Incidence
In the original NDA study report, the applicant also submitted Table 16 showing the proportion of patients who developed at least one gastric ulcer using the primary population of 570 patients in Study HZ-CA-301, a key secondary endpoint.

Table 16 Proportion of patients who developed at least one gastric ulcer in Study HZ-CA-301 (Primary Population)

HZT-501 (N=380)			Ibuprofen (N=190)			Difference			
Porportion[a]	SE[b]	95% CI	Porportion[a]	SE[b]	95% CI	Porportion[a]	SE[b]	95% CI	p-value[c]
13.8%	0.022	10.1%, 18.8%	22.6%	0.034	16.7% 30.1%	8.8%	0.040	0.8%, 16.7%	0.0304

a: Week 24 proportions are estimated from a life table analysis that included a covariate for treatment.
b: Standard errors are Greenwood estimates of the standard errors for the life table estimated Week 24 proportions.
c: p value and standard error are for the difference of the Week 24 estimated proportions of subjects developing at least one UGI ulcer.
CI Confidence Interval, SE Standard Error
(Taken from Table 1, page 19 of section 2.7.3.2.1.4.1 of Summary of Clinical Efficacy of Horizon Therapeutics, Inc., HZT 501)

The primary efficacy endpoint of Study 303 was the incidence of an endoscopic gastric ulcer (ulcer described as having an unequivocal depth and at least 3 mm in diameter) during the 24-week treatment period compared to ibuprofen in patients at risk for NSAID-induced ulcers. In

the original NDA study report, the applicant had submitted Table 17 showing the proportion of patients who developed at least one gastric ulcer using the primary population of 812 patients in Study 303. As shown below, the proportion of patients treated with HZT-501 who developed a gastric ulcer was 12.9% as compared to the incidence of 25.3% in patients who received only ibuprofen. The difference between the treatment groups was 12.4% with a p-value of 0.0009 which was statistically quite significant for the treatment effect.

Table 17 Proportion of patients who developed at least one gastric ulcer in Study HZ-CA-303 (Primary Population)

HZT-501 (N=550)			Ibuprofen (N=262)			Difference			
Porportion[a]	SE[b]	95% CI	Porportion[a]	SE[b]	95% CI	Porportion[a]	SE[b]	95% CI	p-value[c]
12.9%	0.017	9.8%, 16.7%	25.3%	0.033	19.5% 32.5%	12.4%	0.037	5.1%, 19.7%	0.0009

a: Week 24 proportions are estimated from a life table analysis that included a covariate for treatment.
b: Standard errors are Greenwood estimates of the standard errors for the life table estimated Week 24 proportions.
c: p value and standard error are for the difference of the Week 24 estimated proportions of subjects developing at least one UGI ulcer.
CI Confidence Interval, SE Standard Error
(Taken from Table 4, page 27 of section 2.7.3.2.2.4.1 of Summary of Clinical Efficacy of Horizon Therapeutics, Inc., HZT 501)

Table 18 shows a re-analysis of the data from Study 303 that included all the early terminations as treatment failures. The difference between the treatment groups was 15.0% with a p-value of 0.0001 which was statistically quite significant for the treatment effect.

Table 18 Re-analysis of results with all early terminations counted as treatment failures

HZT-501 (N=550)			Ibuprofen (N=262)			Difference			
Proportion*	SE**	95% CI	Proportion*	SE**	95% CI	Proportion*	SE**	95% CI	p-value***
17.0%	0.019	13.6%, 21.1%	32.0%	0.034	25.8% 39.2%	15.0%	0.039	7.4%, 22.7%	0.0001

* Week 24 proportions are estimated from a life table analysis that includes a covariate for treatment.
**Standard errors are Greenwood estimates of the standard errors for the life table estimated Week 24 proportions.
***P-value and standard error are for the difference of the Week 24 estimated proportions of subjects developing at least one ulcer.
(Taken from applicant amendment to submission dated October 21, 2010, table 14.6.6.1.1)

Table 19 Crude Incidence Rates for Development of Ulcer by Treatment Group for Study HZ-CA-303 (Primary Population)

Endpoint	HTZ-501 (N=550)	Ibuprofen (N=262)	P-value[a]	P-value[b]	P-value[c]
	% (n/N)	% (n/N)			
Gastric ulcer					
Crude rate without ET[d]	10.0% (55/550)	19.8% (52/262)	0.0002	0.0002	0.0002
Crude rate with ET[e]	23.5% (129/550)	37.4% (99/262)	<0.0001	<0.0001	<0.0001
UGI ulcer					
Crude rate without ET[d]	11.3% (62/550)	23.3% (61/262)	<0.0001	< 0.0001	<0.0001
Crude rate with ET[e]	24.0% (132/550)	38.5% (101/262)	<0.0001	<0.0001	<0.0001
Duodenal ulcer					
Crude rate without ET[d]	1.3% (7/550)	5.3% (14/190)	0.0014	0.0015	0.0006
Crude rate with ET[e]	22.0% (121/550)	35.5% (93/262)	<0.0001	<0.0001	<0.0001

a: From a Fisher's exact test;
b: From a Chi-Square test with a continuity correction adjustment;
c: From a Cochran-Mantel-Haenszel test stratified by randomization strata.
d: without including the early terminated subjects as having an ulcer;
e: including the early terminated subjects as having an ulcer.

The results of the crude incidence rates (Table 19) show a statistically significant decrease in the incidence of gastric ulcers in patients receiving HZT-501 treatment as compared to patients who only received ibuprofen treatment if patients who terminated early were not counted as treatment failures (a 9.8% difference). Furthermore, the result remains statistically significant when patients who terminated early were counted as treatment failures, the most conservative analysis; therefore, this represents a robust finding.

Site 389 was one of the sites chosen for a random audit by the Agency given the high number of patients that were enrolled in the study at that site. The inspection found that the investigator failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60] and failed to maintain adequate and accurate case histories. Furthermore, additional good clinical practice deviations were noted including but not limited to the re-dispensing of the study medication to 33 patients at Week 8 and/or Week 16 in violation of the protocol, allowing multiple patients to continue on the study at Week 4 without having assessed their compliance with dosing, numerous out-of-window visits and a patient's continuing to take the study medication after the discovery of a gastric ulcer (see section 3.2). Given the above issues, the patients from Site 389 have been excluded when discussing the efficacy outcome of the study in this review. Table 20 illustrates the ulcer incidence in Study HZ-CA-303 (MITT patients) excluding patients from Site 389. The gastric ulcer incidence was 9.2% in the HZT-501 group and the incidence was 15.1% for the group of patients receiving the ibuprofen. The duodenal ulcer incidence for the HZT-501 group was 1.3%, and for the ibuprofen group, the incidence was 3.6%. Even with the removal of the patients from Site 389, it appears that HZT-501 did offer some protection in patients with regards to the incidence of gastric ulcers during the 24-week treatment period (9.2% study medication vs. 15.1% ibuprofen group).

Table 20 Gastric and Duodenal ulcer Incidence in Study HZ-CA-303 excluding Site 389 (MITT Population)

Treatment (N)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 (459)	42 (9.2)	6 (1.3)
Ibuprofen (225)	34 (15.1)	8 (3.6)

Table 21 Gastric and Duodenal ulcer Incidence in Study HZ-CA-303 excluding Site 389 (MITT Population) minus 4 pts. from Site 363

Treatment (N)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 (457)	42 (9.2)	6 (1.3)
Ibuprofen (223)	34 (15.2)	8 (3.6)

Table 21 illustrates the gastric ulcer incidence in Study HZ-CA-303 (MITT patients) excluding the 4 patients from Site 363 (see section 3.2 for explanation of the removal of these four patients). As noted above, the differences between Tables 20 and 21 with regards to the ulcer incidences are negligible.

Table 22 shows the revised results of the crude incidence rate of gastric ulcers when the data from site 389 and 4 patients from site 363 are removed. No substantive effect on the overall results is noted when these data are removed.

Table 22 Crude gastric ulcer incidence rate including early terminated patients as treatment failures, excluding patients from site 389 and 4 patients for site 363 using the primary population

	HZT-501 (H) (N=445)	Ibuprofen (I) (N= 214)	Difference (I-H)		
	Proportion*	Proportion	Proportion	95% CI	*p-value***
All Patients (N=659)	21.60% (96/445)	37.0% (79/214)	15.40%	(-23.0%, -8.0%)	< 0.0001

6.1.5 Analysis of Secondary Endpoints(s)

The secondary objectives of Study HZ-CA-301 included measuring:

1. The proportion of patients developing at least 1 endoscopically-diagnosed gastric ulcer during the 24-week treatment period

2. The proportion of patients developing at least 1 endoscopically-diagnosed duodenal ulcer in the 24-week treatment period

3. The incidence rate of NSAID-associated serious GI complications in the 24-week treatment period

The secondary objectives of Study HZ-CA-303 included measuring:

1. The proportion of patients developing at least 1 endoscopically-diagnosed UGI ulcer during the 24-week treatment period

2. The proportion of subjects developing at least 1 endoscopically-diagnosed duodenal ulcer in the 24-week treatment period

3. The incidence rate of NSAID-associated serious GI complications in the 24-week treatment period

As described above, the incidence of gastric, duodenal, and total upper GI ulcers was evaluated as the primary endpoint for analysis purposes. Therefore, the primary and secondary endpoints for both studies were all evaluated as important efficacy endpoints.

6.1.6 Other Endpoints

Apart from the primary and the secondary endpoints as discussed above, no other endpoints were noted for this study.

6.1.7 Subpopulations

Several subpopulations were chosen and are discussed fully in the next few sections.

Table 23 Gastric and Duodenal ulcer Incidence in Study HZ-CA-301 by Age (MITT Population)

Treatment (N)	Age (N)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 (390)	< 65 (319)	29 (9.1)	3 (0.9)
	≥ 65 (71)	10 (14.1)	0 (0.0)
Ibuprofen (198)	< 65 (162)	28 (17.3)	3 (1.9)
	≥ 65 (36)	6 (16.7)	1 (2.8)

Table 23 illustrates the ulcer incidence in Study HZ-CA-301 by age. In patients who were less than 65 years old and who received HZT-501, the gastric ulcer incidence was 9.1%; the incidence of patients less than 65 years old receiving ibuprofen was 17.3%. Conversely, in patients who were 65 years or older, the incidence of gastric ulcers was 14.1% in patients receiving the study medication and it was 16.7% in the ibuprofen group. The incidence for duodenal ulcers in patients less than 65 years was 0.9% for patients receiving HZT-501 and 1.9% for patients receiving ibuprofen. In patients greater than or equal to 65 years old, the incidence of duodenal ulcers was 0% in patients receiving the study medication and 2.8% in patients receiving ibuprofen.

