CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number:	22519
Drug Name:	HZT 501 (ibuprofen 800 mg and famotidine 26.6 mg)
Indication(s):	Risk reduction of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen
Applicant:	Horizon Therapeutics, Inc.
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Biometrics Division:	Division of Biometrics 3 (HFD-725)
Statistical Reviewer:	Wen-Jen Chen, Ph.D.
Concurring Reviewer:	Mike Welch, PhD, Dep. Dir., DB3
Medical Division:	Gastroenterology Products (HFD-180)
Clinical Team:	Ali Niak, MD, Lynne Yao MD, CDTL
Project Manager:	Jagjit Grewal, M.P.H.

Statistical Keywords: Clinical studies; NDA review.

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1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

In this original NDA application, Horizon Therapeutics, Inc. submitted two randomized, double-blind, multicenter studies HZ-CA-301 and HZ-CA-303 to support the use of HZT-501 for the proposed indication: reduction of the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen. The pre-specified primary analysis method was based on Life Table analysis. Key supportive (sensitivity) analyses were based on crude rates.

Based upon this review, we conclude that only Study HZ-CA-303 provides a persuasive level of evidence of efficacy in support of the intended indication. Study HZ-CA-301does not provide persuasive evidence since its conclusions depend on the assumed outcomes of early terminated subjects. If subjects who discontinued the study early are treated as ulcer patients, efficacy of the study drug based on the Life Table analysis could not be demonstrated. Based on a crude rate analysis, efficacy comparisons for Study 301 were also not statistically significant.

1.2 Statistical Issues and Findings

1.2.1 Study HZ-CA-301

The comments given below are based upon this reviewer's analysis result and the applicant's analysis results from the original NDA submission (dated 03/23/2010) along with the applicant's response (dated 10/21/2010) to the Agency's IR letter (dated 10/05/2010).

Comments on Upper gastrointestinal ulcer

- For the risk reduction on the upper gastrointestinal (GI) ulcer reported by the original NDA study dated 03/23/2010, HZT-501 showed superiority to ibuprofen with a borderline p-value (p 0.0304), close to the two-sided significance level of 0.05. However, this reviewer notes that for site 180 in the HZT-501 group, only one out of 14 patients identified to have upper gastrointestinal ulcer; the proportion of upper gastrointestinal ulcer in the HZT-501 group (7.0%) is 31% lower than that of the ibuprofen group (38%).
- The result of sensitivity analysis performed by this reviewer shows that after excluding data from site 180, the applicant's analysis of upper gastrointestinal ulcer rate of HZT-501 no longer shows a statistically significant lower rate compared to ibuprofen. Thus, the sponsor's claimed superiority of HZT-501 to ibuprofen assessed by the upper gastrointestinal ulcer rate is sensitive to individual site results.
- The applicant's Life Table analysis (submitted on 10/21/2010) on time to upper GI ulcer, included subjects as treatment failures who were early terminated and, as stated by the applicant, did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug. This analysis shows that HZT-501 did not significantly reduce the upper GI ulcer rate as compared to ibuprofen. In a T-Con held on 03/11/2011, the applicant agreed with the Agency that those early terminated patients without negative endoscopy for ulcer

should have been included as having an ulcer in the Life Table analysis in the original NDA submission.

- Accordingly, based upon the results of this reviewer's sensitivity analysis and the applicant's Life Table analysis in response to the Agency IR letter dated 10/05/2010 regarding the inclusion of early terminated subjects as having an ulcer, Study HZ-CA-301 does not provide persuasive evidence to conclude that HZT-501 is significantly better than ibuprofen alone in reducing the upper gastrointestinal ulcer rate.

  In addition, the result of the crude rate analysis including early terminated subjects as having an ulcer (recommended by the Agency at the protocol stage) also indicated that HZT-501 did not significantly reduce the risk of developing upper GI ulcer when compared to ibuprofen.

Comments on Gastric and Duodenal ulcers

- First, the Life Table analysis result from the original study report dated 03/23/2010 showed that the proportion of subjects who developed at least one gastric ulcer for HZT-501 was not significantly lower than that of ibuprofen.
- In addition, the results from the crude rate analyses including early terminated subjects as having an ulcer (recommended by the Agency at the protocol stage) showed the results that were consistent with the Life Table analysis. Accordingly, HZT-501 did not demonstrate improvement over ibuprofen alone in reducing the gastric ulcer rate.
- Finally, we note that in the protocol, the reduction of the gastric ulcer rate was pre-specified as the first secondary-endpoint and the pre-specified Life Table analysis failed to demonstrate the superiority of HZT-501 over ibuprofen for reduction of the gastric ulcer rate. Then, by the fixed sequence (hierarchical) testing procedure pre-specified in the protocol, the duodenal ulcer rate which was pre-specified as the second secondary-endpoint could not be formally tested, and HZT-501 should not be considered effective for this endpoint, regardless of the rate observed.

Accordingly, based upon the efficacy data provided by Study HZ-CA-301, one may deem that the efficacy of the study drug HZT-501 is not supported with persuasive evidence for the proposed indication in reduction of the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen.

1.2.2 Study HZ-CA-303

The comments given below are based upon this reviewer's analysis and the applicant's results from the original NDA submission and the applicant's response documents (dated 12/16/2010) to the Agency's IR letter (dated 12/07/2010) excluding data from site 389 which was deemed unreliable by site inspection of the Agency. Although reducing the gastric ulcer rate is the primary endpoint for this study, the proposed indication was to reduce the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen. Accordingly, this reviewer gives comments on the upper GI ulcer first and comments on the gastric ulcer follow.

Comments on Upper gastrointestinal ulcer

- First, from this reviewer's efficacy comparison by site assessed based upon the proportions of upper gastrointestinal ulcer, we note that no particular site abnormally dominates the superiority of HTZ-501 to ibuprofen claimed by the applicant.
- In addition, the results of Life Table analyses from both the original NDA study report and the applicant's response document (dated 12/16/2010) to the IR letter issued on 12/07/2010 all indicate that study drug HZT-501 significantly reduces the risk of having upper gastrointestinal ulcer when compared to ibuprofen. We note that the applicant's re-analysis on time to upper gastrointestinal ulcer used the primary population excluding data from site 389 and including subjects who were early terminated and (as stated by the applicant) did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer.
- Finally, the results of the crude rate analyses including early terminated patients as having an ulcer (as recommended by the Agency in the protocol stage) using the primary population with and without data from site 389 all show HZT-501 as significantly reducing the upper gastrointestinal ulcer rate when compared to ibuprofen. As a consequence, the effect of HZT-501 on the reduction of upper gastrointestinal ulcer rate, compared to ibuprofen alone, has been adequately demonstrated.

Comments on Gastric ulcer

- For the gastric ulcer occurrence, the results of Life Table analyses from both the original NDA study report and the applicant's response documents to the IR letter issued on 12/07/2010 all showed that HZT-501 significantly reduces the risk of gastric ulcer when compared to ibuprofen.

Comments on Duodenal ulcer

- Similarly, for the Duodenal ulcer, the results of Life Table analyses from both the original NDA study report and the applicant's response document to the IR letter issued on 12/07/2010 all showed that HZT-501 significantly reduces the risk of duodenal ulcer when compared to ibuprofen.

It is noted that additionally excluding data from the four subjects from site 363 identified as non-reliable by the Division of Scientific Investigations in the FDA on 03/10/2011, the results from the Life Table analyses and crude rate analyses on the three types of ulcers (upper GI, gastric, and duodenal ulcers) are unaffected.

Accordingly, based upon the efficacy data provided by Study HZ-CA-303, one may conclude that the effect of study drug HZT-501 is supported with persuasive evidence for the proposed indication of reduction of the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen.

2.0 INTRODUCTION

2.1 Overview

In the introduction of the clinical study report, the applicant made the following observations with regard to study drug HZT 501:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are important agents in the management of arthritic and inflammatory conditions, and are among the most frequently prescribed medications in the US and Europe. HZT-501 (a combination oral tablet containing ibuprofen 800 mg and famotidine 26.6 mg and designed for administration TID) is in development by Horizon Therapeutics, Inc. (Horizon). The indication sought for HZT-501 is risk reduction of ibuprofen associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen. By combining ibuprofen and famotidine into a single oral tablet, it is anticipated that ibuprofen's gastrointestinal safety profile will be improved by famotidine's reduction of gastric acid-induced upper gastrointestinal ulceration without altering ibuprofen's ability to reduce pain and inflammation.

In this original NDA application, Horizon Therapeutics, Inc. submitted two studies HZ-CA-301 and HZ-CA-303 to support the use of HZT-501 for the proposed indication: reduction of the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen.

A major review finding was that for both studies, the sponsor did not count certain early terminated subjects as treatment failures who may have been likely candidates for failure. More specifically, subjects who terminated early and who "did not have a negative endoscopy" (sponsor's terminology) for ulcer within 14 days of the last dose of study drug were not counted as having ulcers in the Life Table analysis performed in the original NDA study reports. Since those early terminated patients with no negative endoscopy were very likely to be ulcer patients, they should have been counted as having an ulcer in the Life Table analysis reported by the study reports. In order to assess the bias caused by not including those early terminated patients in the Life Table analysis presented in the original NDA submission, the Agency issued an IR letter dated October 5, 2010 to request the applicant to re-perform the Life Table analyses on the three types of ulcers (Upper Gastrointestinal Ulcer, Gastric Ulcer, and Duodenal Ulcer). Besides ulcers identified in the pre-specified visiting windows, each of the three Life Table analyses was requested to include subjects who early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer.

In addition, in the same IR letter, the applicant was also requested to perform Crude Rate analyses on the three types of ulcers (Upper Gastrointestinal Ulcer, Gastric Ulcer, and Duodenal Ulcer). (Crude rate analyses were pre-specified by the applicant as supportive analyses, even though the Agency noted in an advice letter dated 07/22/2009, the crude rate analyses would need to show positive results to provide substantial evidence of efficacy, and that the Agency considered the crude rate analysis, with early drop-outs imputed as treatment failures, as the primary analysis for regulatory purposes.) Besides ulcers identified in the pre-specified visiting windows, each of the three types of Crude Rate analysis is recommended to include subjects with any one of the following four characteristics as having an ulcer: Adverse Events, Lost to Follow-Up, early terminated by Investigator or Applicant, and early terminated and without a

negative endoscopy for ulcer within 14 days of the last dose of study drug. The applicant's response document to the IR letter (issued by the Agency on October 5, 2010) was received by the Agency on October 21, 2010.

The Division of Scientific Investigations (DSI) indicated that for Study HZ-CA-303, data provided by site 389 lack of integrity and were not reliable. Consequently, the Agency issued another IR letter (dated December 7, 2010) to request that for Study HZ-CA-303, the applicant re-perform the efficacy analyses (i.e., Life Table and Crude rate analyses) based upon the requirements stated in the IR letter issued on October 5, 2010 but excluding data from site 389. The applicant's response document to the Agency IR letter (dated December 7, 2010) was received by the Agency on December 16, 2010. In addition, on 03/10/2011, DSI informed the Medical Division that for Study HZ-CA-303, data for the four patients (subject numbers 050, 005, 021, and 100) in site 363 were found unreliable and should be excluded from the efficacy analysis.

Based upon a T-Con with the applicant on 03/11/2011, the applicant indicated that subjects who early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug were either subjects who had a positive endoscopy or subjects who had no endoscopy. The applicant agreed that for both cases, these early terminated patients should be treated as ulcer patients in the Life Table analysis.

2.1.1 Study HZ-CA-301

The primary objective for Study HZ-CA-301 was to evaluate the efficacy of HZT-501 in reducing the proportion of subjects who develop at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer (of unequivocal depth and at least 3 mm in diameter) during the 24-week treatment period, as compared to ibuprofen, in subjects at risk for nonsteroidal anti-inflammatory drug (NSAID) induced ulcers.

The secondary objectives were to evaluate the efficacy of HZT-501, in subjects at risk for NSAID-induced ulcers, as compared to ibuprofen, in reducing (1) the proportion of subjects who develop at least one endoscopically-diagnosed gastric ulcer during the 24-week treatment period; (2) the proportion of subjects who develop at least one endoscopically-diagnosed duodenal ulcer during the 24-week treatment period; and (3) the incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding) during the 24-week treatment period.

This Phase 3, multicenter, randomized, double-blind, parallel group study was designed to evaluate the efficacy, as measured by endoscopically-diagnosed gastrointestinal ulcers, and safety of HZT-501 compared with ibuprofen. Approximately 600 subjects (40 to 80 years of age inclusive) who had not used an NSAID within the 30 days prior to study entry, and who were expected to require daily administration of an NSAID for at least the coming six months, were planned to be enrolled.

The primary efficacy endpoint was the proportion of subjects who developed at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period (defined as up to and including Week 26.7). The primary analysis method was based on a Life Table analysis. Crude rate analyses were also pre-specfiied as supportive or sensitivity analyses.

Secondary efficacy endpoints consisted of the following:

- Proportion of subjects who developed at least one endoscopically-diagnosed gastric ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week treatment period (defined as up to and including Week 26.7);
- Proportion of subjects who developed at least one endoscopically-diagnosed duodenal ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week treatment period (defined as up to and including Week 26.7); and
- Incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding) during the 24-week treatment period (defined as up to and including Week 28.7).

A total of 570 subjects (380 in HTZ-501 and 190 in ibuprofen) who received at least one dose of study drug, underwent a baseline endoscopic examination, and had at least the Week 8 endoscopic examination comprises the primary population.

2.1.2 Study HZ-CA-303

The primary objective of the study was to evaluate the efficacy of HZT-501 in reducing the proportion of subjects who develop at least one endoscopically-diagnosed gastric ulcer (of unequivocal depth and at least 3 mm in diameter) during the 24-week Treatment Period, as compared to ibuprofen, in subjects at risk for nonsteroidal anti-inflammatory drug (NSAID) induced ulcers.

