CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

REV-BIOMETRICS-02 (Review Noted (NAI))
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This is a Complete Response (CR) resubmission of NDA 205103 for YOSPRALA (aspirin/omeprazole) delayed release tablets, for use in the secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers, to the Complete Response (CR) letter dated April 25, 2014. The CR letter identified two issues regarding facility inspections and labeling. This submission contains the responses to the CR letter, revised product labeling and safety update requested by the CR letter. Since this submission contains no new clinical efficacy data for this formulation and the indication being pursued, a formal statistical evaluation is not needed.

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/s/

FREDA COONER
10/06/2014

Statistical Team Leader Memorandum

Submission: NDA 205103/000
Product: Yosprala® (aspirin and omeprazole tablet)
Sponsor: POZEN Inc.
Indication: Secondary prevention of cardio- and cerebro-vascular events in patients at risk of developing aspirin-associated gastric ulcers.
Medical Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Reference: Statistical Review and Evaluation dated March 28, 2014.

The purpose of this memorandum is to summarize conclusions regarding the statistical issues discussed in the primary reviewer's evaluation of the original NDA submission, and to present the Team Leader's perspective on the study results.

The products for this application are PA8140 and PA32540 tablets (PA tablets) containing 81 mg and 325 mg delayed release aspirin, respectively, and 40 mg immediate release (IR) omeprazole. This is a 505(b)(2) submission to establish a bridge between the PA tablets (PA8140 and PA32540) and the reference listed drugs (RLD) Ecotrin® (325 mg and 81 mg), and to demonstrate the benefit of IR-omeprazole.

Two identically designed, adequate and well-controlled studies (PA32540-301 and PA32540-302) were concurrently conducted to investigate the efficacy of the PA32540 tablet. The sponsor is also seeking marketing approval of the PA8140 tablet, which has not been investigated in any phase 3 efficacy studies. Both PA8140 and PA32540 tablets are intended for use as a once a day (QD) therapy in the secondary prevention of cardiovascular and cerebrovascular events in patients at risk for developing aspirin-associated gastric ulcers.

The primary endpoint was the proportion of subjects developing gastric ulcers throughout six months of study treatment. The reviewer refers to this definition as "cumulative" rate and states in Section 3.1.1.4.1.1 that it is "the same as last-observation carried-forward (LOCF) analysis of this endpoint". It should be clarified that the definition of the primary endpoint precludes implementation of the LOCF method for missing data imputation. For the primary analysis, only the subjects with endoscopic finding of gastric ulcer during the 6-month treatment period were counted as having gastric ulcer. As pre-specified, all other subjects were counted as gastric-ulcer free. These subjects included those who had six-month endoscopic results free of gastric ulcer or who discontinued before the study completion (either without endoscopic results or with endoscopic results showing no gastric ulcer). Conventionally, discontinued subjects are treated as "non-responders" or having gastric ulcers in this case. However, due to the fact that the comparator 325 mg EC-aspirin arm had more discontinuations than the treatment PA32540 arm in both studies, this conventional method would over-estimate the treatment effect. In other words, the pre-specified method of assuming discontinued subjects as gastric-ulcer free was conservative from our perspective.

The reviewer conducted exploratory analyses using "crude rate", where "the subjects who were withdrawn prior to the study completion were assumed to be non-responders" (having gastric

ulcer) as defined by the reviewer. Although the definition coincides with the conventional method mentioned above, the results presented in Sections 3.1.1.4.1.2 and 3.1.2.3.1.1 of the primary review did not match the reviewer's definition. Instead, the results were the same as those from the primary analysis where discontinuations were counted as gastric-ulcer free. Moreover, the reviewer used the Fisher's exact test when the assumptions underlying the FDA recommended Cochran–Mantel–Haenszel (CMH) test statistics are defensible, and the proper p-value for the primary comparison should be based on that pre-specified CMH analysis.

Extensive sensitivity analyses using different imputation methods on the missing data, including the worst-case analysis, were requested by the FDA and conducted by the sponsor. All the results showed favorable treatment effect for PA32540 comparing to EC-aspirin. The statistical significance stated in the primary review should be viewed with caution due to the exploratory nature of these sensitivity analyses. One should note that the aspirin-associated ulcer rate is generally low and with the relatively high discontinuation rates in both treatment arms, it is expected that some sensitivity analyses would generate p-values less than 5%. However, the results of these analyses, including the p-values, are exploratory only.