Table 24 Gastric and Duodenal ulcer Incidence by Age in Study HZ-CA-303 excluding Site 389 (MITT Population)

Treatment (N)	Age (N)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 (459)	< 65 (367)	25 (6.8)	5 (1.4)
	≥ 65 (92)	17 (18.5)	1 (1.1)
Ibuprofen (225)	< 65 (176)	29 (16.5)	6 (3.4)
	≥ 65 (49)	9 (18.4)	2 (4.1)

Table 24 illustrates the ulcer incidence in Study HZ-CA-303 (excluding Site 389) by age. This table demonstrates that there are no differences in patients 65 years of age and older between the HZT-501 treatment group (18.5%) compared to treatment with ibuprofen (18.4%). Excluding the 4 patients from site 363 (patients #005, #021, #050, and #100) from the above data set did not change the ulcer incidences.

Table 25 Gastric and Duodenal ulcer Incidence in Study HZ-CA-301 by Gender (MITT Population)

Treatment (N)	Sex (N)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 (390)	F (254)	22 (8.7)	1 (0.4)
	M (136)	17 (12.5)	2 (1.5)
Ibuprofen (198)	F (143)	30 (21.0)	2 (1.4)
	M (55)	4 (7.3)	2 (3.6)

Table 25 shows ulcer incidence by gender in Study HZ-CA-301. The gastric ulcer incidence in female patients was 8.7% in the group who received HZT-501, as compared to the ibuprofen group who showed an incidence of 21.0%. The gastric ulcer incidence in male patients was 12.5% in the group who received HZT-501, as compared to the ibuprofen group who showed an incidence of 7.3%. The duodenal ulcer incidence in female patients was 0.4% in the group who received HZT-501, as compared to the ibuprofen group who showed an incidence of 1.4%. The duodenal ulcer incidence in male patients was 1.5% in the group that received HZT-501, as compared to the ibuprofen group which showed an incidence of 3.6%. In female patients, the incidence of gastric ulcers was lower in the group receiving HZT-501 as compared to the group which was receiving ibuprofen treatment. However, in male patients, the incidence of gastric ulcers was actually greater in the patients who received the study medication. As described earlier, the statistical reviewer also found, using life table analyses, that there was a higher proportion of men in the HZT-501 treatment group who developed upper gastrointestinal ulcers compared to the ibuprofen group (-15.5%; p 0.065); however, this finding was not statistically significant. It is not clear why men in this study would have had a worse outcome.

Table 26 Gastric and duodenal ulcer Incidence by Gender in Study HZ-CA-303 excluding Site 389 (MITT Population)

Treatment (N)	Sex (N)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 (459)	F (308)	32 (10.4)	1 (0.3)
	M (151)	10 (6.6)	5 (3.3)
Ibuprofen (225)	F (153)	24 (15.7)	5 (3.3)
	M (72)	14 (19.4)	3 (4.2)

Table 26 shows ulcer incidence by gender in Study HZ-CA-303 with the exclusion of patients from site 389. The gastric ulcer incidence in female patients was 10.4% in the group who received HZT-501, as compared to the ibuprofen group who showed an incidence of 15.7%. The gastric ulcer incidence in male patients was 6.6% in the group who received HZT-501, as compared to the ibuprofen group who showed an incidence of 19.4%. In both genders, patients who received the study medication showed decreased incidences of gastric ulcers as compared to the patients receiving ibuprofen. Excluding the 4 patients from site 363 (patients #005, #021, #050, and #100) from the above data set did not change ulcer incidence.

Table 27 Gastric and Duodenal ulcer Incidence in Study HZ-CA-301 by Race (MITT Population)

Treatment N (%)	Race	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 (390)	Black	3 (0.8)	0(0.0)
	Other	1 (0.3)	0(0.0)
	White	35 (9.0)	3 (0.8)
Ibuprofen (198)	Black	3 (1.5)	0(0.0)
	Other	0(0.0)	0(0.0)
	White	26(13.1)	4 (2.0)

Table 27 shows ulcer incidence by race in Study HZ-CA-301. In the Caucasian (white) population, the gastric ulcer incidence was 9.0% in the study medication group as compared to 13.1% in the ibuprofen group. The duodenal ulcer incidence for this population was 0.8% in the study medication group and 2.0% in the group receiving ibuprofen. In the African-American (black) population, the gastric ulcer incidence was 0.8% in the group receiving HZT-501 and 1.5% in the ibuprofen group. In the population listed as "Other" (composed of Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native), the incidence of gastric ulcers was 0.3% in the group of patients receiving HZT-501 and 0.0% in the patients receiving ibuprofen. The duodenal ulcer incidence in this African-American population and the "Other" population showed no incidence of duodenal ulcers in either the study medication group or the ibuprofen group. A conclusion cannot be obtained regarding the patients in the "Other" and African-American population groups because of the small number of patients involved.

Table 28 Gastric and Duodenal ulcer Incidence by Race in Study HZ-CA-303 excluding Site 389 (MITT Population)

Treatment (N)	Race (N)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 (459)	Black (48)	3 (6.3)	1 (2.1)
	Other (19)	1 (5.3)	0 (0.0)
	White (392)	38 (9.7)	5 (1.3)
Ibuprofen (225)	Black (31)	4 (12.9)	2 (6.5)
	Other (7)	1 (14.3)	0 (0.0)
	White (187)	33 (17.6)	6 (3.2)

Table 28 shows ulcer incidence by race in Study HZ-CA-303 with the exclusion of patients from Site 389. In the Caucasian population, the gastric ulcer incidence for this population was 9.7% in the study medication group and 17.6% in the group receiving ibuprofen. In the African-American (black) population, the gastric ulcer incidence for this population was 6.3% in the study medication group and 12.9% in patients receiving ibuprofen. In the population listed as "Other" (composed of Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native), the gastric ulcer incidence in patients receiving the study medication was 5.3% and the incidence of gastric ulcers in patients receiving only ibuprofen was 14.3%. However, a conclusion cannot be obtained regarding the patients in the "Other" population group because of the small number of patients involved. Excluding the 4 patients from site 363 (patients #005, #021, #050, and #100) from the above data set did not change the ulcer incidences.

Table 29 Gastric and Duodenal ulcer Incidence in Study HZ-CA-301 in Patients On Anticoagulants and Aspirin (MITT Population)

Treatment N (%)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 61/390 (16)	8 (13.1)	0 (0.0)
Ibuprofen 27/198 (14)	5 (18.5)	1 (3.7)

Table 29 illustrates the ulcer incidence in patients in Study HZ-CA-301 (total of 88 patients) who were on oral anticoagulants (warfarin) and low-dose aspirin (≤ 325 mg/day). The incidence of gastric ulcers incidence was 13.1% in the HZT-501 group and 18.5% in the ibuprofen group. The duodenal ulcer incidence for the study medication group was 0%, and for the ibuprofen group, the incidence was 3.7%. It appears that a patient who was on oral anticoagulants and low-dose aspirin and who received HZT-501 may have a lower incidence of gastric ulcers as compared to a patient who received only ibuprofen. However, no clear conclusions can be made because of the small sample sizes.

Table 30 Gastric and Duodenal ulcer Incidence in Study HZ-CA-303 (excluding Site 389) in Patients On Anticoagulants and Aspirin (MITT Population)

Treatment N (%)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 69/459 (15)	10 (14.5)	0 (0.0)
Ibuprofen 26/225 (12)	6 (23.1)	1 (3.8)

Table 30 illustrates the ulcer incidence in Study HZ-CA-303 (excluding patients from Site 389) in patients (total of 95 patients) who were on oral anticoagulants (warfarin) and low-dose aspirin.

The incidence of gastric ulcers incidence was 14.5% in the HZT-501 group and 23.1% in the ibuprofen group. The duodenal ulcer incidence for the study medication group was 0%, and for the ibuprofen group, the incidence was 3.8%. It appears that a patient who was on oral anticoagulants and low-dose aspirin and who received HZT-501 may have a lower incidence of gastric ulcers as compared to a patient who received only ibuprofen (14.5% incidence in the study medication vs. 23.1% in the ibuprofen group), however, no clear conclusions can be made because the sample sizes were small. No changes were noted with regards to ulcer incidence in Study HZ-CA-303 patients who were on anticoagulants when 4 patients (#005, #021, #050, and #100) were excluded from site 363.

Table 31 Gastric and Duodenal ulcer Incidence in Study HZ-CA-301 in Patients on Anticoagulants (MITT Population)

Treatment N (%)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 3/390 (0.8)	0 (0.0)	0 (0.0)
Ibuprofen 2/198 (1.0)	2 (100.0)	0 (0.0)

Table 31 shows the ulcer incidence in patients in Study HZ-CA-301 (total of 5 patients) who were on oral anticoagulants. The incidence of gastric ulcers incidence was 0.0% in the HZT-501 group and 100.0% in the ibuprofen group. The duodenal ulcer incidence for both the study medication group and the ibuprofen group was 0.0%. No conclusions can be made because of the small sample sizes.

Table 32 Gastric and Duodenal ulcer Incidence in Study HZ-CA-303 in Patients on Anticoagulants, excluding patients from site 389 (MITT Population)

Treatment N (%)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 2/459 (0.4)	2 (100.0)	0 (0.0)
Ibuprofen 1/225 (0.4)	1 (100.0)	0 (0.0)

Ulcer incidence in patients who were on anticoagulants (warfarin) in Study HZ-CA-303 and excluding patients from site 389 is shown in Table 32. Of the 2 patients receiving the study medication, both patients were positive for gastric ulcer (100% incidence). In the group receiving ibuprofen, one patient was also positive for gastric ulcer (100.0% incidence). The numbers of patients are much too small to reach a conclusion regarding the effects of HZT-501 on a patient who is already on an anticoagulant.

Table 33 Gastric and Duodenal ulcer Incidence in Study HZ-CA-301 in Patients on Low-Dose Aspirin (MITT Population)

Treatment N (%)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 59/390 (15.1)	8 (13.6%)	0 (0.0%)
Ibuprofen 29/198 (14.6)	5 (17.2%)	1 (3.4%)

Table 33 illustrates the ulcer incidence in Study HZ-CA-301 in patients (total of 88 patients) who were on low-dose aspirin (≤ 325 mg per day). The incidence of gastric ulcers incidence was 13.6% in the HZT-501 group and 17.2% in the ibuprofen group. The duodenal ulcer incidence for the study medication group was 0%, and for the ibuprofen group, the incidence was 3.4%. It appears that patients on low-dose aspirin who received HZT-501 may have a lower incidence of gastric ulcer as compared to ibuprofen (13.6% incidence in the study medication vs. 17.2% in

the ibuprofen group), however, no clear conclusions can be made because the sample sizes were small.

Table 34 Gastric and Duodenal ulcer Incidence in Study HZ-CA-303 in Patients on Low-Dose Aspirin, excluding site 389 (MITT Population)

Treatment N (%)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 67/459 (14.6)	8 (11.9%)	1 (1.5%)
Ibuprofen 25/225 (11.1)	8 (32.0%)	1 (4.0%)

Table 34 illustrates the ulcer incidence in Study HZ-CA-303 (excluding patients from Site 389) in patients (total of 92 patients) who were on low-dose aspirin. The incidence of gastric ulcers incidence was 11.9% in the HZT-501 group and 32.0% in the ibuprofen group. The duodenal ulcer incidence for the study medication group was 1.5%, and for the ibuprofen group, the incidence was 4.0%. It appears that a there was a lower incidence of a gastric ulcers as compared to ibuprofen (11.9% incidence in the study medication vs. 32.0% in the ibuprofen group), however, no clear conclusions can be made because the sample sizes were small. No changes were noted with regards to ulcer incidence in Study HZ-CA-303 patients who were on low-dose aspirin when 4 patients (#005, #021, #050, and #100) were excluded from site 363.