The secondary objective of the study was to evaluate, in subjects at risk for NSAID-induced ulcers, the efficacy of HZT-501, as compared to ibuprofen, in reducing (1) the proportion of subjects who develop at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer during the 24-week Treatment Period; (2) the proportion of subjects who develop at least one endoscopically-diagnosed duodenal ulcer during the 24-week Treatment Period; and (3) the incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding) during the 24-week Treatment Period.

This Phase 3, multicenter, randomized, double-blind, parallel group study was designed to evaluate the efficacy, as measured by endoscopically-diagnosed gastrointestinal ulcers, and safety of HZT-501 compared with ibuprofen. Approximately 875 subjects, 40 to 80 years of age inclusive, who had not used an NSAID within the 30 days prior to study entry, and who were expected to require daily administration of an NSAID for at least the coming six months, were planned to be enrolled.

The primary efficacy endpoint was the proportion of subjects who developed at least one endoscopically-diagnosed gastric ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period defined as up to and including Week 26.7. The primary analysis was based on a Life Table analysis.

Secondary efficacy endpoints consisted of the following:
• The proportion of subjects who developed at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period (defined as up to and including Week 26.7).
• The proportion of subjects who developed at least one endoscopically-diagnosed duodenal ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period (defined as up to and including Week 26.7).
• The incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding; this analysis was performed for the primary and the safety populations) during the 24-week Treatment Period (defined as up to and including Week 28.7).

A total of 812 subjects (550 subjects in HZT-501 and 262 subjects in ibuprofen) who received at least one dose of study drug, underwent a baseline endoscopic examination, and had at least the Week 8 endoscopic examination comprises the primary population.

2.2 Data Sources

To assess the clinical efficacy of HZT-501 used in the risk reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen, this reviewer reviewed the original electronic NDA supplement submission, dated 03/23/2010 and located at "\\CDSESUB1\EVSPROD\NDA022519\0000".

In addition, on October 21, 2010, the Agency received the applicant's response document to the IR letter issued by the Agency on October 5, 2010. This response document is located at "\\CDSESUB1\EVSPROD\NDA022519\022519.enx" and is reviewed by this reviewer.

Finally, on December 16, 2010, the Agency received the applicant's response document to the IR letter issued by the Agency on December 7, 2010. This response document is also located at "\\CDSESUB1\EVSPROD\NDA022519\022519.enx" and is reviewed by this reviewer.

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study HZ-CA-301

3.1.1.1 Study Design and Endpoints

The primary objective for Study HZ-CA-301 was to evaluate the efficacy of HZT-501 in reducing the proportion of subjects who develop at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer (of unequivocal depth and at least 3 mm in diameter) during the 24-week treatment period, as compared to ibuprofen, in subjects at risk for Nonsteroidal anti-inflammatory drug (NSAID) induced ulcers.

The secondary objectives were to evaluate the efficacy of HZT-501, in subjects at risk for NSAID-induced ulcers, as compared to ibuprofen, in reducing (1) the proportion of subjects who develop at least one endoscopically-diagnosed gastric ulcer during the 24-week treatment period; (2) the proportion of subjects who develop at least one endoscopically-diagnosed duodenal ulcer during the 24-week treatment period; and (3) the incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding) during the 24-week treatment period.

This Phase 3, multicenter, randomized, double-blind, parallel group study was designed to evaluate the efficacy, as measured by endoscopically-diagnosed gastrointestinal ulcers, and safety of HZT-501 compared with ibuprofen. Approximately 600 subjects (40 to 80 years of age inclusive) who had not used an NSAID within the 30 days prior to study entry, and who were expected to require daily administration of an NSAID for at least the coming six months, were planned to be enrolled.

After written Informed Consent had been obtained and subject eligibility had been established, study center personnel obtained the subject's identification number and randomized, blinded, treatment assignment from the IVRS. The randomization scheme was designed to ensure an overall balance of approximately 2:1 of assignment to the two treatment arms (HZT-501 and ibuprofen), with stratification based on the following two risk factors for ulcer development: (1) concomitant use of low dose aspirin and/or other anticoagulant medication; and (2) history of an upper gastrointestinal ulcer.

All doses of study drug were self-administered orally, on a blinded basis three times daily (TID) for up to 24 consecutive weeks. Subjects were instructed to ensure there was at least a six-hour interval between administrations of consecutive doses of study drug. There were no restrictions on dosing of study drug with regard to food or liquid consumption. 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 (Horizon Protocol HZ-CA-304). Subjects who did not enter Horizon Protocol HZ-CA-304 were monitored for safety for an additional four weeks, follow-up period, through Week 28 via a telephone visit.

All randomized subjects who received at least one dose of study drug and who underwent a baseline and at least the Week 8 (visit window allowance $\geq$ 6.7 weeks) endoscopic examination were included in the primary population for all primary and secondary efficacy analyses. The protocol specified 24-week Treatment Period, due to visit window allowance, was defined as up to and including Week 26.7, except for Secondary Objective #3 for which the 24-week treatment

period was defined as up to and including Week 28.7 to include any data that were collected during the safety four-week Follow-up Period.

The schedule of assessments is Screen Visit (Day -30 to -1), Treatment Period (Day 0, week 4, Week 8, week 16, and Week 24), and Follow-up Period (Week 28). Endoscopic examinations were performed during Screening (baseline) Visit and at Weeks 8, 16, and 24, with a four-day window prior to the actual clinic visit day as well as a plus/minus five-day window around the target clinic visit day. Subjects were 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. Subjects who terminated early for reasons other than development of an endoscopically-diagnosed upper gastrointestinal ulcer were to undergo an endoscopic examination at a Termination Visit that was to be conducted as soon as possible after administration of their final dose of study drug.

The HZT-501 and the ibuprofen tablets were comparable to each other with respect to size, shape, color, and weight, to enable administration of both medications on a double-blind basis. All study drugs were administered to study subjects on a double-blind basis. All subjects, investigators, study center personnel, sponsor personnel, and CRO personnel (with the exception of the un-blinded individual who developed the randomization scheme for the IVRS, and a drug supply consultant who aided coordination of shipments with the distributor (b) (4)) remained blinded to all subjects' treatment assignments until after the study database had been locked.

Un-blinded data were provided to the Independent Data Monitoring Committee (IDMC) by an un-blinded statistician at the CRO who ensured that no unauthorized un-blinding occurred, as specified in the written IDMC Charter. The applicant and the project team did not have access to the individual subject treatment assignments until after the study database had been locked.

3.1.1.2 Statistical Methodologies

The primary efficacy endpoint was the proportion of subjects who developed at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period (defined as up to and including Week 26.7).

Secondary efficacy endpoints consisted of the following:

- Proportion of subjects who developed at least one endoscopically-diagnosed gastric ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week treatment period (defined as up to and including Week 26.7);
- Proportion of subjects who developed at least one endoscopically-diagnosed duodenal ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week treatment period (defined as up to and including Week 26.7); and
- Incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding) during the 24-week treatment period (defined as up to and including Week 28.7).

The data from Week 26.7 to Week 28.7 included any data that were collected during the safety four-week Follow-up Period.

If a subject had any endoscopic examination at least 6.7 weeks after the date of first dose of study drug (see explanation following), the subject was considered to have satisfied the criterion of having at least a Week 8 endoscopic examination. The applicant further indicated that because of the plus/minus five-day visit window and the specification that the endoscopic examination could be performed up to four days before a visit, an endoscopic examination performed between nine days before calendar Week 8 (i.e., at or after Week 6.7) and five days after calendar Week 8 (at or including Week 8.7) qualified as a Week 8 endoscopic examination.

Safety Population: All randomized subjects who received at least one dose of study drug. Safety Population will be used in all safety analyses.

Primary Population: All randomized subjects who received at least one dose of study drug and who underwent a baseline endoscopic examination and at least the Week 8 endoscopic examination were included in the primary population for all primary and secondary efficacy analyses. Also included in this primary population were (1) endoscopic examinations performed as part of the early termination procedures for subjects who terminated early within the window specified for Week 8 (i.e., ≥ 6.7 to ≤ 8.7 weeks); and (2) endoscopic examinations subsequent to the Week 8 visit and up to and including Week 26.7.

The analyses using Primary Population, subjects were grouped in accordance with the treatment to which they were randomized, regardless of the treatment each subject actually received; in this study the actual treatment and randomized treatment were the same for all subjects.

Per-protocol Population: The primary population with the exclusion of subjects having major protocol violations (assessed prior to un-blinding). Analyses of the primary and secondary efficacy parameters (with the exception of the incidence rate of NSAID-associated serious gastrointestinal complications) were also performed on the per-protocol population. Analyses involving the per-protocol population were to be performed using actual treatment received initially; on this study the actual treatment and randomized treatment were the same for all subjects.

All efficacy variables were analyzed for both the primary and per-protocol populations (with the exception of the incidence rate of NSAID-associated serious gastrointestinal complications which was to be analyzed for both the primary and the safety populations), and the treatment groups were compared using a Chi-Square test unadjusted for covariates. All efficacy endpoints were compared using the estimated failure rates from a life table analysis and their standard errors.

The intervals used for the life table analyses followed the visit windows for clinic visits (i.e., plus/minus five days) and endoscopies (i.e., at most four days before the clinic visit) outlined in the protocol for subject convenience.

The intervals used were:
• Interval 1: Weeks 6.7 to 8.7.
• Interval 2: Weeks 8.8 to 14.5.
• Interval 3: Weeks 14.6 to 16.7.
• Interval 4: Weeks 16.8 to 22.5.
• Interval 5: Weeks 22.6 to 26.7.
• Interval 6: Weeks 26.8 to 28.7.

The life table estimate for the probability that a subject developed an ulcer by the end of Interval 5 represents a statistical estimate of the primary endpoint. This proportion is referred to as the "Week 24 estimate" or the "Week 24 proportion" due to allowance for planned windows around the measurement times.

The primary and secondary efficacy endpoints were tested with a fixed sequence (hierarchical) testing procedure in the order of primary endpoint first, then secondary endpoints. The testing started with the primary efficacy endpoint. After the primary efficacy endpoint showing significant result, the secondary efficacy endpoints were to be tested in the following order:
1) The proportion of subjects who developed at least one endoscopically-diagnosed gastric ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period (defined as up to and including Week 26.7).
2) The proportion of subjects who developed at least one endoscopically-diagnosed duodenal ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period (defined as up to and including Week 26.7).
3) The incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding) during the 24-week Treatment Period (defined as up to and including Week 28.7).

Failure to reject the first null hypothesis at the two-sided 0.05 level resulted in immediate failure to reject all subsequent null hypotheses in the sequence. In accordance with this approach, no alpha adjustment was required and all alternative hypotheses accepted were claimed significant at the 0.05 level.

In addition, the following sensitivity analyses were conducted and are presented in Section 11.4.1.3 of the study report.

1) The crude rates for the ulcer endpoints were explored as sensitivity analyses for the primary population. The number of subjects who experienced an ulcer through the Week 24 estimate, up to and including Week 26.7, in each treatment arm was tested for statistical significance using a Fisher's Exact test, a Chi-Square test adjusted for continuity, and a Cochran-Mantel-Haenszel (CMH) test.
2) The crude rates for all ulcer endpoints for the primary population were explored for sensitivity to ulcer definition by examining ulcer incidence crude rates when subjects with an ulcer plus subjects who withdrew from the study early were both considered as having experienced an ulcer. The number of subjects who experienced an ulcer, plus those who terminated early

through the Week 24 estimate, up to and including Week 26.7, in each treatment arm was tested for statistical significance using a Fisher's Exact test, a Chi-Square test adjusted for continuity, and a CMH test.

The primary analysis and sensitivity analyses detailed above were also intended to be conducted using the actual treatment that each subject received; however these additional analyses were not performed because all subjects received the treatment to which they were randomized.

The sample size was chosen based on specification of Type 1 and Type 2 error rates and the anticipated effect size. A sample size of 600 subjects was selected in order to provide approximately 90% power to detect a difference of 6% versus 16% in the proportion of subjects in the two treatment arms who developed at least one upper gastrointestinal ulcer during the 24-week Treatment Period, with a two-sided α 0.05 using a CMH test controlling for randomization strata. This sample size accounted for the 2:1 randomization and a 15% dropout rate for reasons other than ulcer development.

3.1.1.3 Patient Disposition

All randomized subjects received at least one dose of study drug and therefore are included in the safety population. A total of 627 subjects were randomized and received at least one dose of blinded study drug; these subjects comprise the safety population. There were 415 subjects in the HZT-501 group and 212 subjects in the ibuprofen group in the safety population.

Table 3.1.1.3.1 presents subjects early terminated by treatment group using safety population.

Table 3.1.1.3.1 (Applicant's) Subjects early terminated by treatment group (Safety Population)

	HZT-501 % (n)	Ibuprofen % (n)	Total % (n)	p-value[a]
All Subjects				
Number of Subjects	415	212	627	
Completed Study	65.5 (272)	57.5 (122)	62.8 (394)	
Early Termination	34.5 (143)	42.5 (90)	37.2 (233)	0.0500
Reasons for Early Termination				
Death	0.0 (0)	0.0 (0)	0.0 (0)	
Adverse Event(s)	5.8 (24)	7.1 (15)	6.2 (39)	
Subject Withdrew Consent	10.4 (43)	12.3 (26)	11.0 (69)	
Protocol Violation(s)	1.2 (5)	0.0 (0)	0.8 (5)	
Subject Lost to Follow-up	5.3 (22)	2.4 (5)	4.3 (27)	
Discretion of Investigator or Sponsor	2.4 (10)	4.2 (9)	3.0 (19)	
Endoscopically Diagnosed UGI Ulcer	8.0 (33)	16.0 (34)	10.7 (67)	
Subject Required Excluded Medication	0.2 (1)	0.5 (1)	0.3 (2)	
Other	1.2 (5)	0.0 (0)	0.8 (5)	

For the safety population, the overall incidence of early termination was lower in the HZT-501 group compared to the ibuprofen group (34.5% vs 42.5%; p-value 0.0500), with the most frequent reason for early termination being subject withdrawal of consent (HZT-501, 10.4%; ibuprofen, 12.3%).