Table 35 Gastric and Duodenal ulcer Incidence in Study HZ-CA-301 in Patients with a prior history of upper gastrointestinal ulcer (MITT Population)

Treatment N (%)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 20/390 (5.1)	3 (15.0)	0 (0.0)
Ibuprofen 12/198 (6.1)	1(8.3)	1 (8.3)

Table 35 shows ulcer incidence in Study HZ-CA-301 in patients with an ulcer history. The incidence of gastric ulcers was 15.0% in patients who received HZT-501 and it was 8.3% in patients who were treated with ibuprofen. The incidence of duodenal ulcers was 0.0% in patients who received HZT-501 and it was 8.3% in patients who were treated with ibuprofen. The increase in incidence of gastric ulcers in HZT-501 treated patients compared to ibuprofen only is concerning because it appears that treatment with HZT-501 did not provide any benefit in this high-risk patient population.

Table 36 Gastric and duodenal ulcer Incidence in Study HZ-CA-303 (minus Site 389) in Patients with a prior history of upper gastrointestinal ulcer (MITT Population)

Treatment N (%)	Gastric Ulcer Incidence N (%)	Duodenal Ulcer Incidence N (%)
HZT-501 34/459 (7.4)	7 (20.6)	1 (2.9)
Ibuprofen 13/225 (5.8)	2 (15.4)	1 (7.7)

Table 36 shows ulcer incidence in Study HZ-CA-303 (excluding patients from site 389) in patients with an ulcer history. The incidence of gastric ulcers was 20.6% in patients receiving the study medication and it was 15.4% in patients receiving the ibuprofen treatment. The incidence of duodenal ulcers was 2.9% in patients who received HZT-501 and it was 7.7% in patients who were treated with ibuprofen. Again, the increase in incidence of gastric ulcers in HZT-501 treated patients compared to ibuprofen only is concerning because it appears that treatment with HZT-501 did not provide any benefit in this high-risk patient population.. No substantive differences in results were noted with regards to ulcer incidence in this group of patients (excluding Site 389) with an ulcer history in Study HZ-CA-303 when 4 patients (#005, #021, #050, and #100) were excluded from site 363.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dose of HZT-501 was employed in Studies HZ-CA-301 and HZ-CA-305. No dose-ranging studies were performed.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

None.

6.1.10 Additional Efficacy Issues/Analyses

Please refer to section 6.1.7 for subpopulation analyses and additional efficacy issues.

7 Review of Safety

Safety Summary

DUEXIS is a combination medication composed of ibuprofen and famotidine; both of these medications have been marketed in the U.S. for more than 25 years. Of the 1533 patients who were enrolled in the study and received at least one dose of study medication (the primary safety population), 997 patients completed the study and 536 patients terminated early. One death occurred in a patient who received ibuprofen treatment only in Study HZ-CA-303 (section 7.3.1). The incidences of nonfatal serious adverse events (AEs) were similar in the two treatment groups. Serious nonfatal adverse events were noted in 3.2% of the patients receiving the study medication as compared to 3.3% of the patients who received only ibuprofen in the safety population. A majority of the serious AEs of interest related to famotidine and ibuprofen were GI in origin (erosive gastritis, gastric erosions, anemia as a result of hemorrhage). The incidences of serious nonfatal adverse events were similar in the two treatment groups of the safety follow-on-population as well.

However, there was a small imbalance in the development of acute renal failure between the two treatment groups. Three patients who received the HZT-501 treatment developed acute renal failure while no cases of acute renal failure were noted in patients receiving the ibuprofen treatment. Of the patients who developed acute renal failure, all of them had a history of diabetes mellitus and were on medications (diuretics and/or angiotensin converting enzymes and/or angiotensin receptor blockers) that could predispose to the development of acute renal failure. A review of the medical history of the safety population showed similar distribution of patients with a medial history of diabetes mellitus in both treatment groups; in Study HZ-CA-301, 10.0% of the patients receiving HZT-501 were diagnosed with diabetes mellitus as opposed to 10.4% of the patients receiving ibuprofen, and in Study HZ-CA-303, 12.2% of the patients receiving HZT-501 were diagnosed with diabetes mellitus as compared to 11.7% of the patients in the ibuprofen treatment group who had diabetes mellitus. With regards to hypertension, there was also a similar distribution of patients in both treatment groups; in Study HZ-CA-301, 34.9% of the patients receiving HZT-501 were diagnosed with hypertension as opposed to 38.2% of the patients receiving ibuprofen, and in Study HZ-CA-303, 42.7% of the patients receiving HZT-501 were diagnosed with hypertension as compared to 44.8% of the patients in the ibuprofen treatment group who had hypertension. There was also an imbalance in patients who developed increases in serum creatinine overall. However, these differences were not consistent between the studies.

The AEs leading to discontinuation in this study were similar amongst the two treatment groups; however, there were slight differences amongst the two pivotal studies (section 7.3.3). GI adverse events were the leading cause of discontinuation from the overall study. The most

common GI related adverse events that led to discontinuation in the safety population were dyspepsia (1.8%), nausea (1.0%), abdominal pain (0.8%), stomach discomfort (0.6%), and upper abdominal pain (0.6%).

The incidences of AEs leading to discontinuations in the safety population were the same in both groups of patients. It does not appear that the famotidine component decreased the incidence of GI disorders in patients taking HZT-501 as compared to the patients who only took ibuprofen.

A boxed warning for the risk of cardiovascular events (including myocardial infarction and stroke) is included in the label for ibuprofen. The boxed warning also includes a contraindication for treatment of pain by ibuprofen in the setting of coronary artery bypass graft surgery. Additionally, the boxed warning also notes an increased risk of serious gastrointestinal adverse events which include bleeding, ulceration, and perforation of the stomach or the intestines. It is of note that there were no increases in the above types of adverse events for patients in either treatment groups (HZT-501 and ibuprofen treatment groups) in the primary safety population or the extension study (Study HZ-CA-301).

The highest number of common AEs was classified as GI disorders. The most common GI AEs were dyspepsia, nausea, diarrhea, constipation, and upper abdominal pain. There was a greater incidence of dyspepsia noted in the patients (safety population) receiving ibuprofen treatment only. Otherwise, the differences in the AEs found amongst the two different treatment groups were negligible.

The laboratory findings from baseline were similar along the two treatment groups in the study. This was pattern was also observed in the vital signs of the patients in the two treatment groups.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary data set for the safety population are pooled from the two pivotal studies; Study HZ-CA-301 and Study HZ-CA-303. Additionally, patients who participated in Studies HZ-CA-301 or HZ-CA-303 had the option at the completion of the study, to continue their assigned treatment in and extension study, Study HZ-CA-304. 179 patients enrolled, 132 patients received HZT-501 and 47 patients received 800 mg ibuprofen). Overall, 107 patients in the HZT-501 group and 36 patients in the ibuprofen group completed Study HZ-CA-304; each of these patients completed a total of 1 year of dosing with study drug under the combined Phase 3 study protocols. Patients participating in the follow-on study continued to receive treatment (blinded) with the same double-blind study drug they had received while participating in Studies HZ-CA-301 or HZ-CA-303. For the purposes of this review, safety data were pooled for studies 301 and 303, however, safety data from study 304 were reviewed separately.

7.1.2 Categorization of Adverse Events

Safety was assessed in the pivotal studies by monitoring the occurrence of adverse events (AEs) and changes in clinical laboratory values, vital signs, and physical examination findings over the 24-week treatment period as well as during the 4-week follow-up period. Endoscopies were performed at baseline and at Weeks 8, 16, and 24 during the treatment period.

The applicant coded adverse events (AEs) by System Organ Class (SOC) and AE preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The applicant appears to have used appropriate and consistent terms in coding AEs. These definitions and codes appear to be adequate to assess the safety profile of DUEXIS.

Safety data was reviewed from the two pivotal studies, Studies HZ-CA-301 and HZ-CA-303. This reviewer's safety analysis was compared to the applicant's analysis and both analyses appeared to quite similar.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from the two pivotal studies were examined by this reviewer individually and pooled together. Both pivotal studies were of the same duration and the patient population demographics for both studies were similar. Although the primary efficacy endpoints of the two pivotal studies were different, their secondary efficacy endpoints were the reverse of each other. The same tools and criteria were employed to obtain safety data for both studies. Therefore, it is appropriate for pooling of the two studies in order to obtain safety data. However, safety data from study 304 were reviewed separately.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety population that was assessed in this review was comprised of the populations from Studies HZ-CA-301 (627patients) and HZ-CA-303 (906 patients) for a total of 1533 patients. In Study HZ-CA-301, there were 415 patients who received HZT-501 and there were 212 patients who received ibuprofen. Study HZ-CA-303 was comprised of 607 patients who received the study medication and 299 patients who received ibuprofen (Table 37).

Table 37 Safety Population

	HZ-CA-301	HZ-CA-303
Number of patients receiving HZT-501	415	607
Number of patients receiving ibuprofen	212	299
Total number of patients (1533)	627	906

The demographics of the safety population were similar across the two treatment groups, with no statistically significant differences between groups except for ethnicity (Table 41). The mean age at the time of informed consent was 55.4 ± 9.1 years in the HZT-501 group and 55.8 ± 9.4 years in the ibuprofen group. Most patients were less than 65 years of age, female, and white. The mean subject weight was not different between groups, and mean height was also similar (see Table 38).

Table 38 Demographics and baseline characteristics for the safety population

	Statistic	HZT-501 (N=1022)	Ibuprofen (N=511)	Total (N=1533)	P-value*
Age (years)					0.4262
	Mean (SD)	55.4 (9.1)	55.8 (9.4)	55.5 (9.2)	
	Min, Max	39, 80	40, 79	39, 80	
Age Group					0.4524
<65 years	% (n)	82.4 (842)	80.8 (413)	81.9 (1255)	
≥65 years	% (n)	17.6 (180)	19.2 (98)	18.1 (278)	
Gender					0.2126
Male	% (n)	32.7 (334)	29.5 (151)	31.6 (485)	
Female	% (n)	67.3 (688)	70.5 (360)	68.4 (1048)	
Ethnicity					0.0213
Hispanic/Latino	% (n)	16.8 (172)	12.1 (62)	15.3 (234)	
Not Hisp./Lat.	% (n)	81.7 (835)	85.3 (436)	82.9 (1271)	
Not Reported	% (n)	1.5 (15)	2.5 (13)	1.8 (28)	
Race					0.5376
White	% (n)	78.8 (805)	79.8 (408)	79.1 (1213)	
Black	% (n)	17.7 (181)	15.9 (81)	17.1 (262)	
Other[a]	% (n)	3.5 (36)	4.3 (22)	3.8 (58)	
Height (cm)					0.2620
	Mean (SD)	167.33 (10.12)	166.74 (9.40)	167.13 (9.89)	
	Min, Max	117, 206	142, 194	117, 206	
Weight (kg)					0.9321
	N	1020	511	1531	
	Mean (SD)	88.21 (21.37)	88.31 (22.10)	88.24 (21.61)	
	Min, Max	38, 188	42, 186	38, 188	

* P-value is for the integrated data from an analysis of covariance for continuous variables and from a Cochran-Mantel-Haenszel test for categorical responses, controlling for study.
[a] Other class includes the following races: Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native, and races reported as "Other."
SD = standard deviation
(Taken from Table 5, page 25 of Section 2.7.4 Summary of Clinical Safety of HZT 501)

As expected, the demographic data for the safety follow-on population (Table 39) were similar to that of the safety population, as noted in Table 38 [the safety follow-on population was defined as patients who upon completion of Studies HZ-CA-301 and HZ-CA-303 continued their assigned treatment in Study HZ-CA-304 and receiving at least one dose of the study medication in Study HZ-CA-304]. The safety follow-on population comprised of 179 patients, 132 patients receiving the Phase 3 combination tablet HZT-501 and 47 patients receiving 800 mg of ibuprofen; 107 patients in the study medication group and 36 patients in the ibuprofen group

completed Study HZ-CA-304; each of these patients completed a total of one year of dosing with the study medication under the combined Phase 3 study protocols. The mean age at the time of informed consent was 55.2 ± 9.6 years in the HZT-501 treatment group and 53.1 ± 9.3 years in the ibuprofen group. Most patients were less than 65 years of age, female, and white. The mean subject weight was not different between the groups, and mean height was also similar.

Table 39 Demographics and baseline characteristics for the safety follow-on population

	Statistic	HZT-501 (N=132)	Ibuprofen (N=47)	Total (N=179)	P-value*
Age (years)					0.1785
	Mean (SD)	55.2 (9.6)	53.1 (9.3)	54.6 (9.6)	
	Min, Max	40, 79	41, 75	40, 79	
Age Group					0.6461
<65 years	% (n)	84.8 (112)	87.2 (41)	85.5 (153)	
≥65 years	% (n)	15.2 (20)	12.8 (6)	14.5 (26)	
Gender					0.9846
Male	% (n)	31.8 (42)	31.9 (15)	31.8 (57)	
Female	% (n)	68.2 (90)	68.1 (32)	68.2 (122)	
Ethnicity					0.2140
Hispanic/Latino	% (n)	15.9 (21)	6.4 (3)	13.4 (24)	
Not Hisp./Lat.	% (n)	83.3 (110)	91.5 (43)	85.5 (153)	
Not Reported	% (n)	0.8 (1)	2.1 (1)	1.1 (2)	
Race					0.4662
White	% (n)	90.2 (119)	89.4 (42)	89.9 (161)	
Black	% (n)	6.8 (9)	4.3 (2)	6.1 (11)	
Other[a]	% (n)	3.0 (4)	6.4 (3)	3.9 (7)	
Height (cm)					0.7903
	Mean (SD)	166.90 (10.53)	166.40 (8.38)	166.76 (9.99)	
	Min, Max	145, 193	150, 185	145, 193	
Weight (kg)					0.6910
	Mean (SD)	87.73 (22.91)	86.14 (21.55)	87.31 (22.15)	
	Min, Max	48, 170	42, 161	42, 170	

* P-value is for the integrated data from an analysis of covariance for continuous variables and from a Cochran-Mantel-Haenszel test for categorical responses, controlling for study.
a Other class includes the following races: Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native, and races reported as "Other."
SD = standard deviation
(Taken from Table 5, page 27 of Section 2.7.4 Summary of Clinical Safety of HZT 501)

7.2.2 Explorations for Dose Response

One dose of HZT-501 (ibuprofen 800 mg/famotidine 26.6 mg) was proposed and used throughout the study. The applicant is relying on clinical efficacy data for ibuprofen and famotidine based on bioequivalence studies; therefore, no dose exploration was performed.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Routine safety laboratory studies were performed for studies 301, 303, and 304. Laboratory studies obtained were Laboratory results are discussed in Section 7.4.2.

7.2.5 Metabolic, Clearance, and Interaction Workup

HZT-501 is a combination product of two previously approved medications (ibuprofen and famotidine). Both famotidine and ibuprofen components have been shown to be bioequivalent to their respective reference products and the slight pharmacokinetic interactions are for reference only and not relevant to dosing of the proposed product.[11] For a complete review, please refer to Dr. Peifan Bai's pharmacology review from 3-01-2011.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal (nausea, vomiting, epigastric pain, diarrhea, abdominal distress, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, GI hemorrhage, and abnormal liver function tests). Central nervous system adverse reactions (dizziness, headache, nervousness, paresthesias, depression, and insomnia) have also been noted with the use of ibuprofen. Rash, edema, and acute renal failure have also been documented. Additionally, hematuria, a decreased creatinine clearance, azotemia, and cystitis have been noted in patients who have been on ibuprofen. The hematologic causes of ibuprofen are believed to be causal in relationship.[12]

Serious adverse events occur in patients who have been treated by H_2-receptor antagonists that include rash, angioedema, and cardiac rhythm abnormalities (AV-block, palpitations, bradycardia, tachycardia, and arrhythmias). Additionally, nausea and vomiting, abdominal discomfort, agranulocytosis, leukopenia, and thrombocytopenia have been noted in some patients on H_2-receptor antagonists. Furthermore, patients with or without renal insufficiency have exhibited CNS toxicities (delirium, psychosis, confusion, disorientation, hallucinations, hostility, mental status changes, irritability, obtundation, seizures, or agitation).[13] Amongst patients with impaired renal function, rare cases of prolonged QT interval have also been reported.

There are several important boxed warnings for the ibuprofen label. Ibuprofen and other NSAIDs may increase the risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal; the risk may increase with duration of use. Additionally, all NSAIDs (including ibuprofen) are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft surgery. NSAIDs (including ibuprofen) increase the risk of serious gastrointestinal (GI) adverse reactions including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Reactions can occur at any time without warning symptoms. Elderly patients are at greater risk.

---

[11] Pharmacology review for HZT-501 by Dr. Peifan J. Bai (3-01-2011, Division of Pharmacology, FDA
[12] Motrin Label.
[13] Cantu TG and JS Korek, Central nervous system reactions to histamine-2 receptor blockers. *Ann Inter Med* 1991; 114: 1027-1034.

Several warnings and precautions are also raised in the ibuprofen label. Of note, an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke have been mentioned. Additionally, new onset hypertension or worsening of pre-existing hypertension are noted that could also contribute to the increased incidence of cardiovascular events. Fluid retention and edema are also mentioned. Long-term administration of NSAIDs (including ibuprofen) resulting in renal papillary necrosis and other renal injury is included as a warning/precaution in this section as well. The dangers of the usage of NSAIDs in patients with aspirin-sensitive asthma and the possibility of the development of severe bronchospasm (with possible fatality) are also mentioned. Possible elevation of liver function tests and the possibility of rare cases of severe hepatic reactions, including jaundice, fulminant hepatitis, liver necrosis, and hepatic failure (fatal at times) are also included in this section. Hematologic effects (platelet aggregation inhibition leading to prolonged bleeding time and alterations in platelet function) are noted in the warning/precaution section of the label as well.

The assessment of safety in this review included an evaluation of the adverse events noted in the patient population of the two studies with close attention to the above adverse events as noted in the two medications composing HZT-501.

7.3 Major Safety Results

7.3.1 Deaths

There was a single death in the safety population. Subject 340-019 was randomized to ibuprofen in Study HZ-CA-303. The patient was a 48 year-old white female with a past medical history significant for bilateral knee replacement surgery (in 2003), osteoarthritis, low back pain, chronic obstructive pulmonary disease, hypercholesterolemia, cold sores, hypertension, depression, anxiety, chronic sinusitis, hypothyroidism, allergy to morphine and penicillin, carpal tunnel syndrome, and hiatal hernia. Relevant medications taken at the time of the event included lisinopril, lovastatin, levothyroxine, tiotropium bromide (Spiriva), clonazepam, risedronate sodium (Actonel), calcium, hydrocodone/acetaminophen (Lortab), diazepam (Valium), citalopram, mitrazepine, vitamin B, and tramadol.

The patient was brought to the emergency room by emergency medical services 154 days after the start of the blinded study medication with decreased mental status and general unresponsiveness. Laboratory results, physical exam, and an electrocardiogram resulted in the diagnosis of acute sepsis, acetaminophen poisoning, acute liver failure, acute renal failure secondary to acute tubular necrosis, acute hypovolemic shock, and an elevated blood alcohol level (sponsor to submit BAL value). Resuscitation was attempted, but was unsuccessful, and the patient died on the day of admission. No autopsy was performed. The patient's death was reported to be secondary to be cardiopulmonary arrest and multi-organ failure due to Tylenol toxicity. The applicant noted that in the opinion of the investigator, the events were not likely related to the study medication.

7.3.2 Nonfatal Serious Adverse Events

The incidences of serious adverse events (SAE) were similar in the two treatment groups. Serious treatment emergent adverse events (TEAEs) were noted in 3.3% of the safety population (3.2 % in patients receiving the HZT-501 and 3.3% in the patients receiving the ibuprofen). Table 40 lists the incidence of serious TEAEs noted in ≥0.3% of the patients in the safety population. In the gastrointestinal disorder class, 5 patients receiving the study medication experienced serious TEAEs. Of these 5 patients, one patient receiving HZT-501 (in Study HZ-CA-301) experienced a serious side effect that was considered to be due to the study medication. The workup of this patient revealed an esophageal ulcer. Pantoprazole was initiated and the patient recovered.

The serious adverse events of interest for patients receiving HZT-501 are related to famotidine and ibuprofen. A boxed warning for the risk of cardiovascular events (including myocardial infarction and stroke) is included in the label for ibuprofen. The boxed warning also includes a contraindication for treatment of pain by ibuprofen in the setting of coronary artery bypass graft surgery. Additionally, the boxed warning also notes an increased risk of serious gastrointestinal adverse events which include bleeding, ulceration, and perforation of the stomach or the intestines. The labeling for famotidine does not included a boxed warning. Significant adverse events that are included in the famotidine label include arrhythmias, liver enzyme abnormalities, agranulocytosis, pancytopenia, leukopenia, thrombocytopenia, anaphylaxis, seizures, toxic epidermal necrolysis, and psychiatric disturbances.

GI disorders, bleeding episodes, cardiac disorders (chest pain, arrhythmias, AV-blocks, palpitations), edema, renal disorders (acute renal failure, decreasing creatinine clearance), infections (pneumonia), central nervous system adverse reactions (dizziness, headache, nervousness, paresthesias, depression, insomnia) were paid close attention to in this review given that these serious adverse events are also listed in the labels for ibuprofen and famotidine.