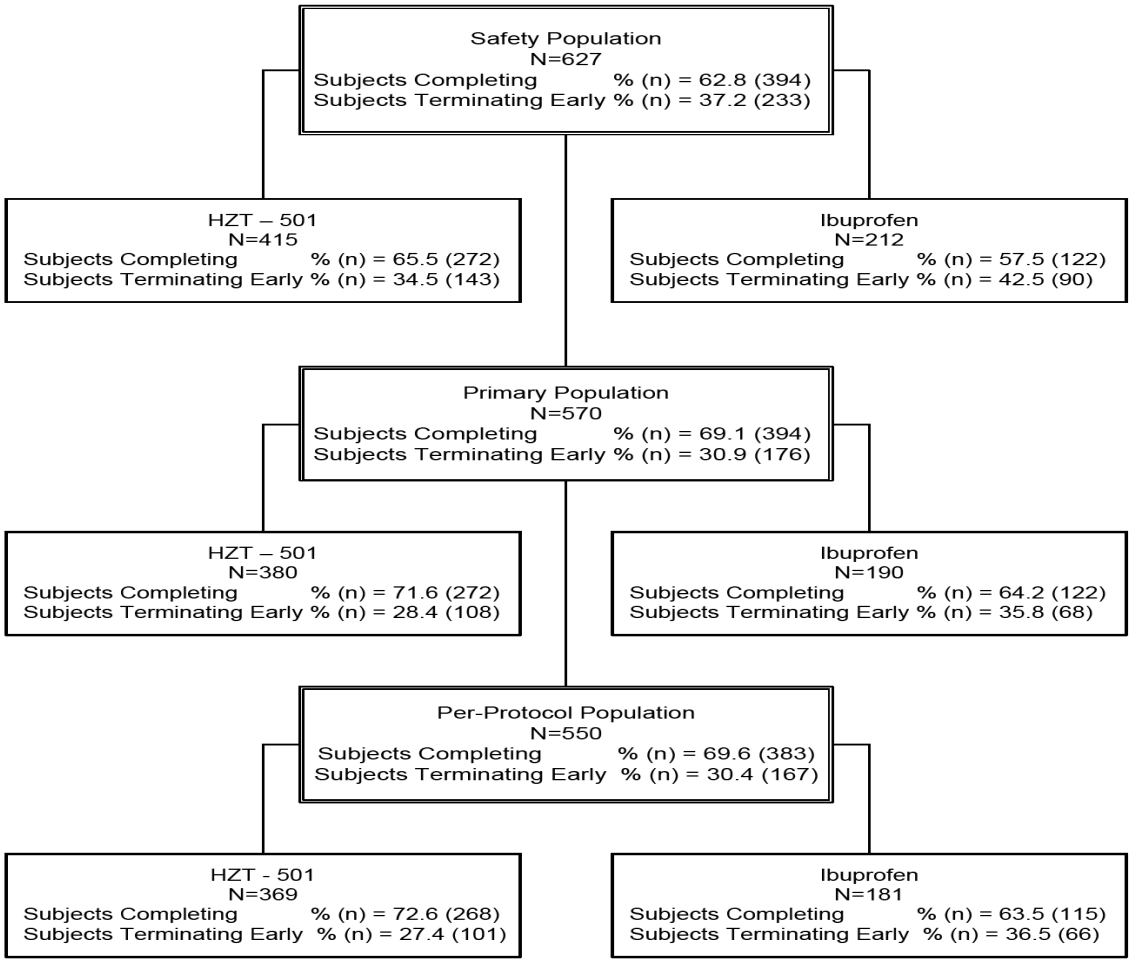
A total of 570 subjects received at least one dose of study drug, underwent a baseline endoscopic examination, and had at least the Week 8 endoscopic examination (visit window allowance 6.7 weeks); these subjects comprise the primary population. There were a total of 380 subjects in the HZT-501 group and 190 subjects in the ibuprofen group in the primary population. The incidence of early termination in the primary population trended toward lower in the HZT-501 group (28.4%) compared to the ibuprofen group (35.8%; p-value 0.0726).

Approximately one-third of the subjects in the primary population terminated early; the reasons for early termination were similar between the two treatment groups with the exception of diagnosis of ulcer. Other than ulcer diagnosis, the most common reasons for early termination were subject withdrew consent (HZT-501, 8.2%; ibuprofen, 8.4%) and adverse event (HZT-501, 3.9%; ibuprofen, 3.7%). A numerically higher percentage of subjects in the HZT-501 group terminated early due to lost to follow-up (HZT-501, 3.4%; ibuprofen, 1.6%) and a numerically higher percentage of subjects in the ibuprofen group terminated early due to the discretion of the Investigator (HZT-501, 2.1%; ibuprofen, 3.7%).

A total of 550 subjects were included in the per-protocol population (i.e., the primary population with the exclusion of subjects who had major protocol violations). There were 369 subjects in the HZT-501 group and 181 subjects in the ibuprofen group in the per-protocol population. The incidence of early termination in the per-protocol population was lower in the HZT-501 group (27.4%) compared to the ibuprofen group (36.5%).

Figure 3.1.1.3.1 presents the three populations: Safety, Primary, and Per-Protocol.

Figure 3.1.1.3.1 (Applicant's) Subject Disposition



3.1.1.4 Demographics and Baseline Characteristics

The applicant indicated that the demographic characteristics of the primary population were similar for the two treatment groups, and there were no statistically significant differences between the groups for any demographic variable. The mean age of the primary population at the time of Informed Consent was 55.4 years, with a range of 39 to 79 years. The majority of subjects (82.5%) were less than 65 years of age. Overall the primary population was 67.7% female, 82.6% White, and 84.2% non-Hispanic or Latino; 13.5% of the primary population was Black or African American. The mean height was 167.74 cm, the mean weight was 88.14 kg, and the median number of gastrointestinal tract erosions at Screening was zero. Table 3.1.1.4.1 displayed the baseline demographics.

Table 3.1.1.4.1 (Applicant's) Baseline demographics by treatment group using primary population

	Statistic	HZT-501 (N=380)	Ibuprofen (N=190)	Total (N=570)	p-value[a]
Age (years)					0.5892
	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					0.8762
< 65 years	% (n)	82.6 (314)	82.1 (156)	82.5 (470)	
≥ 65 years	% (n)	17.4 (66)	17.9 (34)	17.5 (100)	
Gender					0.1634
Male	% (n)	34.2 (130)	28.4 (54)	32.3 (184)	
Female	% (n)	65.8 (250)	71.6 (136)	67.7 (386)	
Ethnicity					0.4726
Hispanic or Latino	% (n)	16.3 (62)	12.6 (24)	15.1 (86)	
Not Hispanic or Latino	% (n)	82.9 (315)	86.8 (165)	84.2 (480)	
Not Reported	% (n)	0.8 (3)	0.5 (1)	0.7 (4)	
Race					0.2728
White	% (n)	81.6 (310)	84.7 (161)	82.6 (471)	
Black or African American	% (n)	15.0 (57)	10.5 (20)	13.5 (77)	
Other[b]	% (n)	3.4 (13)	4.7 (9)	3.9 (22)	
Weight (kg)					0.7909
	Mean (SD)	88.31 (21.51)	87.80 (21.42)	88.14 (21.46)	
	Median	85.65	85.50	85.65	
	Min, Max	48.4, 188.3	49.0, 154.2	48.4, 188.3	
Height (cm)					0.0846
	Mean (SD)	168.23 (9.83)	166.75 (9.42)	167.74 (9.71)	
	Median	167.60	165.10	167.30	
	Min, Max	139.7, 192.0	146.8, 190.5	139.7, 192.0	

a: p-value is from a two-sample t-test for continuous variables and from a Pearson Chi-Square test for categorical responses.
b: "Other" class includes the following races: Native Hawaiian or other Pacific Islander, Asian,

In addition, the applicant also indicated that the percentage of subjects in the primary population who were using low dose aspirin and/or anticoagulant medication at study entry was 14.7%, the percentage of subjects with a history of upper gastrointestinal ulcer was 5.1%, the percentage of subjects using low aspirin and/or other anticoagulant medication at study entry and having a positive upper ulcer history was 0.9%, and the percentage of subjects not using low dose aspirin or other anticoagulant medication at study entry and not having a positive history of upper ulcer was 81.1%. Table 3.1.1.4.2 displays the baseline characteristics.

Table 3.1.1.4.2 (Applicant's) Baseline characteristics by treatment group using primary population

	Statistic	HZT-501 (N=380)	Ibuprofen (N=190)	Total (N=570)	p-value[a]
Positive UGI Ulcer History					0.5898
No	% (n)	95.3 (362)	94.2 (179)	94.9 (541)	
Yes	% (n)	4.7 (18)	5.8 (11)	5.1 (29)	
Use of LDA and/or OAC and Positive UGI Ulcer History					0.7508
No	% (n)	99.2 (377)	98.9 (188)	99.1 (565)	
Yes	% (n)	0.8 (3)	1.1 (2)	0.9 (5)	
No Use of LDA and/or OAC and No UGI Ulcer History					0.6502
No	% (n)	19.5 (74)	17.9 (34)	18.9 (108)	
Yes	% (n)	80.5 (306)	82.1 (156)	81.1 (462)	
Number of Erosions of Gastrointestinal Tract					0.6087
	Mean (SD)	0.5 (1.1)	0.4 (1.0)	0.5 (1.0)	
	Median	0.0	0.0	0.0	
	Min, Max	0, 4	0, 4	0, 4	
Use of LDA and/or OAC					0.4521
No	% (n)	84.5 (321)	86.8 (165)	85.3 (486)	
Yes	% (n)	15.5 (59)	13.2 (25)	14.7 (84)	

a: p-value is from a two-sample t-test for continuous variables and from a Pearson Chi-Square test for categorical responses.
LUA = Low Uose Aspirm, OAC; = Other Anticoagulant Me&cation, UUl = Upper Uastrointestinal.

3.1.1.5 Applicant's Efficacy Analysis Results and Conclusions

The following efficacy analysis results are copied from the original NDA study report while the original efficacy analysis results and the applicant's response documents to the Agency IR letter issued on 10/05/2010 are commented in the section of "Statistical Reviewer's Analysis and Comments" (Section 3.1.1.6). In addition, it is noted that the censoring times for most early terminated patients were located in the 5-th interval (week 22.6 to week 26.8) of the Life Table analysis.

1) Primary endpoint analysis - Upper gastrointestinal (i.e., gastric and/or duodenal) ulcer

For the primary endpoint analysis using primary population, the applicant indicated that there was a statistically significant reduction in the proportion of subjects who developed at least one upper gastrointestinal ulcer in the HZT-501 group (13.8%) compared to the ibuprofen group (22.6%; p-value 0.0304). Table 3.1.1.5.1 presents the efficacy analysis result.

Similar results were seen for the per-protocol population, for which there was a statistically significant reduction in the proportion of subjects who developed at least one upper

gastrointestinal ulcer in the HZT-501 group (13.8%) compared to the ibuprofen group (23.2%; p-value 0.0248).

Table 3.1.1.5.1 (Applicant's) Proportion of Subjects developed at least one upper gastrointestinal ulcer using 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 upper gastrointestinal ulcer.
CI = Confidence Interval, SE =Standard Error

2) Secondary endpoint analysis

Gastric ulcer

For the gastric ulcer analysis using primary population, the applicant indicated that the proportion of subjects who developed at least one gastric ulcer in the HZT-501 group (13.0%) was not significantly less that that of the ibuprofen group (19.7%; p-value 0.0795). Table 3.1.1.5.2 presented the efficacy analysis result.

Similar results were seen for the per-protocol population, for which there was not a statistically significant reduction in the proportion of subjects who developed at least one gastric ulcer in the HZT-501 group (13.0%) compared to the ibuprofen group (20.2%; p-value 0.0679).

Table 3.1.1.5.2 (Applicant's) Proportion of Subjects developed at least one gastric ulcer using 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)	13.0%	0.022	9.3%, 18.0%	19.7%	0.031	14.3%, 26.7%	6.7%	0.038	-0.8%, 14.2%	0.0795[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 gastric ulcer.
CI = Confidence Interval, SE =Standard Error

Duodenal ulcer

For the duodenal ulcer analysis using primary population, the applicant indicated that there was a numerical reduction in the proportion of subjects who developed at least one duodenal ulcer in the HZT-501 group (0.9%) compared to the ibuprofen group (6.6%). Given the hierarchical

testing rule and the finding that the test for the proportion of subjects who developed at least one gastric ulcer was not statistically significant at the 0.05 level, the testing procedure was stopped and no further testing was to be performed for duodenal ulcer. Then, by the pre-specified hierarchical testing rule, the duodenal ulcer rate of HZT-501 was claimed not significantly higher than that of Ibuprofen. Table 3.1.1.5.3 presented the estimates of duodenal ulcer rates for both treatments.

Similar results were seen for the per-protocol population, for which there was a reduction in the proportion of subjects who developed at least one duodenal ulcer in the HZT-501 group (1.0%) compared to the ibuprofen group (6.4%).

Table 3.1.1.5.3 (Applicant's) Proportion of Subjects developed at least one duodenal ulcer using 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
All Subjects (N=570)	0.9%	0.005	0.3%, 2.9%	6.6%	0.023	3.3%, 12.8%	5.6%	0.023	1.0%, 10.2%

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

NSAID-Associated Serious Gastrointestinal Complications

The applicant indicated that there were no NSAID-associated serious gastrointestinal complications reported during this study.

3) Sensitivity analysis

The applicant indicated that sensitivity analyses on the primary and secondary endpoints were undertaken to assess the impact of analysis methodology and the impact of the ulcer-related assumptions for subjects who terminated early. The analysis results for crude incidence rates are presented in Table 3.1.1.5.4.