Table 40 Incidence of Serious TEAE in the Safety Population (≥0.3% of patients)

	HZ-CA-301		HZ-CA-303		Integrated Data		
	HZT-501 (N=415)	Ibuprofen (N=212)	HZT-501 (N=607)	Ibuprofen (N=299)	HZT-501 (N=1022)	Ibuprofen (N=511)	Total (N=1533)
Syst. Organ Class Preferred Term	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Total No. of Patients with at Least One Serious TEAE	2.7 (11)	1.9 (4)	3.6 (22)	4.3 (13)	3.2 (33)	3.3 (17)	3.3 (50)
Cardio-respiratory Arrest	0.0 (0)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.2 (1)	0.1 (1)
Chest pain	0.2 (1)	0.0 (0)	0.3 (2)	0.3 (1)	0.3 (3)	0.2 (1)	0.3 (4)
Abdominal Hernia	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Hemorrhoidal Hemorrhage	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Hemorrhoids	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Inguinal Hernia	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Esophageal Ulcer	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Non-cardiac Chest Pain	0.0 (0)	0.5 (1)	0.2 (1)	0.0 (0)	0.1 (3)	0.2 (1)	0.3 (4)
Peripheral Edema	0.0 (0)	0.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.2 (1)	0.1 (1)
Pneumonia	0.0 (0)	0.0 (0)	0.2 (1)	0.7 (2)	0.1 (1)	0.4 (2)	0.2 (3)
Cellulitis	0.0 (0)	0.0 (0)	0.3 (2)	0.0 (0)	0.2 (2)	0.0 (0)	0.1 (2)
Abscess	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Bronchitis	0.0 (0)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.2 (1)	0.1 (1)
Diverticulitis	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Infection	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Staphylococcal Abscess	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Upper Resp. Tract Infect.	0.0 (0)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.2 (1)	0.1 (1)
Acute Renal Failure	0.0 (0)	0.0 (0)	0.5 (3)	0.0 (0)	0.3 (3)	0.0 (0)	0.2 (3)
Ureteric Calculus	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Asthma	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Bronchospasm	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
COPD	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Dyspnea	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (0)	0.1 (1)	0.2 (1)	0.1 (2)

(Taken from Table 3.4, page 314 of Horizon Therapeutics, Inc., Integrated Summary of Safety)

There were 2 patients in Study HZ-CA-301 who exhibited serious GI complications. The first patient exhibited signs and symptoms consistent with an inguinal hernia and it did not appear to be related to the study medication.

The second patient (301-168-006) was a 60 year old white male with a medical history of myopia, chronic sinusitis, tinnitus, hyperlipidemia, gallstones, osteoarthritis of the neck and back, chronic back pain, lumbar disc herniation, benign prostatic hypertrophy, penicillin allergy,

insomnia and intermittent headache. The patient experienced chest pain and the cardiac work-up was negative. The patient was started on pantoprazole for possible gastroesophageal reflux disease. An esophagogastroduodenoscopy (EGD) revealed that the patient had a new onset of esophageal ulcers. Appropriate medical interventions were initiated. The investigator's opinion was that this adverse effect was related to the study medication and was consistent with the reported adverse event profile for ibuprofen.

One patient receiving HZT-501 in Study HZ-CA-301 did exhibit signs and symptoms of a trans-ischemic attack (TIA) which was considered "mild" by the investigator; the study medication administration was not interrupted as a result of the TIA and the investigator concluded that the occurrence of the TIA and the study medication were probably not related. Another patient in the same treatment group did exhibit "moderate" chest pain; the study medication was not interrupted as a result of the chest pain. The investigator concluded that the occurrence of the chest pain and the study medication were probably not related. A patient who was receiving ibuprofen, did exhibit "severe multi-vessel" coronary artery disease for which the ibuprofen was stopped. Another patient receiving ibuprofen treatment exhibited "non-cardiac, mild" chest pain that caused the treatment to be interrupted.

There were 3 patients in Study HZ-CA-303 who exhibited serious GI complications. Patient 303-377-010 was a 61 year-old white male with a history of osteoarthritis and spinal stenosis. The patient was taking aspirin as a concomitant medication during the study. The patient developed erosive gastritis and anemia. Endoscopy showed no ulcers, but 10 erosions were noted. The study medication was discontinued after 153 days.

Patient 303-377-011 was a 78 year-old white female with a history of osteoarthritis and peptic ulcer disease. The patient was on no anticoagulants prior or during the study. The patient developed erosive gastritis and anemia during the study and underwent an upper endoscopy, whereby, 3 erosions were discovered. The study medication was discontinued after 140 days.

Patient 303-377-031 was a 52 year old black female with a history of osteoarthritis and reflux esophagitis. The patient was on no anticoagulants prior to during the study. The patient developed erosive gastritis and anemia during the study and underwent an upper endoscopy and discovered to have 29 erosions. The study medication was discontinued after 112 days.

There were 3 patients (receiving HZT-501) who experienced chest pain; these were termed "non-cardiac chest pain" as per the investigators after the workup for all three patients was negative for any cardiac etiology. As per the investigators, the chest pain in the patients was probably not related to the study medication. One patient receiving the ibuprofen treatment also exhibited chest pain. The patient's cardiac workup showed coronary artery disease and the patient was treated accordingly. The investigator concluded that the coronary artery disease was probably not related to the study medication. No strokes or TIAs were noted in any patients in Study HZ-CA-303.

In Study HZ-CA-303, three patients who received the HZT-501 treatment developed acute renal failure while no cases of acute renal failure were noted in patients receiving the ibuprofen treatment. Of the patients who developed acute renal failure, all of them had a history of diabetes mellitus and were on medications (diuretics and/or angiotensin converting enzymes and/or angiotensin receptor blockers) that could predispose to the development of acute renal failure. A review of the medical history of the safety population showed similar distribution of patients with a medial history of diabetes mellitus and hypertension in both treatment groups (Table 41).

Table 41 Incidence of Patients with Hypertension and Diabetes Mellitus in the Two Pivotal Studies in the Safety Population_

Treatment (Total No. of Patients)	No. of Patients with Hypertension (% from individual population)	No. of Patients with Diabetes Mellitus (% from individual population)
Study HZ-CA-301		
HZT-501 (415)	145 (34.9%)	42 (10.0%)
Ibuprofen (212)	81 (38.2%)	22 (10.4%)
Total (627)	226 (36.0%)	64 (10.2%)
Study HZ-CA-303		
HZT-501 (607)	259 (42.7%)	74 (12.2%)
Ibuprofen (299)	134 (44.8%)	35 (11.7%)
Total (906)	393 (43.4%)	109 (12.0%)

There was a total of 11 serious treatment emergent adverse events (TEAEs) occurring during the safety follow-on population (extension study, HZ-CA-304). No patients who had experienced a serious adverse event (SAE) while participating in Studies HZ-CA-301 or HZ-CA-303 were enrolled into Study HZ-CA 304 (safety follow-on population). The incidence of serious adverse events was 6.1% in the HZT-501 group (Studies HZ-CA-301 and HZ-CA-303) and 6.4% in the ibuprofen group. The highest incidence of severe TEAEs was reported for the gastrointestinal (GI) disorders (Study HZ-CA-303) and General Disorders (Study HZ-CA-303), followed by Infections/Infestations, Metabolism Disorders, Nervous System Disorders, Respiratory Disorders, and Vascular Disorders.

For the safety follow-on population, there were no serious cardiovascular complications such as myocardial infarction or stroke. However, two patients (one from each treatment group) did exhibit chest pain but the chest pain for either patient was concluded by the investigator not to be cardiac in origin.

In GI Disorders, one patient receiving the HZT-501 experienced an abdominal hernia (1.2%) and a second patient experienced diabetic gastroparesis (1.2% -the study medication was withdrawn in this patient). In the case of the patient with the abdominal hernia, the investigator's

conclusion was that this event was not related to the study medication. This reviewer is an agreement with that assessment. It appears that the diabetic gastroparesis was also not related to the study medication. One patient in the ibuprofen group developed esophageal stenosis (3.1%). In the General Disorders, 2 patients (2.4%) receiving HZT-501 experienced chest pain that was determined not to be related to a cardiac etiology; this reviewer is in agreement with this conclusion as well. Under the Hepatobiliary Disorders, one patient experienced cholecystitis (1.2% -the study medication was interrupted and restarted upon the cholecystectomy) and one patient receiving the ibuprofen was diagnosed with viral gastroenteritis (3.1%). It appears that the cholecystitis episode and the study medication were not related.

In Metabolism and Nutritional Disorders, one patient (1.2%) receiving the study medication experienced new-onset diabetes. The patient was obese and was not on any diet. The patient was evaluated and a diet was initiated along with medications to control her diabetes. The investigator concluded that the adverse event was unrelated to the study medication. This reviewer is in agreement with the assessment of the investigator. One patient in the ibuprofen group (3.1%), who had a history of good glucose control, exhibited hypgerglycemia.

One patient (1.2%) receiving the study medication in the Nervous System Disorders, experienced migraine headaches (determined to be unrelated to the study medication as per the investigator). In the Respiratory Disorders, one patient (1.2%) on HZT-501 experienced dyspnea. This was concluded to be unrelated to the study medication as per the investigator; this reviewer is in agreement with the investigator's conclusion. In the Vascular Disorders, one patient (1.2%) receiving the study medication, experienced hypertension. The investigator concluded that the hypertension was due to the patient's history of obesity and lack of any diet; the patient was started on a regimental diet low in sodium and an exercise program; additionally, an antihypertensive was initiated for the blood pressure control. This reviewer is in agreement with the investigator's assessment.

7.3.3 Dropouts and/or Discontinuations

In Study HZ-CA-301, there were no deaths. Overall, the adverse events leading to discontinuation in this study were similar amongst the two treatment groups; the incidence of adverse events leading to discontinuation was 6.7% in the HZT-501 group of patients as compared to 7.1% incidence in patients who received only ibuprofen. However, a further breakdown shows some slight differences amongst the two treatment groups. Table 44 shows the incidence of AEs that led to discontinuation in ≥0.5% of the patients. The incidence of gastrointestinal AEs leading to discontinuation were generally similar between the two treatment groups.

In Study HZ-CA-303, one death occurred in a patient who was receiving ibuprofen treatment (please refer to section 7.3.1). Overall, the incidence of adverse events leading to discontinuation in this study was lower in patients receiving HZT-501; 6.6% in the HZT-501 group of patients as compared to 8.0% incidence in the ibuprofen group. A further breakdown shows some slight differences amongst the two treatment groups. Table 42 shows the incidence

of AEs that led to discontinuation in ≥0.5% of the patients. The incidence of dyspepsia leading to discontinuation amongst the patients who received only the ibuprofen was about 7.5 times that of the incidence amongst patients who were on the study medication (2.3% vs. 0.3%, respectively). The incidences of AEs that led to discontinuation of the patients from the study as result of gastrointestinal complaints were similar between the two treatment groups.

When combining the data from Studies HZ-CA-301 and HZ-CA-303 together, 7.0% (107 of 1533) of subjects discontinued as a result of an adverse event. GI adverse events were the leading cause of discontinuation from the overall study. Table 41 lists the incidence of the AEs occurring in ≥0.5% of the patients that led to discontinuation in the safety population. The most common GI related adverse events that led to discontinuation in the safety population were dyspepsia (1.8%), nausea (1.0%), abdominal pain (0.8%), stomach discomfort (0.6%), and upper abdominal pain (0.6%).

The differences in incidence of adverse events leading to discontinuation between the study medication group and the ibuprofen group in all the patients was 0.9%, and when considering the GI disorder group overall, it was 1.1%. It appears that the incidences of AEs leading to discontinuations in the safety population were similar in both groups of patients.

Table 42 Incidence of AEs Leading to Discontinuation (≥0.5% of patients)

	HZ-CA-301		HZ-CA-303		combined safety population		
	HZT-501 (N=415)	**Ibuprofen (N=212)**	**HZT-501 (N=607)**	**Ibuprofen (N=299)**	**HZT-501 (N=1022)**	**Ibuprofen (N=511)**	**Total (N=1533)**
Syst. Organ Class Preferred Term	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Total Patients with a TEAE Leading to Discontinuation	6.7 (28)	7.1 (15)	6.6 (40)	8.0 (24)	6.7 (68)	7.6 (39)	7.0 (107)
GI Disorders	3.9 (16)	5.2 (11)	4.1 (25)	5.0 (15)	4.0 (41)	5.1 (26)	4.4 (67)
Dyspepsia	0.7 (3)	0.9 (2)	0.3 (2)	2.3 (7)	0.5 (5)	1.8 (9)	0.9 (14)
Nausea	0.5 (2)	0.9 (2)	1.2 (7)	1.0 (3)	0.9 (9)	1.0 (5)	0.9 (14)
Abd. Pain –upper	1.2 (5)	0.5 (1)	0.7 (4)	0.7 (2)	0.9 (9)	0.6 (3)	0.8 (12)
Abd. Pain	0.5 (2)	0.9 (2)	0.3 (2)	0.7 (2)	0.4 (4)	0.8 (4)	0.5 (8)
Stomach discomfort	0.2 (1)	0.5 (1)	0.5 (3)	0.7 (2)	0.4 (4)	0.6 (3)	0.5 (7)
Diarrhea	0.0 (0)	0.0 (0)	0.5 (3)	0.7 (2)	0.3 (3)	0.4 (2)	0.3 (5)
GERD	0.2 (1)	0.5 (1)	0.3 (2)	0.3 (1)	0.3 (3)	0.4 (2)	0.3 (5)
Erosive Gastritis	0.2 (1)	0.5 (1)	0.2 (1)	0.0 (0)	0.2 (2)	0.2 (1)	0.2 (3)
Gastritis	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)
Rectal Hemorrhage	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)	0.0 (0)	0.1 (1)

(Taken from Table 3.5, page 319 of Horizon Therapeutics, Inc., Integrated Summary of Safety)

There were 6 patients who discontinued from the extension study (study 304). One patient who was originally assigned to the HZ-CA-303 study group receiving HZT-501 developed gastroparesis and had to discontinue from the study. The investigator considered the gastroparesis to be of serious intensity requiring hospitalization and probably not related to the

study medication. Another patient receiving HZT-501 in the HZ-CA-301 study group developed increased serum creatinine (urea nitrogen of 12.0 mmol/L and serum creatinine of 150 µmol/L at time of early termination visit) and had to discontinue from the study. A third patient in the HZ-CA-303 receiving ibuprofen developed throat irritation and had to discontinue from the study. The investigator considered the throat irritation to be of mild severity and possibly related to the study drug. The throat irritation resolved about 2 weeks after termination from the study.

One patient who was originally receiving HZT-501 developed left elbow cellulitis while on a cruise ship. The medical workup revealed an abscess posterior to the elbow. Incision and drainage was performed and the patient was started on antibiotics. The infection resolved. The investigator considered the left elbow cellulitis serious secondary to hospitalization and the event was considered probably not related to the study medication. Another patient who was on HZT-501 experienced chest pain requiring hospitalization. The workup revealed it to be non-cardiac in origin and the patient recovered and was discharged from the hospital. In the opinion of the investigator, this was not related to the study medication. Another patient who was receiving ibuprofen treatment developed hyperglycemia and was hospitalized. The workup revealed a hyperosmolar, nonketotic state and was considered serious by the investigator and probably not related to the study medication. No stroke or myocardial infarctions were noted in the extension study.

Based on the review of the safety data, no apparent cardiovascular signals were noted in either pivotal study.

Table 43 Patient Disposition in the Safety Population

	HZ-CA-301		HZ-CA-303		Integrated Data		
	HZT-501 % (n)	**Ibuprofen % (n)**	**HZT-501 % (n)**	**Ibuprofen % (n)**	**HZT-501 % (n)**	**Ibuprofen % (n)**	**Total % (n)**
No. of Subjects	100.0 (415)	100.0 (212)	100.0 (607)	100.0 (299)	100.0 (1022)	100.0 (511)	100.0 (1533)
Completed Study	65.5 (272)	57.5 (122)	71.3 (433)	56.9 (170)	69.0 (705)	57.1 (292)	65.0 (997)
Early Termination	34.5 (143)	42.5 (90)	28.7 (174)	43.1 (129)	31.0 (317)	42.9 (219)	35.0 (536)
Reasons for ET*							
Death	0.0 (0)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.2 (1)	0.1 (1)
AE (s)	5.8 (24)	7.1 (15)	6.3 (38)	7.7 (23)	6.1 (62)	7.4 (38)	6.5 (100)

(Taken from Table 1.1, page 1 of Horizon Therapeutics, Inc., Integrated Summary of Safety)

Table 43 shows the patient disposition in both pivotal studies individually and when integrated in the safety population. Although, in both pivotal studies, the incidence for early termination for the ibuprofen treatment group was similar (42.5% in Study HZ-CA-301 and 43.1% in Study HZ-CA-303), the early termination as listed for the patients receiving HZT-501 was greater (34.5% in Study HZ-CA-301 and 28.7% in Study HZ-CA-303).

Table 44 Patient Disposition in the Safety Follow-on Population

	HZ-CA-301		HZ-CA-303		Integrated Data		
	HZT-501 % (n)	**Ibuprofen % (n)**	**HZT-501 % (n)**	**Ibuprofen % (n)**	**HZT-501 % (n)**	**Ibuprofen % (n)**	**Total % (n)**
No. of Subjects	100.0 (47)	100.0 (15)	100.0 (85)	100.0 (32)	100.0 (132)	100.0 (47)	100.0 (179)
Completed Study	78.7 (37)	86.7 (13)	88.2 (75)	78.1 (25)	84.8 (112)	80.9 (38)	83.8 (150)
Early Termination	21.3 (10)	13.2 (2)	11.8 (10)	21.9 (7)	15.2 (20)	19.1 (9)	16.2 (29)
Reasons for ET*							
Death	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
AE (s)	2.1 (1)	0.0 (0)	2.4 (2)	3.1 (1)	2.3 (3)	2.1 (1)	2.2 (4)

(Taken from Table 1.2, page 2 of Horizon Therapeutics, Inc., Integrated Summary of Safety)

Table 44 shows the patient disposition in both pivotal studies individually and when integrated in the safety follow-on population. The incidence for early termination amongst patients receiving HZT-501 was greater in Study HZ-CA-301 (21.3%) as compared to Study HZ-CA-303 (11.8%). Regarding the early termination amongst patients receiving ibuprofen, the incidence was smaller in Study HZ-CA-301 (13.2%) as compared to Study HZ-CA-303 (21.9%).

7.3.4 Significant Adverse Events

The significant adverse events discussed in this section include the significant adverse events as noted in the labels of famotidine and ibuprofen. GI disorders, bleeding episodes, cardiac disorders (chest pain, arrhythmias, AV-blocks, palpitations), edema, renal disorders (acute renal failure, decreasing creatinine clearance), infections (pneumonia), central nervous system adverse reactions (dizziness, headache, nervousness, paresthesias, depression, insomnia) were paid close attention to. Table 45 shows the significant AEs in at least 1% of the patients in the two studies.

As noted in the table, dyspepsia was one of the higher incidence AEs experienced by the patients. It appears that patients who were receiving HZT-501 in either study group experienced about half of the incidents of dyspepsia as compared to the patients receiving ibuprofen (4.1% vs. 8.5%, respectively, in Study HZ-CA-301, 5.1% vs. 7.7, respectively in Study HZ-CA-303). Additionally, patients who were on HZT-501 treatment experienced lesser incidents of gastritis and GERD than patients who received ibuprofen treatment only.

The incidents of edema, headaches, depression, dizziness, nausea, vomiting, abdominal pain, and abdominal tenderness, were similar in patients within both treatment groups.

Table 45 Significant AEs in at least 1% of the Patients (safety population)

	HZ-CA-301		HZ-CA-303		combined safety population		
	HZT-501 (N=415)	**Ibuprofen (N=212)**	**HZT-501 (N=607)**	**Ibuprofen (N=299)**	**HZT-501 (N=1022)**	**Ibuprofen (N=511)**	**Total (N=1533)**
Syst. Organ Class Preferred Term	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Total Pts. with at least 1 AE	53.0(220)	54.7(116)	56.3(342)	61.5(184)	55.0 (562)	58.7 (300)	56.2 (862)
Abdominal distension	1.2 (5)	0.9 (2)	0.7 (4)	1.7 (5)	0.9 (9)	1.4 (7)	1.0 (16)
Abdominal pain	1.7 (7)	1.9 (4)	1.3 (8)	1.3 (4)	1.5 (15)	1.6 (8)	1.5 (23)
Abdominal pain –upper	3.3 (14)	2.8 (6)	3.3(20)	2.3 (7)	3.3 (34)	2.5 (13)	3.1 (47)
Abdominal tenderness	0.7 (3)	0.5 (1)	0.8 (5)	1.3 (4)	0.8 (8)	1.0 (5)	0.8 (13)
Dyspepsia	4.1 (17)	8.5(18)	5.1 (31)	7.7 (23)	4.7(48)	8.0 (41)	5.8 (89)
Gastritis	1.7 (7)	1.4 (3)	0.5 (3)	1.3 (4)	1.0 (10)	1.4 (7)	1.1 (17)
GERD	2.2(9)	3.8 (8)	1.6 (10)	2.7 (8)	1.9 (19)	3.1 (16)	2.3 (35)
Nausea	4.6 (19)	5.2 (11)	6.6 (40)	4.3 (13)	5.8 (59)	4.7 (24)	5.4 (83)
Stomach discomfort	1.0 (4)	1.9 (4)	2.3 (14)	1.3 (4)	1.8 (18)	1.6 (8)	1.7 (26)
Vomiting	1.9 (8)	0.5 (1)	2.5 (15)	2.7 (8)	2.3 (23)	1.8 (9)	2.1 (32)
Peripheral edema	1.4 (6)	1.4 (3)	2.3 (14)	2.0 (6)	2.0(20)	1.8 (9)	1.9 (29)
Bronchitis	2.9 (12)	0.9 (2)	2.8 (17)	1.7 (5)	2.8 (29)	1.4 (7)	2.3 (36)
Gastroenteritis	1.4 (6)	1.4 (3)	1.6 (10)	0.3 (1)	1.6 (16)	0.8 (4)	1.3 (20)
Pneumonia	0.5 (2)	0.0 (0)	0.5 (3)	1.3 (4)	0.5 (5)	0.8 (4)	0.6 (9)
Dizziness	0.7 (3)	0.9 (2)	1.5 (9)	1.7 (5)	1.2 (12)	1.4 (7)	1.2 (19)
Headache	2.6 (11)	3.8 (8)	3.8 (23)	3.0 (9)	3.3 (34)	3.3 (17)	3.3 (51)
Depression	1.0 (4)	0.9 (2)	0.7 (4)	0.3 (1)	0.8 (8)	0.6 (3)	0.7 (11)
Insomnia	1.0 (4)	1.9 (4)	1.1 (7)	0.3 (1)	1.1 (11)	1.0 (5)	1.0(16)
Hypertension/BP increase	2.7 (11)	1.9 (4)	4.4 (27)	3.0 (9)	3.7 (38)	2.5 (13)	3.3 (51)
Anemia	0.7 (3)	2.4 (5)	2.1 (13)	0.7 (2)	1.6 (16)	1.4 (7)	1.5 (23)
Increased creatinine	1.0 (4)	0.0 (0)	0.8 (5)	0.7 (2)	0.9 (9)	0.4 (2)	0.7 (11)

(Taken from Table 16 on page 85 of HZ CA 301 Safety Summary and Table 19 on page 90 of HZ CA 303 Safety Summary from Horizon Therapeutics, Inc.)