Table 3.1.1.5.4 (Applicant's) Crude incidence rates of subjects developed at least one upper gastrointestinal (Gastric and/or Duodenal), gastric, or duodenal ulcer using primary population

Endpoint	HZT-501 (N=380) % (n/N)	Ibuprofen (N=190) % (n/N)	P-value[a]	P-value[b]	P-value[c]
UGI ulcer					
Crude rate without ET[d]	10.5% (40/380)	20.0% (38/190)	0.0028	0.0029	0.0018
Crude rate with ET[e]	30.3% (115/380)	37.4% (71/190)	0.0893	0.1072	0.0898
Gastric ulcer					
Crude rate without ET[d]	9.7% (37/380)	17.9% (34/190)	0.0070	0.0081	0.0051
Crude rate with ET[e]	30.3% (115/380)	36.8% (70/190)	0.1290	0.1371	0.1156
Duodenal ulcer					
Crude rate without ET[d]	0.8% (3/380)	4.7% (9/190)	0.0035	0.0054	0.0017
Crude rate with ET[e]	28.4% (108/380)	36.3% (69/190)	0.0679	0.0681	0.0540

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.

Based upon the crude rare analysis results without including early terminated subjects as having an ulcer, shown by Table 3.1.1.5.4, it was noted that for the three types of ulcers (upper gastrointestinal ulcer, gastric ulcer, and duodenal ulcer), HZT-501 significantly reduced the ulcer rates when compared to ibuprofen.

However, the results from the crude rate analyses including the early terminated subjects as having an ulcer showed that the rate of subjects who developed at least one upper gastrointestinal ulcer (HZT-501 30.3% vs. ibuprofen 37.4%; p 0.0893), at least one gastric ulcer (HZT-501 30.3% vs. ibuprofen 36.8%; p-value 0.129), or at least one duodenal ulcer (HZT-501 28.4% vs. ibuprofen 36.3%; p-value 0.0679), for HZT-501, were not significantly lower than that of ibuprofen, in the sense of exploratory analysis.

The applicant commented that for the upper gastrointestinal ulcer, the result from the crude rate analysis without including early terminated subjects as having an ulcer was consistent with the pre-specified life table analysis. However, even for the upper gastrointestinal ulcer, the crude rate analysis including early terminated subjects as having an ulcer indicated that HZT-501 did not significantly reduce the risk of developing ulcer when compared to ibuprofen.

Similarly, for gastric ulcer (secondary endpoint), the rate reduction, for HZT-501, was statistically significant lower than that of ibuprofen using crude rate analysis without including the early terminated subjects as having an ulcer. However, on the contrary, the rate reduction, for HZT-501, was not statistically significant lower than that of ibuprofen using crude rate analysis including the early terminated subjects as having an ulcer.

In conclusion, the applicant stated that the pre-specified life table analysis for gastric ulcers trended toward lower in the HZT-501 group. Because this difference was not statistically

significant using life table analysis, by the pre-specified fixed sequence (hierarchical) multiplicity adjustment procedure, the proportion of subjects who developed at least one duodenal ulcer was not formally tested statistically by life table analysis and a non-significant result should be concluded for HZT-501 vs. ibuprofen.

3.1.1.6 Statistical Reviewer's Analysis and Comments

In order to validate the applicant's claim (made in the original NDA study report) on the superiority of HZT-501 to ibuprofen assessed by the upper gastrointestinal ulcer rate, this reviewer performs the following two analyses based upon upper gastrointestinal ulcers using data submitted with the original NDA application on March 23, 2010: i) Efficacy comparison by investigator site, ii) Sensitivity analysis. Then, comments on the applicant's responses to the Agency IR letter dated 10/05/2010. Finally, this reviewer makes comments on the efficacy strength of HZT-501.

Statistical Reviewer's Analysis

i) Efficacy comparison by investigator site

In the efficacy comparison by site, this reviewer compares the efficacy of HZT-501 versus ibuprofen only using data submitted through the original NDA submission dated 03/23/2010 since superiority of HZT-501 to ibuprofen is no longer shown when using data including subjects who were early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer in the Life Table analysis, as requested by the Agency IR letter dated 10/05/2010.

Since a small site has no capability to dominate the superiority of HZT-501 to ibuprofen, in this efficacy analysis, the sites with numbers of patients enrolled no less than ten are explored and the result is presented in Table 3.1.1.6.1 using data submitted through original NDA submission.

Table 3.1.1.6.1 (Reviewer's) proportions of upper gastrointestinal ulcers by site using primary population

SITE NUMBER	HZT-501 (H) % (n/N)	IBUPROFEN (I) % (n/N)	DIF. H I	SITE NUMBER	HTZ-501 (H) % (n/N)	IBUPROFEN (I) % (n/N)	DIF. H I
Site 112	0.0 (0/8)	50.0 (3/6)	50.0%	**Site 152**	12.0 (2/17)	18.0 (2/9)	6.0%
Site 113	11.0 (1/9)	50.0 (1/2)	39.0%	**Site 153**	10.0 (1/10)	17.0 (1/6)	7.0%
Site 115	13.0 (1/8)	0.0 (0/8)	13.0%	**Site 159**	0.0 (0/6)	0.0 (0/4)	0.0%
Site 116	22.0 (2/9)	0.0 (0/4)	22.0%	**Site 160**	0.0 (0/7)	20.0 (1/5)	20.0%
Site118	0.0 (0/7)	0.0 (0/3)	0.0%	**Site 162**	25.0 (2/8)	40.0 (2/5)	15.0%
Site 121	14.0 (3/21)	20.0 (2/10)	6.0%	**Site 163**	0.0 (0/10)	0.0 (0/8)	0.0%
Site 123	0.0 (0/7)	33.0 (2/6)	33.0%	**Site 166**	0.0 (0/10)	0.0 (0/1)	0.0%
Site 126	0.0 (0/9)	0.0 (0/4)	0.0%	**Site 168**	0.0 (0/7)	17.0 (1/6)	17.0%
Site 130	0.0 (0/7)	0.0 (0/3)	0.0%	**Site 177**	17.0 (1/6)	50.0 (2/4)	33.0%
Site 144	14.0 (4/29)	0.0 (0/4)	14.0%	**Site 180**	7.0 (1/14)	38.0 (3/8)	31.0%
Site 146	11.0 (1/9)	0.0 (0/5)	11.0%				
Site 149	20.0 (3/15)	38.0 (3/8)	18.0%	**Overall**	10.5 (40/380)	20.0 (38/190)	9.5%

Based upon the results from Table 3.1.1.6.1, although for the five (sites 112, 113, 123, 177, and 180), the upper ulcer rates of HZT-501 are more than 30% lower than that of ibuprofen, the number of subjects enrolled for the four sites (sites 112, 113, 123, and 177) were small, less than 15. Unlike the four sites (sites 112, 113, 123, and 177), site 180 enrolled more than twenty patients and only one out of fourteen patients in the HZT-501 group identified to have upper gastrointestinal ulcer. In order to explore whether this site dominate the superiority of HZT-501 to ibuprofen, this reviewer would like to perform the sensitivity analysis.

ii) Sensitivity analysis

In this section, this reviewer performs the Life Table analysis method proposed by the applicant using primary population excluding patients in site 180 to explore the possibility of this site dominating the superiority of HZT-501 to ibuprofen. The efficacy analysis result is presented by Table 3.1.1.6.2.

Table 3.1.1.6.2 (Reviewer's) Proportion of Subjects developed at least one upper gastrointestinal ulcer using primary population excluding patients from site180

	HZT-501 (H) (N=366)		Ibuprofen (I) (N= 182)		Difference (H- I)			
	Proportion[a]	SE[b]	Proportion	SE	Proportion	SE	95%CI	p-value[c]
All Subjects (N=548)	14.2%	0.023	22.0%	0.035	-7.8%	0.041	(-15.8%, 0.4%)	0.064

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

Table 3.1.1.6.2 indicates that at two-sided significance level of 0.05, the proportion of subjects who developed at least one upper gastrointestinal ulcer in the HZT-501 group (14.2%) is no longer significantly less that that of the ibuprofen group (22.0%; p-value 0.064) using primary population excluding patients from site180. By this sensitivity analysis result, one may deem that the superiority of HZT-501 to ibuprofen is not robust.

Comments on Applicant's response to the agency's IR letter

In order to further validate the effect of HZT-501 short of robustness on the reduction of Upper GI ulcer rate, Table 3.1.1.6.3 presents applicant's Life Table analysis on time to upper GI ulcer including subjects who were early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer, as agreed by the applicant on a T-Con held on 03/11/2011. This Life Table analysis result is copied from the applicant's response documents (dated 10/21/2010) to the Agency IR letter (dated 10/05/2010).

Table 3.1.1.6.3 (Applicant's) Proportion of Subjects developed at least one upper gastrointestinal ulcer based upon IR letter request using 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]
All Subjects (N=548)	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

Table 3.1.1.6.3 indicates that after including subjects who early terminated and (according to the sponsor) did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer, HZT-501 is no longer to significantly reduce the proportion of subjects who developed at least one upper gastrointestinal ulcer when compared to Ibuprofen (HZT-501, 21.3%; Ibuprofen, 28.0%; p-value 0.123).

In addition, the result of Life Table analysis on time to gastric ulcer including subjects who were early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer also shows that HZT-501 fails to significantly reduce the proportion of subjects who developed at least one gastric ulcer when compared to Ibuprofen (HZT-501, 20.8%; ibuprofen, 25.3%; p-value 0.2802).

As commented in the section of 2.1 (Overview), the early terminated patients without a negative endoscopy for ulcer should have been included as having an ulcer in the Life Table analysis reported in the original NDA submission since those patients were very likely to be ulcer patients.

Accordingly, the results from the applicant's response document to the Agency IR letter dated 10/05/2010 issued a critical signal that Study HZ-CA-301 did not provide persuasive evidence to support that the effect of HTZ-501 better than that of ibuprofen on the reduction of upper GI ulcer rate.

Comments on the overall efficacy strength

This reviewer would like to make the following three comments regarding the efficacy strength provided by the study: i) analysis results on upper gastrointestinal ulcer, ii) applicant's analysis results on gastric ulcer, and iii) overall assessment on the strength of HZT-501.

i) Analysis results on upper gastrointestinal (GI) ulcer

First, for testing the risk reduction on the upper gastrointestinal ulcer reported by the original study dated March 23, 2010, HZT-501 showed superior to ibuprofen with a borderline p-value (p

0.0304), close to the two-sided significance level of 0.05. In addition, this reviewer notes that for site 180, in the HZT-501 group, only one out of 14 patients identified to have upper gastrointestinal ulcer; the proportion of upper gastrointestinal ulcer in HZT-501 (7.0%) is 31% lower than that of ibuprofen (38%).

In order to assess the robustness of the superior result for HZT-501 to ibuprofen, this reviewer performs a sensitivity analysis based upon the proportion of patients developed at least one upper gastrointestinal ulcer (primary endpoint) using primary population excluding patients from site 180. The result of sensitivity analysis showed that the upper gastrointestinal ulcer rate of HZT-501 is no longer significantly lower than that of ibuprofen. Thus, it appears that the superiority of HZT-501 to ibuprofen assessed by the upper gastrointestinal ulcer rate may not be robust.

In addition, Life Table analysis on time to upper GI ulcer (including subjects who were early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer) shows that HZT-501 fails to significantly reduce the upper GI ulcer rate as compared to Ibuprofen. As commented in the previous sub-section, those subjects who were early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug were very likely to be ulcer patients, as agreed by the applicant on a T-Con held on 03/11/2011. Thus, from the rationale of efficacy comparison, those subjects who early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug should have been counted as having an ulcer in the Life Table analysis results reported by the original study report.

Accordingly, based upon the results of this reviewer's sensitivity analysis and the Life Table analysis on the Upper GI ulcer including subjects who early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer, Study HZ-CA-301 does not provide persuasive evidence to support the effect of HTZ-501 better than that of ibuprofen on the reduction of Upper GI ulcer rate.

In addition, the results of the crude rate analyses including early terminated subjects as having an ulcer presented by Table 3.1.1.5.4 also indicated that HZT-501 did not significantly reduce the risk of developing upper GI ulcer when compared to ibuprofen. HZT-501 is further validated to be no better effect than ibuprofen in reducing the upper GI ulcer rate.

ii) Applicant's analysis results on gastric ulcer

First, it is noted that Life Table analysis result from the original study report (without including subjects who early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer) already showed that the proportion of subjects developed at least one gastric ulcer for HZT-501 was not significantly lower than that of ibuprofen.

In addition, the results of the crude analysis including early terminated subjects as having an ulcer presented by Table 3.1.1.5.4 showed the same result as the Life Table analysis.

Accordingly, HZT-501 is further validated to be no better effect than ibuprofen in reducing the gastric ulcer rate.

Finally, in the protocol, the reduction of the gastric ulcer rate was pre-specified as the first secondary-endpoint and the associated Life Table analysis which was pre-specified as the primary analysis failed to demonstrate the superiority of HZT-501 to ibuprofen on the reduction of the gastric ulcer rate. Then, by the fixed sequence (hierarchical) testing procedure pre-specified in the protocol, HZT-501 was declared to be no better effect than ibuprofen on the reduction of duodenal ulcer rate which was pre-specified as the second secondary-endpoint.

iii) Overall assessment on the strength of HZT-501

From this reviewer's sensitivity analysis and applicant's analysis results including analyses requested by the Agency IR letter issued on October 5, 2010, we deem that Study HZ-CA-301 does not provide persuasive evidence to support the effect of HTZ-501 better than that of ibuprofen on the reduction of upper gastrointestinal ulcer rate.