Overall, no substantial changes from the baseline clinical laboratory parameters were noted and any small changes that did occur were similar in both treatment groups. However, there were slight imbalances between the development of hypertension and increase creatinine in the studies (see table 45). Table 46 shows the increases in serum creatinine in both treatment groups and both pivotal studies. As noted, there does not appear to be any clear differences between the two treatment groups. In Study HZ-CA-301, a higher percentage of patients who received HZT-501

(4%) exhibited an increase in serum creatinine (defined as a serum creatinine > 1.4 mg/dl) than the patients who received ibuprofen (2%). However, the reverse was noted in the Study HZ-CA-303; a higher percentage of patients who received ibuprofen (4%) exhibited an increase in serum creatinine than the patients who received HZT-501 (2%).

Table 46 Shift Table of Serum Creatinine, Normal to Abnormal*** in Controlled Studies**

		Study HZ-CA-301		Study HZ-CA-303	
Baseline	Post-Baseline*	HZT-501 N=414 % (n)	Ibuprofen N=207 % (n)	HZT-501 N=598 % (n)	Ibuprofen N=296 % (n)
Normal**	Abnormal***	4 (17)	2 (4)	2 (15)	4 (12)

*At any point after baseline level
**serum creatinine normal range is 0.5 – 1.4 mg/dL or 44-124 micromol/L
***serum creatinine >1.4 mg/dL

Labeling, additional language has been added to labeling to instruct prescribers to monitor for signs and symptoms of nephrotoxicity. Additionally, the labeling has been updated to recommend that patients with moderate to severe renal insufficiency (GFR <50 cc/min) should not take HZT-501. Additionally, patients with hypertension who are on medications such as diuretics, angiotensin receptor blockers, and/or angiotensin converting enzyme inhibitors should be monitored closely for any signs of possible acute renal failure.

7.3.5 Submission Specific Primary Safety Concerns

Overall, the patients receiving HZT-501 did not exhibit any notable pattern of adverse events as noted in the famotidine label. There was little to no difference between patients in either group exhibiting cardiovascular events (arrhythmia, AV block, or palpitations). There was no preponderance of nervous system or psychiatric adverse reactions in patients receiving HZT-501. No GI adverse events as noted in the famotidine label were predominating in the patients receiving the study medication. There was a single death in a patient receiving ibuprofen treatment in Study HZ-CA-303. The AEs leading to discontinuation of the study showed similar percentages in both treatment groups in the two pivotal studies. GI disorders (dyspepsia, upper abdominal pain, and nausea) were the leading causes of AEs that led to discontinuation amongst the patients across both treatment groups.

With regards to the serious AE's, a patient exhibited esophageal ulcers and a second patient developed inguinal hernia in Study HZ-CA-301. In Study HZ-CA-303, 3 patients developed erosive gastritis and anemia. There were a total of 11 serious AEs during the safety follow-on population (Study HZ-CA-304). Abdominal hernia, diabetic gastroparesis, and esophageal stenosis were listed, along with cholecystitis, new-onset diabetes, and viral gastroenteritis. Chest

pain, hypertension, dyspnea, and migraine headaches were other causes of the serious AEs. It is of note that 3 patients who received the HZT-501 in Study HZ-CA-303 did experience acute renal failure. In the opinion of the investigator, the acute renal failure in these 3 cases was possibly related to the study medication. Further investigation into the medical history of these 3 patients revealed that all 3 patients had a history of diabetes mellitus, and additionally, 2 of the 3 patients also had a history of hypertension. Additionally, 2 patients receiving HZT-501 in Study HZ-CA-303 who developed hypertension had medical histories of hypertension; furthermore, one of these 2 patients also had a history of diabetes mellitus.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 47 shows the incidence of TEAEs occurring in ≥3% of the safety population. In the patients receiving the HZT-501, 55.0% of the patients exhibited at least one TEAE and in the group who received ibuprofen, there were 58.7% of the patients experiencing at least one TEAE. The highest number of TEAEs was classified as GI disorders. The most common GI TEAEs were dyspepsia, nausea, diarrhea, constipation, and upper abdominal pain. Of these symptoms, there was a notable difference between the group of patients receiving the study medication and the group of patients receiving ibuprofen; 4.7% of the patients receiving HZT-501 exhibited dyspepsia, but 8.0% of the patients receiving ibuprofen, experienced dyspepsia. It appears that in patients taking HZT-501, about 50% had a decreased likelihood (at least, in the short term) of experiencing dyspepsia as compared to patients who were only on ibuprofen. The differences in the TEAEs found amongst the two different groups were, otherwise, negligible.

Table 47 Incidence of Treatment-Emergent Adverse Events (TEAE) Occurring in ≥3% of the safety population

	HZ-CA-301		HZ-CA-303		Integrated Data		
	HZT-501 (N=415)	**Ibuprofen (N=212)**	**HZT-501 (N=607)**	**Ibuprofen (N=299)**	**HZT-501 (N=1022)**	**Ibuprofen (N=511)**	**Total (N=1533)**
Syst. Organ Class Preferred Term	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Total No. of Patients with at Least One TEAE	53.0 (220)	54.7 (116)	56.3(342)	61.5 (184)	55.0 (562)	58.7 (300)	56.2 (862)
Dyspepsia	4.1 (17)	8.5 (18)	5.1 (31)	7.7 (23)	4.7 (48)	8.0 (41)	5.8 (89)
Nausea	4.6 (19)	5.2 (11)	6.6 (40)	4.3 (13)	5.8 (59)	4.7 (24)	5.4 (83)
Diarrhea	4.1 (17)	4.2 (9)	4.9 (30)	4.3 (13)	4.6 (47)	4.3 (22)	4.5 (69)
Constipation	3.6 (15)	3.8 (8)	4.4 (27)	4.3 (13)	4.1 (42)	4.1 (21)	4.1 (63)
Abdominal Pain -Upper	3.4 (14)	2.8 (6)	3.3 (20)	2.3 (7)	3.3 (34)	2.5 (13)	3.1 (47)
Upper Resp. Tract Infect.	3.9 (16)	5.2 (11)	3.8 (23)	3.3 (10)	3.8 (39)	4.1 (21)	3.9 (60)
Nasopharyngitis	3.1 (13)	2.8 (6)	2.0 (12)	2.7 (8)	2.4 (25)	2.7 (14)	2.5 (39)
Headache	2.7 (11)	3.8 (8)	3.8 (23)	3.0 (9)	3.3 (34)	3.3 (17)	3.3 (51)

(Taken from Table 3.1, page 43 of Horizon Therapeutics, Inc., Integrated Summary of Safety)

Table 48 shows the incidence of TEAEs occurring in ≥3% of the safety follow-on population. In the patients receiving the HZT-501, 68.2% of the patients exhibited at least one TEAE and in the group who received ibuprofen, there were 68.1% of the patients experiencing at least one TEAE.

The most common GI TEAEs in the safety follow-on population were diarrhea, dyspepsia, constipation, and nausea. Unlike the dyspepsia results in the safety population, there were a greater number of patients in the study medication experiencing dyspepsia as compared to the ibuprofen group (6.1% of patients in the HZT-501 group vs. 2.1% of patients in the ibuprofen group). In the safety population groups, the famotidine appeared to decrease the incidence of dyspepsia in patients taking the study medication, but this effect did not appear to persist into the safety follow-on population.

With regards to the vascular disorders, it is of interest to note that the incidence of hypertension was greater in the patients receiving the study medication; 8.3% of the patients receiving HZT-501 experienced hypertension vs. 2.1 % if the patients receiving ibuprofen who exhibited hypertension.

Table 48 Incidence of Treatment-Emergent Adverse Events (TEAE) Occurring in ≥3% of the Safety Follow-on Population