As for the gastric ulcer rate, both the Life Table analysis and the crude rate analysis including early terminated subjects as having an ulcer all demonstrate that HTZ-501 has no effect to reduce the risk of having gastric ulcer. Then, by the proposed hierarchical multiplicity adjustment method, HTZ-501 is declared to be no effect in the reduction of duodenal ulcer rate.

Accordingly, Study HZ-CA-301 does not provide persuasive evidence to support that the effect of study drug HTZ-501 is better than that of ibuprofen on risk reduction of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen.

3.1.2 Study HZ-CA-303

3.1.2.1 Study Design and Endpoints

The primary objective of the study was to evaluate the efficacy of HZT-501 in reducing the proportion of subjects who develop at least one endoscopically-diagnosed gastric ulcer (of unequivocal depth and at least 3 mm in diameter) during the 24-week Treatment Period, as compared to ibuprofen, in subjects at risk for NSAID-induced ulcers.

The secondary objective of the study was to evaluate, in subjects at risk for NSAID-induced ulcers, the efficacy of HZT-501, as compared to ibuprofen, in reducing (1) the proportion of subjects who develop at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer during the 24-week Treatment Period; (2) the proportion of subjects who develop at least one endoscopically-diagnosed duodenal ulcer during the 24-week Treatment Period; and (3) the incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding) during the 24-week Treatment Period.

This Phase 3, multicenter, randomized, double-blind, parallel group study was designed to evaluate the efficacy, as measured by endoscopically-diagnosed gastrointestinal ulcers, and safety of HZT-501 compared with ibuprofen. Approximately 875 subjects, 40 to 80 years of age inclusive, who had not used an NSAID within the 30 days prior to study entry, and who were expected to require daily administration of an NSAID for at least the coming six months, were planned to be enrolled.

Subjects who met the inclusion and not exclusion criteria were assigned randomly, in approximately a 2:1 ratio, to treatment with either HZT-501 (ibuprofen 800 mg/ famotidine 26.6 mg) or ibuprofen (800 mg) for 24 consecutive weeks or until they developed either an endoscopically-diagnosed upper gastrointestinal ulcer and/or terminated early for other reasons (i.e., AE, 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; and (2) history of an upper gastrointestinal ulcer.

The HZT-501 and the ibuprofen tablets were comparable to each other with respect to size, shape, color, and weight, to enable administration of both drugs on a double-blind basis. All subjects, investigators, study center personnel, sponsor personnel, and CRO personnel (with the exception of the un-blinded individual who developed the randomization scheme for the IVRS, and a drug supply consultant who aided coordination of shipments with the distributor (b) (4)) remained blinded to all subjects' treatment assignments until after the study database had been locked. However, un-blinded data were provided to the IDMC by an un-blinded statistician at the CRO who ensured that no unauthorized un-blinding occurred, as specified in the written IDMC Charter. The applicant and the project team did not have access to the individual subject treatment assignments until after the study database had been locked.

The schedule of assessments is Screen Visit (Day -30 to -1), Treatment Period (Day 0, week 4, Week 8, week 16, and Week 24), and Follow-up Period (Week 28). 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 as well as a plus/minus five-day window around the target clinic visit day. Subjects were terminated early from the study for safety in the event they developed an endoscopically-diagnosed upper gastrointestinal ulcer of unequivocal depth and at least 3 mm in diameter. Subjects who terminated early for reasons other than development of an endoscopically-diagnosed upper gastrointestinal ulcer were to undergo an endoscopic examination at a Termination Visit that was to be conducted as soon as possible after administration of their final dose of study drug.

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 (Horizon Protocol HZ-CA-304). Subjects who did not enter the Horizon Protocol HZ-CA-304 were monitored for safety for an additional four weeks (Follow-up Period), through Week 28, via a telephone visit.

Subjects 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. Subjects were prohibited from taking any drugs or interventions that neutralize gastric acid for more than three days during any two-week period in the 24-week Treatment Period. Subjects were prohibited from taking any H2-receptor antagonists and/or any PPIs other than study drug during the 24-week Treatment Period. Subjects taking low dose aspirin and/or other anticoagulant medication could continue to use these medications, on their usual regimen, during the Treatment Period.

Safety assessments consisted of the collection of AEs (all of the AEs collected in this study were Treatment-Emergent Adverse Events [TEAEs]), clinical laboratory evaluations, physical examinations, and vital signs. TEAEs were collected from all subjects beginning at the time of four-week Follow-up Period.

Cardiovascular safety was monitored on a quarterly basis by an Independent IDMC. A written charter defined the makeup and conduct of the IDMC. Un-blinded reports of deaths and serious cardiovascular events, including myocardial infarctions, were provided on a quarterly basis to the IDMC for review.

All randomized subjects 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 protocol specified 24-week Treatment Period, due to visit window allowance, was defined as up to and including Week 26.7, except for Secondary Objective #3 for which the 24-week treatment period was defined as up to and including Week 28.7 to include any data that were collected during the safety four-week Follow-up Period.

3.1.2.2 Statistical Methodologies

The primary efficacy endpoint was the proportion of subjects who developed at least one endoscopically-diagnosed gastric ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period (defined as up to and including Week 26.7).

Secondary efficacy endpoints consisted of the following:
• The proportion of subjects who developed at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period (defined as up to and including Week 26.7).
• The proportion of subjects who developed at least one endoscopically-diagnosed duodenal ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period (defined as up to and including Week 26.7).
• The incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding; this analysis was performed for the primary and the safety populations) during the 24-week Treatment Period (defined as up to and including Week 28.7).

The data from Week 26.7 to Week 28.7 included any data that were collected during the safety four-week Follow-up Period.

Primary Population: All randomized subjects who received at least one dose of study drug and who underwent a baseline endoscopic examination and at least the Week 8 endoscopic examination were included in the primary population for all primary and secondary efficacy analyses. Total 812 patients were included in the Primary Population: 550 in HZT-501 and 262 in ibuprofen.

If a subject had any endoscopic examination at least 6.7 weeks after the date of first dose of study drug (see explanation following), the subject was considered to have satisfied the criterion of having at least a Week 8 endoscopic examination. For these analyses, subjects were grouped in accordance with the treatment to which they were randomized, regardless of the treatment each subject actually received; in this study the actual treatment and randomized treatment were the same for all subjects.

Because of the plus/minus five-day visit window and the specification that the endoscopic examination could be performed up to four days before a visit, an endoscopic examination performed between nine days before calendar Week 8 (i.e., at or after Week 6.7) and five days after calendar Week 8 (at or including Week 8.7) qualified as a Week 8 endoscopic examination.

Per-protocol Population: The primary population with the exclusion of subjects having major protocol violations (assessed prior to un-blinding). Analyses of the primary and secondary efficacy parameters (with the exception of the incidence rate of NSAID-associated serious gastrointestinal complications) were also performed on the per-protocol population. Total 764 patients were included in the Per-protocol Population: 522 in HZT-501 and 242 in ibuprofen.

Analyses involving the per-protocol population were to be performed using actual treatment received initially; on this study the actual treatment and randomized treatment were the same for all subjects.

All efficacy variables were analyzed for both the primary and per-protocol populations (with the exception of the incidence rate of NSAID-associated serious gastrointestinal complications which was to be analyzed for both the primary and the safety populations), and the treatment groups were compared using a Chi-Square test unadjusted for covariates. All efficacy endpoints were compared using the estimated failure rates from a life table analysis and their standard errors.

The intervals used for the life table analyses followed the visit windows for clinic visits (i.e., plus/minus five days) and endoscopies (i.e., at most four days before the clinic visit) outlined in the protocol for subject convenience. The intervals used were:
• Interval 1: Weeks 6.7 to 8.7.
• Interval 2: Weeks 8.8 to 14.5.
• Interval 3: Weeks 14.6 to 16.7.

• Interval 4: Weeks 16.8 to 22.5.
• Interval 5: Weeks 22.6 to 26.7.
• Interval 6: Weeks 26.8 to 28.7.

The life table estimate for the probability that a subject developed an ulcer by the end of Interval 5 represents a statistical estimate of the primary endpoint. This proportion is referred to as the "Week 24 estimate" or the "Week 24 proportion" due to allowance for planned windows around the measurement times.

Safety Population: All randomized subjects who received at least one dose of study drug were included in the safety analyses. Total 906 patients were included in the Safety Population: 607 in HZT-501 and 299 in ibuprofen.

For all analyses involving the safety population, including the incidence rate of NSAID-associated serious gastrointestinal complications, subjects were grouped in accordance with the treatment each subject initially received. In the event that a subject received both study treatments, the subject was grouped for the safety analyses in accordance with the treatment s/he initially received.

Analyses involving the primary population assigned treatment group as the randomized treatment assignment regardless of actual treatment received. Analyses involving the per-protocol population assigned treatment group by actual treatment received initially. The actual treatment and randomized treatment were the same for all subjects.

The primary and secondary efficacy endpoints were tested with a fixed sequence (hierarchical) testing procedure in the order of primary endpoint first, then secondary endpoints. The testing started with the primary efficacy endpoint. After the primary efficacy endpoint, the secondary efficacy endpoints were to be tested in the following order:

1) The proportion of subjects who developed at least one endoscopically-diagnosed upper gastrointestinal ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period (defined as up to and including Week 26.7).

2) The proportion of subjects who developed at least one endoscopically-diagnosed duodenal ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week Treatment Period (defined as up to and including Week 26.7).
3) The incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding) during the 24-week Treatment Period (defined as up to and including Week 28.7).

Failure to reject the first null hypothesis at the two-sided 0.05 level resulted in immediate failure to reject all subsequent null hypotheses in the sequence. In accordance with this approach, no alpha adjustment was required and all alternative hypotheses accepted were claimed significant at the 0.05 level.

In addition, the following sensitivity analyses were conducted:
1. The crude rates for the ulcer endpoints were explored as sensitivity analyses for the primary population. The number of subjects who experienced an ulcer through the Week 24 estimate, up to and including Week 26.7, in each treatment arm was tested for statistical significance using a Fisher's Exact test, a Chi-Square test adjusted for continuity, and a Cochran-Mantel-Haenszel (CMH) test.

2. The crude rates for all ulcer endpoints for the primary population were explored for sensitivity to ulcer definition by examining ulcer incidence crude rates when subjects with an ulcer plus subjects who withdrew from the study early were both considered as having experienced an ulcer. The number of subjects who experienced an ulcer, plus those who terminated early through the Week 24 estimate, up to and including Week 26.7, in each treatment arm was tested for statistical significance using a Fisher's Exact test, a Chi-Square test adjusted for continuity, and a CMH test.

The primary analysis and sensitivity analyses detailed above were also intended to be conducted using the actual treatment that each subject received; however these additional analyses were not performed because there were only four subjects (0.4%) for whom randomized and actual initial treatment may have differed. Given the sample size of the study, the reassignment of these four subjects would not have substantially altered the results or their interpretation.

The sample size for this study was chosen based on specification of Type 1 and Type 2 error rates and the anticipated effect size. A sample size of 875 subjects was selected in order to provide approximately 90% power to detect a difference of 6% versus 14% in the proportion of subjects in the two treatment arms who developed at least one gastric ulcer during the 24-week Treatment Period, with a two-sided a 0.05 using a CMH test controlling for randomization strata. This sample size accounted for the 2:1 randomization, a 15% dropout rate for reasons other than ulcer development, and the estimated 5% occurrence of non-gastric (i.e., duodenal) ulcers that were not included in the primary efficacy endpoint definition.

3.1.2.3 Patient Disposition

All randomized subjects received at least one dose of study drug and therefore are included in the safety population. A total of 906 subjects were randomized and received at least one dose of blinded study drug; these subjects comprise the safety population. There were 607 subjects in the HZT-501 group and 299 subjects in the ibuprofen group in the safety population. Because one subject was randomized twice, 905 unique subjects were enrolled into the study, whereas data for 906 subjects were included in the safety population. The subject who was randomized twice did not meet the requirements for inclusion in the primary or per-protocol populations for the efficacy analyses.

Table 3.1.2.3.1 presents patients early terminated by treatment group using safety population.

Table 3.1.2.3.1 (Applicant's) Patients early terminated by treatment group (Safety Population)

	HZT-501 % (n)	Ibuprofen % (n)	Total % (n)	p-value[a]
All Subjects				
Number of Subjects	607	299	906	
Completed Study	71.3 (433)	56.9 (170)	66.6 (603)	
Early Termination	28.7 (174)	43.1 (129)	33.4 (303)	<0.0001
Reasons for Early Termination				
Death	0.0 (0)	0.3 (1)	0.1 (1)	
Adverse Event(s)	6.3 (38)	7.7 (23)	6.7 (61)	
Subject Withdrew Consent	7.9 (48)	8.7 (26)	8.2 (74)	
Protocol Violation(s)	0.2 (1)	0.3 (1)	0.2 (2)	
Subject Lost to Follow-up	2.6 (16)	3.0 (9)	2.8 (25)	
Discretion of Investigator or Sponsor	2.5 (15)	2.7 (8)	2.5 (23)	
Endoscopically-Diagnosed UGI Ulcer	8.4 (51)	17.1 (51)	11.3 (102)	
Subject Required Excluded Medication	0.2 (1)	1.0 (3)	0.4 (4)	
Other	0.7 (4)	2.3 (7)	1.2 (11)	

For safety population, the applicant indicated that the overall incidence of early termination was significantly lower in the HZT-501 group compared to the ibuprofen group (28.7% vs. 43.1%; p-value <0.0001), with the most frequent reason for early termination being subject withdrawal of consent (HZT-501, 7.9%; ibuprofen, 8.7%). Table 3.1.2.3.1 presents patients early terminated by treatment group using safety population.

A total of 812 subjects (550 subjects in HZT-501 and 262 subjects in ibuprofen) who received at least one dose of study drug, underwent a baseline endoscopic examination, and had at least the Week 8 endoscopic examination comprises the primary population. The incidence of early termination in the primary population was lower in the HZT-501 group (21.5%) compared to the ibuprofen group (34.7%) for all subjects (p-value < 0.0001).