	HZ-CA-301		HZ-CA-303		Integrated Data		
	HZT-501 (N=47)	Ibuprofen (N=15)	HZT-501 (N=85)	Ibuprofen (N=32)	HZT-501 (N=132)	Ibuprofen (N=47)	Total (N=179)
Syst. Organ Class Preferred Term	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Total No. of Patients with at Least One TEAE	66.0 (31)	73.3 (11)	69.4(59)	65.6 (21)	68.2 (90)	68.1 (32)	68.2 (122)
Blood/Lymph. System d/o's	2.1 (1)	0.0 (0)	2.4 (2)	3.1 (1)	2.3 (3)	2.1 (1)	2.2 (4)
Anemia	2.1 (1)	0.0 (0)	2.4 (2)	3.1 (1)	2.3 (3)	2.1 (1)	2.2 (4)
Gastrointestinal Disorders	31.9 (15)	26.7 (4)	23.5(20)	21.9 (7)	26.5 (35)	23.4 (11)	25.7 (46)
Diarrhea	6.4 (3)	13.3 (2)	2.4 (2)	6.3 (2)	3.8 (5)	8.5 (4)	5.0 (9)
Dyspepsia	10.6 (5)	0.0 (0)	3.5 (3)	3.1 (1)	6.1 (8)	2.1 (1)	5.0 (9)
Constipation	0.0 (0)	0.0 (0)	5.9 (5)	6.3 (2)	3.8 (5)	4.3 (2)	3.9 (7)
Nausea	6.4 (3)	0.0 (0)	2.4 (2)	6.3 (2)	3.8 (5)	4.3 (2)	3.9 (7)
Infections/Infestations	31.9 (15)	40.0 (6)	36.5 (31)	34.4 (11)	34.8 (46)	36.2 (17)	35.2 (63)
Upper Resp. Tract Infect.	6.4 (3)	6.7 (1)	5.9 (5)	6.3 (2)	6.1 (8)	6.4 (3)	6.1 (11)
Influenza	6.4 (3)	0.0 (0)	5.9 (5)	3.1 (1)	6.1 (8)	2.1 (1)	5.0 (9)
Viral Gastroenteritis	4.3 (2)	0.0 (0)	3.5 (3)	6.3 (2)	3.8 (5)	4.3 (2)	3.9 (7)
Sinusitis	6.4 (3)	6.7 (1)	3.5 (3)	0.0 (0)	4.5 (6)	2.1 (1)	3.9 (7)
Urinary Tract Infection	0.0 (0)	0.0 (0)	7.1 (6)	0.0 (0)	4.5 (6)	0.0 (0)	3.4 (6)
Bronchitis	4.3 (2)	0.0 (0)	2.4 (2)	3.1 (1)	3.0 (4)	2.1 (1)	2.8 (5)
Nasopharyngitis	2.1 (1)	0.0 (0)	3.5 (3)	3.1 (1)	3.0 (4)	2.1 (1)	2.8 (5)
Gastroenteritis	4.3 (2)	0.0 (0)	2.4 (2)	0.0 (0)	3.0 (4)	0.0 (0)	2.2 (4)
Viral Up.Resp.Tract Infect	0.0 (0)	0.0 (0)	3.5 (3)	3.1 (1)	2.3 (3)	2.1 (1)	2.2 (4)
Otitis Media	4.3 (2)	0.0 (0)	0.0 (0)	0.0 (0)	1.5 (2)	0.0 (0)	1.18 (2)
Investigations	6.4 (3)	0.0 (0)	2.4 (2)	0.0 (0)	3.8 (5)	0.0 (0)	2.8 (5)
Serum Creatinine Increase	4.3 (2)	0.0 (0)	0.0 (0)	0.0 (0)	1.5 (2)	0.0 (0)	1.1 (2)
Metabolism/Nutrition d/o's	0.0 (0)	0.0 (0)	4.7 (4)	12.5 (4)	3.0 (4)	8.5 (4)	4.5 (8)
Diabetes Mellitus	0.0 (0)	0.0 (0)	3.5 (3)	3.1 (1)	2.3 (3)	2.1 (1)	2.2 (4)
Non-insulin depend. DM	0.0 (0)	0.0 (0)	0.0 (0)	3.1 (1)	0.0 (0)	2.1 (1)	0.6 (1)
Musculoskeletal and Connective Tissue d/o's	8.5 (4)	20.0 (3)	15.3 (13)	9.4 (3)	12.9 (17)	12.8 (6)	12.8 (23)
Arthrlagia	2.1 (1)	6.7 (1)	5.9 (5)	3.1 (1)	4.5 (6)	4.3 (2)	4.5 (8)
Back Pain	2.1 (1)	0.0 (0)	4.7 (4)	0.0 (0)	3.8 (5)	0.0 (0)	2.8 (5)
Nervous System Disorders	8.5 (4)	0.0 (0)	11.8 (10)	9.4 (3)	10.6 (14)	6.4 (3)	9.5 (17)
Dizziness	0.0 (0)	0.0 (0)	3.5 (3)	3.1 (1)	2.3 (3)	2.1 (1)	2.2 (4)
Resp/Thoracic/Mediast. d/o	12.8 (6)	0.0 (0)	8.2 (7)	6.3 (2)	9.8 (13)	4.3 (2)	8.4 (15)
Cough	2.1 (1)	0.0 (0)	3.5 (3)	0.0 (0)	3.0 (4)	0.0 (0)	2.2 (4)
Asthma	4.3 (2)	0.0 (0)	0.0 (0)	0.0 (0)	1.5 (2)	0.0 (0)	1.1 (2)
Vascular Disorders	4.3 (2)	0.0 (0)	11.8 (10)	3.1 (1)	9.1 (12)	2.1 (1)	7.3 (13)
Hypertension	2.1 (1)	0.0 (0)	11.8 (10)	3.1 (1)	8.3 (11)	2.1 (1)	6.7 (12)

(Taken from Table 3.10, page 335 of Horizon Therapeutics, Inc., Integrated Summary of Safety)

Table 49 shows the adverse reactions noted in at least 2% of the patients receiving HZT-501 in greater frequency than the patients receiving ibuprofen only.

Table 49 Incidence of Adverse Reactions Occurring in at least 2% of Patients receiving HZT-501 and in Greater Frequency than in Patients receiving Ibuprofen

	HZT-501 N=1022	Ibuprofen N=511
	%	%
Blood and lymphatic system disorders		
Anemia	2%	1%
Gastrointestinal disorders		
Nausea	6%	5%
Diarrhea	5%	4%
Abdominal pain upper	3%	3%
Vomiting	2%	2%
Stomach discomfort	2%	2%
General disorders and administration site conditions		
Edema peripheral	2%	2%
Infections and infestations		
Bronchitis	2%	1%
Musculoskeletal and connective tissue disorders		
Back pain	2%	1%
Respiratory, thoracic and mediastinal disorders		
Pharyngolaryngeal pain	2%	1%
Vascular disorders		
Hypertension	3%	2%

7.4.2 Laboratory Findings

Please refer to section 7.3.4 for a discussion of serum creatinine levels. Otherwise, substantive changes from baseline in clinical laboratory parameters were not observed and changes in baseline laboratory studies were generally comparable between the two treatment groups.

7.4.3 Vital Signs

Vital sign values were collected in the Safety Population at Screening, at Baseline (Study Day 0), and at Weeks 4, 8, 16, and 24. In the Safety Follow-on Population, vital sign values were collected at Baseline (Study Day 0 of HZ-CA-304 [the same day as the Week 24 Termination Visit in Studies HZ-CA-301 and HZ-CA-303]) and at Weeks 14 and 28, resulting in data collection at Baseline and at Weeks 8, 16, 24, 38, and 52. Overall, it appears that the mean values for the vital signs were very similar across both treatment groups and the change from baseline was small for all time points throughout the studies for systolic blood pressure, diastolic blood pressure, heart rate, temperature, and respiratory rate, with the exception of 4 patients (3%) receiving the HZT-501 group who exhibited an adverse event of hypertension; no subjects receiving the ibuprofen exhibited hypertension. No clearly meaningful changes in weight were

noted in the Safety and Safety Follow-on Populations amongst the patients receiving HZT-501 or ibuprofen.

7.4.4 Electrocardiograms (ECGs)

No significant electrocardiogram changes that could be interpreted as a drug effect were noted in patients taking the HZT-501.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials to assess any specific safety concerns.

7.4.6 Immunogenicity

Neither ibuprofen nor famotidine are protein based products, and therefore, the immunogenicity potential for this product was not evaluated.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The dose that each patient received during the study was fixed and no different dosages were given to the patients in the study groups. Therefore, dose dependency for adverse events was not evaluated.

7.5.2 Time Dependency for Adverse Events

A review of the adverse events between the study groups did not reveal time dependency differences between the patients on HZT-501 and the patients on ibuprofen.

7.5.3 Drug-Demographic Interactions

No new interactions were noted in this study. No clear pattern emerged between patients taking the study medication based on demographic interactions.

7.5.4 Drug-Disease Interactions

No new drug-disease interactions were noted in this study.

Drug-Drug Interactions

No drug interactions have been identified with famotidine in studies conducted in man, in animal, and in-vitro models; additionally, no significant interference has been shown with the

disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system.[14]

Ibuprofen is known to interact with various classes of drugs.[15] Concomitant administration of ibuprofen and aspirin is generally not recommended because of the potential for increased adverse events, i.e. gastrointestinal (GI) hemorrhage and renal failure. Renal failure and/or the possibility of reduced efficacy of diuretics have also been shown through the concomitant use of ibuprofen and diuretics. An elevation of plasma lithium levels and a reduction in renal clearance of lithium has also been noted through the use of ibuprofen and lithium. Caution should also be used when NSAIDS are administered in conjunction with methotrexate. The effects of warfarin and NSAIDS on GI bleeding are synergistic. NSAIDS may diminish the antihypertensive effects of angiotensin converting enzyme (ACE) inhibitors and physicians should be aware of this interaction in patients who are prescribed ACE-inhibitors and concomitantly with NSAIDS.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

At the recommended human doses, no evidence of carcinogenicity has been noted in ibuprofen or famotidine.

7.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies reported during the study. In late pregnancy, ibuprofen is contraindicated because it may cause premature closure of the ductus arteriosus. There are no adequate and well-controlled studies in pregnant women. Ibuprofen should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. With regards to famotidine, there are no adequate or well-controlled studies in pregnant women. Since animal studies are not always predictive of human response, famotidine should be used during pregnancy only if clearly needed.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric patients were not enrolled in any studies and therefore the effect of the drug in pediatrics and growth is unknown.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No drug abuse potential or withdrawal was noted in this study and no rebound phenomenon was noted as well.

[14] PEPCID package insert 2007.
[15] MOTRIN package insert 2007.

7.7 Additional Submissions / Safety Issues

As of this writing, no changes in labeling for famotidine or ibuprofen have been noted.

8 Postmarket Experience

No special postmarking risk management activities are recommended by this reviewer for this application.

9 Appendices

9.1 Literature Review

No new literature updates regarding the safety of H_2-blocers has been noted at the time of this review. However, given that H_2-blockers had been approved by the Agency many years ago, it is recommended that new investigations be performed regarding the safety of this class of medications.

For the list of articles cited, please refer to the footnotes of the appropriate pages.

9.2 Labeling Recommendations

The original proposed trade name for HZT-501 was (b) (4). The officer (L. Pincock) of the Division of Medication Errors Prevention and Analysis (DMEPA) reviewed the proposed trade name. (b) (4) Another trade name, "DUEXIS", was submitted by the applicant and a review by DMEPA (Y. Maslov) found the new proposed name, "DUEXIS", to be acceptable.

The final labeling for DUEXIS follows the labeling format as stated in the Physician Labeling Rule (PLR).

9.3 Advisory Committee Meeting

HZT-501 is a combination product composed of ibuprofen (800 mg) and famotidine (26.6 mg). Both ibuprofen and famotidine have been approved in the past and have been widely used as over-the-counter medications by the public. No new concerns regarding this product compared to each of its components were noted during the review of this product submission, and therefore, no advisory committee was convened for HZT-501.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALI NIAK
04/22/2011

LYNNE P YAO
04/22/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22,519 **Applicant: Horizon Therapeutics Inc.** **Stamp Date: March 23, 2010**

Drug Name: HZT-501 **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) Ibuprofen/Famotidine
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:	X			Study HZ-CA-301 measuring efficacy & safety (diagnosing UGI ulcers via endoscopy)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				Study HZ-CA-303 measuring efficacy & safety (diagnosing gastric ulcers via endoscopy)
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	deferred
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ali Niak, M.D.

Reviewing Medical Officer Date

Lynne Yao, M.D.

Clinical Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22519	ORIG-1	HORIZON PHARMA INC	HZT-501

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALI NIAK
05/20/2010

LYNNE P YAO
05/20/2010