The applicant indicated that approximately one-quarter of the subjects in the primary population terminated early; the reasons for early termination were fairly well-balanced between the two treatment groups with the exception of early termination due to ulcer diagnosis (HZT-501, 8.9%; ibuprofen, 19.1%). Other than ulcer diagnosis, the most common reasons for early termination were withdrawal of consent (HZT-501, 5.3%; ibuprofen, 5.3%) and adverse event (HZT-501, 3.6%; ibuprofen, 4.2%).

A total of 764 subjects (522 subjects in HZT-501 and 242 subjects in ibuprofen) were included in the per-protocol population (i.e., the primary population with the exclusion of subjects who had major protocol violations). The incidence of early termination in the per-protocol population was lower in the HZT-501 group (20.9%) compared to the ibuprofen group (33.1%) for all subjects (p-value 0.0003).

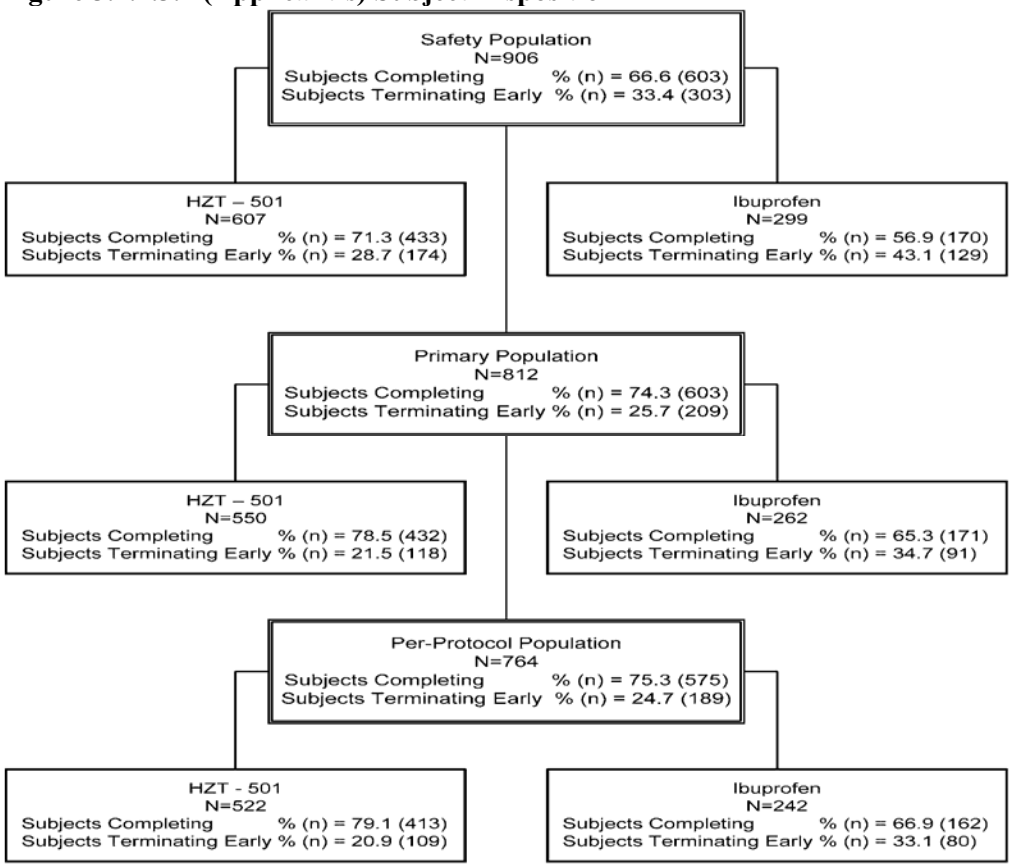
According to the protocol, all subjects who developed at least one upper gastrointestinal (i.e., gastric and/or duodenal) ulcer were to be terminated early at the time of ulcer diagnosis, unless the ulcer was diagnosed at the Week 24 Visit, in which case they were considered to have

completed the study. Fourteen subjects in the HZT-501 group (2.5%) and ten subjects in the ibuprofen group (3.8%) were diagnosed with an ulcer during the Week 24 Visit (Weeks 22.6 to 26.7) and were appropriately indicated on the End of Study eCRF page as having completed the study.

Therefore, in the primary population disposition table, there were 118 subjects in the HZT-501 group (21.5%) and 91 subjects in the ibuprofen group (34.7%) who were indicated as having terminated early, whereas 132 subjects in the HZT-501 group (24.0%) and 101 subjects in the ibuprofen group (38.5%) either developed at least one upper gastrointestinal ulcer or terminated early.

Figure 3.1.2.3.1 presents the three populations: Safety, Primary, and Per-Protocol.

Figure 3.1.2.3.1 (Applicant's) Subject Disposition



3.1.2.4 Demographics and Baseline Characteristics

The applicant indicated that the demographic characteristics of the primary population were similar for the two treatment groups. The only statistically significant demographic difference between the two treatment groups was in ethnicity. The HZT-501 group had more Hispanic or Latino subjects than the ibuprofen group (17.6% vs. 11.8%, respectively; p-value 0.0304). The

mean age of the primary population at the time of Informed Consent was 55.7 years, with a range of 40 to 80 years. The majority of subjects (81.7%) were less than 65 years of age. Overall the primary population was 68.2% female, 77.2% White, and 81.8% non-Hispanic or Latino; 19.7% of the primary population was Black or African American. The mean height was 166.62 cm, the mean weight was 88.9 kg, and the median number of gastrointestinal tract erosions at Screening was zero.

The percentage of subjects in the primary population who were using low dose aspirin and/or other anticoagulant medication at study entry was 15.9%, the percentage of subjects with a positive history of upper gastrointestinal ulcer was 7.0%, the percentage of subjects using low dose aspirin and/or other anticoagulant medication at study entry and having a positive upper gastrointestinal ulcer history was 0.9%, and the percentage of subjects not using low dose aspirin and/or other anticoagulant medication at study entry and not having a positive history of upper gastrointestinal ulcer was 78.0%. Table 3.1.2.4.1 demonstrates the baseline demographics and characteristics by treatment group using primary population.

Table 3.1.2.4.1 (Applicant's) Baseline demographics by treatment group using primary population

	Statistic	HZT-501 (N=550)	Ibuprofen (N=262)	Total (N=812)	p-value[a]
Age (years)					0.9817
	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					0.8347
< 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					0.8407
Male	% (n)	32.0 (176)	31.3 (82)	31.8 (258)	
Female	% (n)	68.0 (374)	68.7 (180)	68.2 (554)	
Ethnicity					0.0304
Hispanic or Latino	% (n)	17.6 (97)	11.8 (31)	15.8 (128)	
Not Hispanic or Latino	% (n)	80.5 (443)	84.4 (221)	81.8 (664)	
Not Reported	% (n)	1.8 (10)	3.8 (10)	2.5 (20)	
Race					0.6573
White	% (n)	77.1 (424)	77.5 (203)	77.2 (627)	
Black or African American	% (n)	19.5 (107)	20.2 (53)	19.7 (160)	
Other[b]	% (n)	3.5 (19)	2.3 (6)	3.1 (25)	
Weight (kg)	N	549	262	811	0.4370
	Mean (SD)	88.49 (21.63)	89.77 (22.89)	88.90 (22.04)	
	Median	85.00	86.60	85.70	
	Min, Max	37.6, 170.1	42.0, 186.4	37.6, 186.4	
Height (cm)					0.9507
	Mean (SD)	166.61 (10.23)	166.66 (9.22)	166.62 (9.91)	
	Median	165.10	165.10	165.10	
	Min, Max	117.3, 205.7	144.3, 191.5	117.3, 205.7	
Number of Erosions of Gastrointestinal Tract					0.1089
	Mean (SD)	0.6 (1.2)	0.5 (1.1)	0.5 (1.2)	
	Median	0.0	0.0	0.0	
	Min, Max	0, 5	0, 4	0, 5	
Use of LDA and/or OAC					0.1738
No	% (n)	82.9 (456)	86.6 (227)	84.1 (683)	
Yes	% (n)	17.1 (94)	13.4 (35)	15.9 (129)	
Positive UGI Ulcer History					0.3190
No	% (n)	92.4 (508)	94.3 (247)	93.0 (755)	
Yes	% (n)	7.6 (42)	5.7 (15)	7.0 (57)	
Use of LDA and/or OAC and Positive UGI Ulcer History					0.8337
No	% (n)	99.1 (545)	99.2 (260)	99.1 (805)	
Yes	% (n)	0.9 (5)	0.8 (2)	0.9 (7)	
No Use of LDA and/or OAC and No UGI Ulcer History					0.0773
No	% (n)	23.8 (131)	18.3 (48)	22.0 (179)	
Yes	% (n)	76.2 (419)	81.7 (214)	78.0 (633)	

a: p value is from a two sample t test for continuous variables and from a Pearson Chi Square test for categorical responses.
b: Other class includes the following races: Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native, and races reported as "Other."
LDA Low Dose Aspirin, OAC Other Anticoagulant Medication, UGI Upper Gastrointestinal.

3.1.2.5 Applicant's Efficacy Analysis Results and Conclusions

In this section, the applicant's efficacy analysis results based upon the original NDA submission (dated 03/23/2010) for Study HZ-CA-303 are regenerated below by this reviewer. Noted by this reviewer, for the Life Table analyses presented in the original NDA submission, patients who were terminated early and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug were not counted as having ulcers. In addition, data from the non-reliable site (389) identified by the inspector is not excluded from the original study report. Finally, it is

noted that as found in Study HZ-CA-301, for this study, the censoring times for most early terminated patients were also located in the 5-th interval (week 22.6 to week 26.8) of the Life Table analysis.

1) Primary endpoint analysis - Gastric ulcer

There was a statistically significant reduction in the proportion of subjects who developed at least one gastric ulcer in the HZT-501 group (12.9%) compared to the ibuprofen group (25.3%; p-value 0.0009) using primary population, as shown in Table 3.1.2.5.1. Similar results were seen for the per-protocol population, for which there was a statistically significant reduction in the proportion of subjects who developed at least one gastric ulcer in the HZT-501 group (12.5%) compared to the ibuprofen group (24.8%; p-value 0.0014).

Table 3.1.2.5.1 (Applicant's) Proportion of Subjects developed at least one Gastric Ulcer Overall using primary population

	HZT-501 (N=550)			Ibuprofen (N=262)			Difference			
	Proportion[a]	SE[b]	95% CI	Proportion[a]	SE[b]	95% CI	Proportion	SE[c]	95% CI	p-value
All Subjects (N=812)	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[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
CI = Confidence Interval, SE =Standard Error

2) Secondary endpoint analysis

Upper Gastrointestinal (i.e., Gastric and/or Duodenal) Ulcer

There was a statistically significant reduction in the proportion of subjects who developed at least one upper gastrointestinal ulcer in the HZT-501 group (14.7%) compared to the ibuprofen group (29.1%; p-value 0.0002) in the primary population. Similar results were seen for the per-protocol population, for which there was a statistically significant reduction in the proportion of subjects who developed at least one upper gastrointestinal ulcer in the HZT-501 group (14.4%) compared to the ibuprofen group (28.3%; p-value 0.0006).

Table 3.1.2.5.2 (Applicant's) Proportion of Subjects developed at least one Upper Gastrointestinal (i.e., Gastric and/or Duodenal) ulcer using primary population

	HZT-501 (N=550)			Ibuprofen (N=262)			Difference			
	Proportion[a]	SE[b]	95% CI	Proportion[a]	SE[b]	95% CI	Proportion	SE[c]	95% CI	p-value
All Subjects (N=812)	14.7%	0.019	11.4%, 18.8%	29.1%	0.034	23.0%, 36.5%	14.5%	0.039	6.8%, 22.1%	0.0002[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 upper gastrointestinal ulcer; CI Confidence Interval, SE Standard Error.

Duodenal ulcer

There was a statistically significant reduction in the proportion of subjects who developed at least one duodenal ulcer in the HZT-501 group (2.1%) compared to the ibuprofen group (7.1%; p-value 0.0226). Similar results were seen for the per-protocol population, for which there was a statistically significant reduction in the proportion of subjects who developed at least one duodenal ulcer in the HZT-501 group (2.2%) compared to the ibuprofen group (6.8%; p-value 0.0435).

Table 3.1.2.5.3 (Applicant's) Proportion of Subjects developed at least one duodenal ulcer using primary population

	HZT-501 (N=550)			Ibuprofen (N=262)			Difference			
	Proportion[a]	SE[b]	95% CI	Proportion[a]	SE[b]	95% CI	Proportion	SE[c]	95% CI	p-value
All Subjects (N=812)	2.1%	0.008	0.9%, 4.6%	7.1%	0.020	4.0%, 12.3%	5.0%	0.022	0.7%, 9.3%	0.0226[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: 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

NSAID-Associated Serious Gastrointestinal Complications

The applicant indicated that NSAID-associated serious gastrointestinal complications were reported in 0.6% of subjects in the HZT-501 group and in 0% of subjects in the ibuprofen group. This difference was not statistically significant (p-value 0.0824).

3) Sensitivity analysis

The applicant indicated that sensitivity analyses were undertaken to assess the impact of analysis methodology and the impact of the ulcer-related assumptions for subjects who terminated early.

The crude incidence rates for subjects in the primary population who developed at least one gastric ulcer, for subjects who developed at least one upper gastrointestinal ulcer, and for subjects who developed at least one duodenal ulcer are analyzed by Fisher's Exact test, a Chi-Square test with a continuity correction adjustment, and from a CMH test.

The results for the sensitivity analysis were presented by Table 3.1.2.5.4.

Table 3.1.2.5.4 (applicant's) Crude incidence rates of subjects developed at least one gastric, upper gastrointestinal (Gastric and/or Duodenal), or duodenal ulcer using primary population

Endpoint	HTZ-501 (N=550) % (n/N)	Ibuprofen (N=262) % (n/N)	P-value[a]	P-value[b]	P-value[c]
Gastric ulce					
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.

Based upon Table 3.1.2.5.4, the results of the crude rate analysis without including early terminated subjects as having an ulcer (Crude rate without ET) showed that there was a statistically significant reduction (by all three statistical tests) in each of the following three types of ulcer rates: the percentage of subjects who developed at least one gastric ulcer (HZT-501, 10.0%; ibuprofen, 19.8%; p-value 0.0002), the percentage of subjects who developed at least one upper gastrointestinal ulcer (HZT-501, 11.3%; ibuprofen, 23.3%; p-value < 0.0001), and the percentage of subjects who developed at least one duodenal ulcer (HZT-501, 1.3%; ibuprofen, 5.3%; p-value 0.0014).

It is noted that the crude rate analyses including early terminated subjects as having an ulcer showed similar results as that of the Crude rate analyses without including ET as having an ulcer.

3.1.2.6 Statistical Reviewer's Analysis and Comments

In this section, this reviewer first performs efficacy comparison by site to explore whether the superiority claim for HZT-501 made by the applicant is dominated by certain sites. Then, this reviewer makes comments on the applicant's response (dated December 16, 2010) to the Agency's IR letter (dated December 07, 2010) regarding the impact of site 389 on the effect of HTZ-501. Finally, this reviewer makes overall assessments on the efficacy strength of HZT-501.

As stated in the section of 2.1 (Overview), the site inspector indicates that for Study HZ-CA-303, data provided by site 389 are lack of integrity and are not reliable. Consequently, data used for this reviewer's efficacy comparison by site does not include site 389. In addition, data used for the analysis were submitted by the applicant through the original NDA submission dated 03/23/2010 and were submitted on 12/16/2010 together with the response documents to the Agency IR letter dated 12/07/2010. In the IR letter, the applicant was requested to perform the

efficacy analyses excluding data from site 389 and including subjects who were early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer in the Life Table analysis.

Statistical Reviewer's Analysis

i) Efficacy comparison by investigator site

It is noted that the proposed indication was to reduce the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen. As a consequence, efficacy comparison by site is first assessed based upon the proportion of upper gastrointestinal ulcers. Then, the result of gastric ulcer is briefly discussed.

In order to explore whether the superiority of HZT-501 to ibuprofen assessed by the upper gastrointestinal ulcers was dominated by certain investigator-sites, this reviewer first uses data from original NDA submission to compare the efficacy of HZT-501 versus ibuprofen by investigator-site based upon the primary population without site 389. Then, the result of efficacy comparison by site using data submitted on 12/16/2010 is discussed.

Since a small site has no capability to dominate the superiority of HZT-501 to ibuprofen, in this clinical trail, the percentages of patients for sites with no less than ten patients are explored and presented in Table 3.1.2.6.1.

Table 3.1.2.6.1 (Reviewer's) proportions of upper gastrointestinal ulcers by site using primary population

SITE NUMBER	HTZ-501 (H) % (n/N)	IBUPROFEN (I) % (n/N)	DIF. H I	SITE NUMBER	HTZ-501 (H) % (n/N)	IBUPROFEN (I) % (n/N)	DIF. H I
Site 320	0.0 (0/6)	50.0 (3/6)	50.0%	**Site 361**	0.0 (0/23)	13.0 (1/8)	13.%
Site 330	0.0 (0/11)	50.0 (1/2)	50.0%	**Site 362**	18.0 (2/11)	14.0 (1/7)	4.0%
Site 337	3.0 (2/61)	3.0 (1/32)	0.0%	**Site 363**	8.0 (4/48)	24.0 (6/25)	16.0%
Site 340	15.0 (3/20)	40.0 (4/10)	25.0%	**Site 367**	14.0 (1/7)	33.0 (1/3)	19.0%
Site 343	29.0 (2/7)	0.0 (0/3)	29.0%	**Site 377**	10.0 (1/10)	50.0 (4/8)	40.0%
Site 347	50.0 (3/6)	67.0 (4/6)	17.0%	**Site 379**	10.0 (1/10)	0.0 (0/2)	10.0%
Site 349	8.0 (1/12)	0.0 (0/2)	8.0%	**Site 382**	0.0 (0/11)	50.0 (1/2)	50.0%
Site 353	7.0 (1/15)	0.0 (0/1)	7.0%	**Site 386**	10.0 (1/10)	11.0 (1/9)	1.0%
Site 360	13.0 (4/30)	18.0 (2/11)	5.0%	**Overall**	10.0 (45/447)	21.0 (46/216)	11.0%

Based upon the results from Table 3.1.2.6.1, for sites (337, 360, 361, and 363) enrolled more than 30 patients, the ulcer rates of HTZ-501 are not abnormally lower than that in ibuprofen when compared to the overall result. Accordingly, it appears that no particular site is deemed to dominate the superiority of HTZ-501 to ibuprofen. Similar result is found using data submitted on 12/16/2010 through the response documents to the Agency IR letter dated 12/07/2010. In this analysis, we include patients who were early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer.

Similar to the upper gastrointestinal ulcer, the efficacy comparison by site based upon gastric ulcer also shows that no particular site is found to dominate the superiority of HTZ-501 to

ibuprofen.

Comments on Applicant's response to the agency's IR letter dated 12/07/2010

In order to further validate the effect of HZT-501 on the reduction of Upper GI ulcer rate, Table 3.1.2.6.2 presents applicant's Life Table analysis (reported by the response document dated 12/16/2010 to the Agency IR letter dated 12/07/2010) on time to upper gastrointestinal ulcer, including subjects who were early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer. In addition, as IR letter requested, in this analysis, data from site 389 are excluded.

Table 3.1.2.6.2 (Applicant's) Proportion of Subjects developed at least one upper gastrointestinal ulcer based upon IR letter request using primary population excluding site 389

	HZT-501 (H) (N=447)		Ibuprofen (I) (N= 216)		Difference (H- I)			
	Proportion[a]	SE[b]	Proportion	SE	Proportion	SE	95%CI	p-value[c]
All Subjects (N=663)	16.0%	0.021	33.0%	0.037	-17.0%	0.042	(-25.1%, -8.5%)	<0.0001

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

Table 3.1.2.6.2 indicates that after excluding non-reliable data from site 389 and including subjects who were early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer, HZT-501 still significantly reduces the proportion of subjects who developed at least one upper gastrointestinal (GI) ulcer when compared to Ibuprofen.

Similarly, the result of Life Table analysis on time to gastric ulcer excluding data from site 389 and including subjects who were early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer also shows that HZT-501 significantly reduces the proportion of subjects who developed at least one gastric ulcer when compared to Ibuprofen (HTZ-501, 14.2%; ibuprofen, 29.3%; p-value 0.0003).

In addition, the result for the crude rate analysis on the subjects who developed at least one upper gastrointestinal ulcer using the primary population excluding site 389 is presented below.

Table 3.1.2.6.3 (Reviewer's) Result of crude rate analysis* on subjects who developed at least one upper gastrointestinal ulcer using the primary population excluding patients from site 389

	HZT-501 (H) (N=447)	Ibuprofen (I) (N= 216)	Difference (H- I)		
	Proportion	Proportion	Proportion	95%CI	p-value
All Subjects (N=663)	22.0% (99/447)	37.5% (81/216)	-15.5%	(-23.0%,-8.0%)	< 0.0001

*: Including early terminated patients as treatment failures.
CI = Confidence Interval, SE =Standard Error.

Based upon Table 3.1.2.6.3, the result of the crude rate analysis including early terminated subjects as having an ulcer and excluding subjects from site 389 indicates that HZT-501 still significantly reduces the proportion of subjects who developed at least one upper gastrointestinal (GI) ulcer when compared to Ibuprofen. Similar results are found for gastric and duodenal ulcers.

Finally, after excluding data from site 389 and data for the four subjects from site 363 identified as non-reliable data by the Division of Scientific Investigations on 03/10/2011, the results for the Life Table analyses and the crude rate analyses on three types of ulcers (upper GI, gastric, and duodenal ulcers) are similar to the ones only exclude data from site 389.

Accordingly, the results from the applicant's response document to the Agency IR letter uphold that Study HZ-CA-303 provides persuasive evidence to support the effect of HZT-501 on the reduction of upper GI ulcer rates.

Overall assessment on the strength of HZT-501

First, from this reviewer's efficacy comparison by site assessed by the proportions of upper gastrointestinal ulcer, we note that no particular site abnormally dominates the superiority of HTZ-501 to ibuprofen claimed by the applicant.

In addition, the results of Life Table analyses from both the original NDA study report and the applicant's response document (dated 12/16/2010) to the IR letter issued on 12/07/2010 indicate that study drug HZT-501 significantly reduces the risk of having upper gastrointestinal ulcer when compared to ibuprofen. We note that in the IR letter issued on 12/07/2010, Life Table analyses on time to upper gastrointestinal ulcer use primary population excluding distrustful data from site 389 and include subjects who were early terminated and did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer. As a consequence, the effect of HZT-501 on the reduction of upper gastrointestinal ulcer rate is supported to be better than that of ibuprofen.

Similarly, for the gastric or duodenal ulcer, the results of Life Table analyses from both the original NDA study report and the applicant's response document (dated 12/16/2010) to the IR

letter issued on 12/07/2010 indicate that HZT-501 significantly reduces the risk of having a gastric or duodenal ulcer when compared to ibuprofen.

Finally, the results of the crude rate analyses including early terminated patients as having an ulcer (recommended by the Agency in the protocol stage) using primary population with and without data from site 389 all support HZT-501 significantly reduces the upper gastrointestinal ulcer and gastric ulcer rates when compared to ibuprofen.

Accordingly, based upon the efficacy data provided by Study HZ-CA-303, one may conclude that the effect of study drug HZT-501 is better than that of ibuprofen on the risk reduction of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen.

3.2 Evaluation of Safety

3.2.1 Study HZ-CA-301

The applicant made the following conclusions for the safety assessments:

- No deaths were reported during the Treatment Period or during the four-week Follow-up Period.
- There were significantly fewer early terminations in the HZT-501 group (34.5%) compared to the ibuprofen group (42.5%; p-value 0.0500).
- The incidence of TEAEs (all AEs reported during this study were TEAEs) reported in the two treatment groups did not differ significantly (HZT-501, 53.0%; ibuprofen, 54.7%; p-value 0.7271).
- The most frequently reported TEAEs by preferred term were dyspepsia (HZT-501, 4.1%; ibuprofen, 8.5%), nausea (HZT-501, 4.6%; ibuprofen, 5.2%), and upper respiratory tract infection (HZT-501, 3.9%; ibuprofen, 5.2%).
- The gastrointestinal disorders SOC had the highest incidence of TEAEs; the incidence was similar in the two treatment groups (HZT-501, 25.8%; ibuprofen, 29.7%).
- The incidence of dyspepsia was statistically significantly lower in the HZT-501 group (4.1%) compared to the ibuprofen group (8.5%; p-value 0.0328). There were no other TEAEs that were statistically significantly different between the two treatment groups.
- The incidence of TEAEs in the cardiac disorders SOC was 0% in the HZT-501 group and 0.5% in the ibuprofen group.
- The incidence of TEAEs leading to discontinuation was similar in the two treatment groups (HZT-501, 6.7%; ibuprofen, 7.1%).
- The incidence of SAEs (HZT-501, 2.7%; ibuprofen, 1.9%) and the incidence of SAEs leading to discontinuation (HZT-501, 0.5%; ibuprofen, 0.9%) were similar in the two treatment groups.
- Changes from baseline in clinical laboratory parameters were generally small, were comparable between the two treatment groups, and were consistent with AEs listed in the prescribing information for ibuprofen and/or famotidine.

- No clinically important differences in vital sign measurements, physical examination findings, or other observations related to safety were observed between the two treatment groups.

3.2.2 Study HZ-CA-303

The applicant made the following conclusions for the safety assessments:

- One death was reported in the ibuprofen group; the death was attributed by the Investigator to acetaminophen (paracetamol) toxicity.
- There were significantly fewer early terminations in the HZT-501 group (28.7%) compared to the ibuprofen group (43.1%; p-value < 0.0001).
- The incidence of treatment-emergent adverse events (TEAEs) reported in the two treatment groups did not differ significantly (HZT-501, 56.3%; ibuprofen, 61.5%; p-value 0.1352). [All AEs reported during this study were TEAEs.]
- The most frequently reported TEAEs by preferred term were dyspepsia (HZT-501, 5.1%; ibuprofen, 7.7%), nausea (HZT-501, 6.6%; ibuprofen, 4.3%), and diarrhea (HZT-501, 4.9%; ibuprofen, 4.3%).
- The gastrointestinal disorders SOC had the highest incidence of TEAEs; the incidence was similar in the two treatment groups (HZT-501, 26.2%; ibuprofen, 27.4%).
- The incidence of dyspepsia was numerically lower in the HZT-501group (5.1%) compared to the ibuprofen group (7.7%).
- The incidence of TEAEs in the cardiac disorders SOC was 0.7% in the HZT-501 group and 1.3% in the ibuprofen group.
- The incidence of TEAEs leading to discontinuation was similar in the two treatment groups (HZT-501, 6.6%; ibuprofen, 8.0%), with the exception that the incidence of dyspepsia leading to discontinuation was significantly lower in the HZT-501 group (0.3%) compared to the ibuprofen group (2.3%; p-value 0.0064).
- The incidence of SAEs (HZT-501, 3.6%; ibuprofen, 4.3%) and the incidence of SAEs leading to discontinuation (HZT-501, 1.0%; ibuprofen, 0.7%) were similar in the two treatment groups.
- Changes from baseline in clinical laboratory parameters were generally small, were comparable between the two treatment groups, and were consistent with AEs listed in the prescribing information for ibuprofen and/or famotidine.
- No clinically important differences in vital sign measurements, physical examination findings, or other observations related to safety were observed between the two treatment

4.0 SUBGROUP ANALYSIS

4.1 Gender, Race, and Age

In order to assess the consistency of the treatment effect for HZT-501 relative to Ibuprofen across subgroups (identified by gender, age group, and race group), this reviewer performs

subgroup analysis applying Life Table analysis method to analyze the proportion of subjects who developed at least one upper gastrointestinal ulcer based upon primary patient population using data submitted (on 10/21/2010) in response to the Agency IR letter dated 10/05/2010 for Study HZ-CA-301 and data submitted (on 12/16/2010) in respond to the Agency IR letter dated 12/07/2010 for Study HZ-CA-303.

4.1.1 Study HZ-CA-301

For Study HZ-CA-301, it is noted that for the two subgroups classified by age and race, more than 80% of patients were enrolled in one category: 82.5% of patients with ages less than 65 and 82.6% of patients with White race. Accordingly, the subgroup analysis performed in this section is only for gender (Male and Female).

Gender group (Male vs. Female)

Table 4.1.1.1 presents the results of treatment efficacy comparisons by gender group (Male vs. Female).

Table 4.1.1.1 (Reviewer's) Proportion of Subjects developed at least one upper gastrointestinal ulcer using primary population

Males

	HZT-501 (H) (N=130)		Ibuprofen (I) (N= 54)		Difference (H- I)			
	Proportion[a]	SE[b]	Proportion	SE	Proportion	SE	95%CI	p-value[c]
All Subjects (N=184)	28.4 %	0.048	15.5%	0.050	12.9%	0.070	(-0.8%, 26.6%)	0.065

Females

	HZT-501 (H) (N=250)		Ibuprofen (I) (N= 136)		Difference (H- I)			
	Proportion[a]	SE[b]	Proportion	SE	Proportion	SE	95%CI	p-value[c]
All Subjects (N=386)	17.6 %	0.027	33.1%	0.045	-15.5%	0.053	(-25.7%, -5.1%)	0.0033

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

Table 4.1.1.1 shows that for the female patients, the proportion of Subjects developed at least one upper gastrointestinal for HZT-501 is significantly lower than that of Ibuprofen (p 0.0033) at the two-sided significance level of 0.05. However, the male patients, the proportion of Subjects developed at least one upper gastrointestinal for HZT-501 is even numerically higher than that of Ibuprofen (p 0.065) at the two-sided significance level of 0.05. A chi-square test shows that the interaction between treatment and gender is significant (p-value < 0.01).

We noted earlier that a treatment effect for this study was not shown in the overall population; the observed gender-treatment interaction further underscores the conclusion that data provided by this study did not provide persuasive evidence to support the study drug HZT-501 for the proposed indication.

4.1.2 Study HZ-CA-303

As mentioned in the section of "Overview" (section 2.1), data from site 389 are not reliable and therefore, are excluded from the subgroup analyses. In addition, after excluding patients from site 389, for the two subgroups classified by age and race, more than 80% of patients were enrolled in one category: 82.5% of patients had ages less than 65 and 84.5% of patients were classified as White. Accordingly, the subgroup analysis performed in this section is only for gender (Male and Female). Finally, data used for the subgroup analysis was submitted (on 12/16/2010) in response to the IR letter issued by the Agency on 12/07/2010.

Gender group (Male vs. Female)

Table 4.1.2.1 presents the results of treatment efficacy comparisons by gender group (Male vs. Female).

Table 4.1.2.1 (Reviewer's) Proportion of Subjects developed at least one upper gastrointestinal ulcer using primary population

Males

	HZT-501 (H) (N=147)		Ibuprofen (I) (N= 71)		Difference (H- I)			
	Proportion[a]	SE[b]	Proportion	SE	Proportion	SE	95%CI	p-value[c]
All Subjects (N=218)	16.9 %	0.038	37.9%	0.065	-21.0%	0.076	(-35.9%, -6.3%)	0.005

Females

	HZT-501 (H) (N=300)		Ibuprofen (I) (N= 145)		Difference (H- I)			
	Proportion[a]	SE[b]	Proportion	SE	Proportion	SE	95%CI	p-value[c]
All Subjects (N=445)	15.6 %	0.024	30.2%	0.045	-14.6%	0.051	(-24.6%, -4.7%)	0.0041

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

Table 4.1.2.1 shows that for both the male and female patients, the proportions of Subjects developed at least one upper gastrointestinal for HZT-501 are significantly lower than that of Ibuprofen (p 0.005 for males and p 0.0041 for females) at the two-sided significance level of 0.05.

4.2 Other Special/Subgroup Populations- Not applicable

5.0 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Study HZ-CA-301

The comments given below are based upon this reviewer's analysis result and the applicant's analysis results from the original NDA submission (dated 03/23/2010) along with the applicant's response (dated 10/21/2010) to the Agency's IR letter (dated 10/05/2010).

Comments on Upper gastrointestinal ulcer

- For the risk reduction on the upper gastrointestinal (GI) ulcer reported by the original NDA study dated 03/23/2010, HZT-501 showed superiority to ibuprofen with a borderline p-value (p 0.0304), close to the two-sided significance level of 0.05. However, this reviewer notes that for site 180 in the HZT-501 group, only one out of 14 patients identified to have upper gastrointestinal ulcer; the proportion of upper gastrointestinal ulcer in the HZT-501 group (7.0%) is 31% lower than that of the ibuprofen group (38%).
- The result of sensitivity analysis performed by this reviewer shows that after excluding data from site 180, the applicant's analysis of upper gastrointestinal ulcer rate of HZT-501 no longer shows a statistically significant lower rate compared to ibuprofen. Thus, the sponsor's claimed superiority of HZT-501 to ibuprofen assessed by the upper gastrointestinal ulcer rate is sensitive to individual site results.
- The applicant's Life Table analysis (submitted on 10/21/2010) on time to upper GI ulcer, included subjects as treatment failures who were early terminated and, as stated by the applicant, did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug. This analysis shows that HZT-501 did not significantly reduce the upper GI ulcer rate as compared to ibuprofen. In a T-Con held on 03/11/2011, the applicant agreed with the Agency that those early terminated patients without negative endoscopy for ulcer should have been included as having an ulcer in the Life Table analysis in the original NDA submission.
- Accordingly, based upon the results of this reviewer's sensitivity analysis and the applicant's Life Table analysis in response to the Agency IR letter dated 10/05/2010 regarding the inclusion of early terminated subjects as having an ulcer, Study HZ-CA-301 does not provide persuasive evidence to conclude that HZT-501 is significantly better than ibuprofen alone in reducing the upper gastrointestinal ulcer rate.

  In addition, the result of the crude rate analysis including early terminated subjects as having an ulcer (recommended by the Agency at the protocol stage) also indicated that HZT-501 did not significantly reduce the risk of developing upper GI ulcer when compared to ibuprofen.

Comments on Gastric and Duodenal ulcers

- First, the Life Table analysis result from the original study report dated 03/23/2010 showed that the proportion of subjects who developed at least one gastric ulcer for HZT-501 was not significantly lower than that of ibuprofen.
- In addition, the results from the crude rate analyses including early terminated subjects as having an ulcer (recommended by the Agency at the protocol stage) showed the results that were consistent with the Life Table analysis. Accordingly, HZT-501 did not demonstrate improvement over ibuprofen alone in reducing the gastric ulcer rate.
- Finally, we note that in the protocol, the reduction of the gastric ulcer rate was pre-specified as the first secondary-endpoint and the pre-specified Life Table analysis failed to demonstrate the superiority of HZT-501 over ibuprofen for reduction of the gastric ulcer rate. Then, by the fixed sequence (hierarchical) testing procedure pre-specified in the protocol, the duodenal ulcer rate which was pre-specified as the second secondary-endpoint could not be formally tested, and HZT-501 should not be considered effective for this endpoint, regardless of the rate observed.

Accordingly, based upon the efficacy data provided by Study HZ-CA-301, one may deem that the efficacy of the study drug HZT-501 is not supported with persuasive evidence for the proposed indication in reduction of the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen.

5.1.2 Study HZ-CA-303

The comments given below are based upon this reviewer's analysis and the applicant's results from the original NDA submission (dated 03/23/2010) and the applicant's response documents (dated 12/16/2010) to the Agency's IR letter (dated 12/07/2010) excluding data from site 389 which was deemed unreliable by site inspection. Although reducing the gastric ulcer rate is the primary endpoint for this study, the proposed indication was to reduce the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen. Accordingly, this reviewer gives comments on the upper GI ulcer first and comments on the gastric ulcer follow.

Comments on Upper gastrointestinal ulcer

- First, from this reviewer's efficacy comparison by site assessed based upon the proportions of upper gastrointestinal ulcer, we note that no particular site abnormally dominates the superiority of HTZ-501 to ibuprofen claimed by the applicant.
- In addition, the results of Life Table analyses from both the original NDA study report and the applicant's response document (dated 12/16/2010) to the IR letter issued on 12/07/2010 all indicate that study drug HZT-501 significantly reduces the risk of having upper gastrointestinal ulcer when compared to ibuprofen. We note that the applicant's re-analysis on time to upper gastrointestinal ulcer used the primary population excluding data from site 389 and including subjects who were early terminated and (as stated by the applicant) did not have a negative endoscopy for ulcer within 14 days of the last dose of study drug as having an ulcer.

- Finally, the results of the crude rate analyses including early terminated patients as having an ulcer (as recommended by the Agency in the protocol stage) using the primary population with and without data from site 389 all show HZT-501 as significantly reducing the upper gastrointestinal ulcer rate when compared to ibuprofen. As a consequence, the effect of HZT-501 on the reduction of upper gastrointestinal ulcer rate, compared to ibuprofen alone, has been adequately demonstrated.

Comments on Gastric ulcer

- For the gastric ulcer occurrence, the results of Life Table analyses from both the original NDA study report and the applicant's response documents to the IR letter issued on 12/07/2010 all showed that HZT-501 significantly reduces the risk of gastric ulcer when compared to ibuprofen.

Comments on Duodenal ulcer

- Similarly, for the Duodenal ulcer, the results of Life Table analyses from both the original NDA study report and the applicant's response document to the IR letter issued on 12/07/2010 all showed that HZT-501 significantly reduces the risk of duodenal ulcer when compared to ibuprofen.

It is noted that additionally excluding data from the four subjects from site 363 identified as non-reliable by the Division of Scientific Investigations on 03/10/2011, the results from the Life Table analyses and crude rate analyses on the three types of ulcers (upper GI, gastric, and duodenal ulcers) are unaffected.

Accordingly, based upon the efficacy data provided by Study HZ-CA-303, one may conclude that the effect of study drug HZT-501 is supported with persuasive evidence for the proposed indication of reduction of the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen.

5.2 Conclusions and Recommendations

In this original NDA application, Horizon Therapeutics, Inc. submitted two randomized, double-blind, multicenter studies HZ-CA-301 and HZ-CA-303 to support the use of HZT-501 for the proposed indication: reduction of the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen. The pre-specified primary analysis method was based on Life Table analysis. Key supportive (sensitivity) analyses were based on crude rates.

Based upon this review, we conclude that only Study HZ-CA-303 provides a persuasive level of evidence of efficacy in support of the intended indication. Study HZ-CA-301does not provide persuasive evidence since its conclusions depend on the assumed outcomes of early terminated subjects. If subjects who discontinued the study early are treated as ulcer patients, efficacy of the study drug based on the Life Table analysis could not be demonstrated. Based on a crude rate analysis, efficacy comparisons for Study 301 were also not statistically significant.

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/s/

WEN JEN CHEN
03/28/2011

MICHAEL E WELCH
03/28/2011
Concur with review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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

Drug Name: HTZ501 **NDA/BLA Type:** Original NDA **Indication:** Risk reduction of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.			**X**	Only Electric Submission.
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Efficacy was investigated for gender, racial, and geriatric subgroups investigated.	X			Sample size might be inadequate for gender and racial subgroup analyses
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			However, primary endpoint for life table analysis can not be identified.

IS THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE ? Yes

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	**X**			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**X**			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			**X**	
Appropriate references for novel statistical methodology (if present) are included.	**X**			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	**X**			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	**X**			

Background

The purpose of this original NDA application submitted by Horizon Therapeutics, Inc. is to support the use of HTZ-501 for the proposed indication: reduction of the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal) ulcers in patients who require use of ibuprofen.

For Study HZ-CA-301, the primary objective is to evaluate the efficacy of HZT-501 in reducing the proportion of subjects who develop at least one *endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer* (of unequivocal depth and at least 3 mm in diameter) during the 24-week Treatment Period, as compared to ibuprofen, in subjects at risk for NSAID-induced ulcers. However, for Study HZ-CA-303, the primary objective is to evaluate the efficacy of HZT-501 in reducing the proportion of subjects who develop at least one *endoscopically-diagnosed gastric ulcer* (of unequivocal depth and at least 3 mm in diameter) during the 24-week Treatment Period, as compared to ibuprofen, in subjects at risk for NSAID-induced ulcers.

Accordingly, for Study HZ-CA-301, the primary endpoint is the proportion of subjects who developed *at least one endoscopically-diagnosed upper gastrointestinal ulcer* during the 24-week Treatment Period while for Study HZ-CA-303, the primary endpoint is the proportion of subjects who developed *at least one endoscopically-diagnosed gastric ulcer* during the 24-week Treatment Period.

Review Issues

For Study HZ-CA-301, the result for the secondary endpoint (proportion of subjects who developed at least one endoscopically-diagnosed gastric ulcer) analysis did not show that the effect of HTZ-501 is superior to that of Ibuprofen (p 0.08). Since the secondary endpoint for Study HZ-CA-301 was the primary endpoint for Study HZ-CA-303, the positive result for the primary endpoint analysis for Study HZ-CA-303 was not replicated.

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

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/s/

WEN JEN CHEN
05/13/2010

MICHAEL E WELCH
05/13/2010