Some additional exploratory analyses results were also presented and/or discussed in the primary review. These analyses included the treatment comparisons on 1-month and 3-month gastric ulcer rates, and the reviewer's Fisher's exact test on the primary endpoint. The statistical significance of the results should also be viewed with caution due to their exploratory nature. Inferential statistics associated with these exploratory analyses are not suitable for the labeling.

In summary, the two phase 3 studies (PA32540-301 and PA32540-302) showed statistically significant benefit of the PA32540 tablet, compared to 325 mg EC-aspirin, as demonstrated by the primary efficacy endpoint and the four secondary and tolerability endpoints. These endpoints were pre-specified in the protocol and properly controlled for multiplicity.

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/s/

FREDA COONER
03/28/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA#:	205,103
Drug Name:	Yosprala PA8140 and PA32540 (aspirin/omeprazole) Tablet
Indication:	Use in the secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers
Applicant:	Pozen Inc.
Date:	Receipt date: March 25, 2013; PDUFA goal date: January 24, 2014 (extended to April 25, 2014)
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Milton C. Fan, Ph.D., DB III
Concurring Reviewers:	Freda Cooner, Ph.D., Team Leader, DB III
Medical Division:	Gastroenterology and Inborn Errors Products (DGIEP)
Clinical Team:	Zana Marks, M.D., Robert Fiorentino, M.D. (TL) (DGIEP)
Project Manager:	Stacy Barley (DGIEP)

Keywords: clinical studies, NDA review, placebo-controlled

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Two studies, Studies PA32540-301 and PA32540-302, were conducted to evaluate PA32540 as compared to enteric-coated (EC)-aspirin 325 mg to support the proposed indication:

In both Studies PA32540-301 and PA32540-302, the cumulative proportion of subjects developing gastric ulcers throughout six months was significantly lower with PA32540 vs. EC aspirin 325 mg. The treatment differences were 5% in Study PA32540-301 and 6% in Study PA32540-302.

1.2 Brief Overview of Clinical Studies

Studies PA32540-301 and PA32540 were identically design as a 6-month, phase 3, multi-center, randomized, double-blind, parallel-group, controlled trial to evaluate the incidence of gastric ulcers following administration of either PA32540 or EC aspirin 325 mg in subjects who are risk for developing aspirin-associated ulcer.

The primary objective of these studies was to demonstrate that PA32540 causes fewer gastric ulcers in subjects at risk for developing aspirin-associated gastric ulcers compared to EC aspirin 325 mg.

The secondary objectives were:

- To demonstrate that PA32540 causes fewer gastric and/or duodenal ulcers in subjects at risk for developing aspirin-associated ulcers compared to EC aspirin 325 mg;
- To compare between treatments, the proportion of subjects with "Treatment Success", defined as those subjects without gastric ulcers and without upper gastrointestinal (UGI)adverse events (AEs) leading to discontinuation;
- To compare between treatments, the proportion of subjects discontinuing the study due to UGI AEs;
- To compare between treatments, the proportion of subjects with heartburn resolution, defined as the answer "None" on the heartburn assessment question;
- To evaluate the overall safety of PA32540 as compared to EC aspirin 325 mg.

Each study began with a screening period followed by a double-blind treatment period. After all entrance criteria were satisfied, subjects were randomized to either PA32540 or EC aspirin 325 mg, taken orally, once daily.

1.3 Statistical Issues and Findings

Two studies, Studies PA32540-301 and PA32540-302, were conducted to evaluate PA32540 as compared to EC aspirin 325 mg to support the proposed indication.

In both studies, if an UGI ulcer was detected, the subject would be discontinued from the study. Interim endoscopies could be performed if clinically indicated. Ulcer was pre-specified as of size greater than or equal to 3 mm.

This reviewer performed analyses of the crude rate and the modified crude rate using the Fisher's exact test. For the crude rate analysis, the subjects who were withdrawn prior to completion of the study were considered non-responders. This turns out to be the same as the primary analysis. For the modified crude rate analysis, the subjects who were withdrawn prior to completion of the study were excluded from the analysis. This turns out to be the same as the completed-case analysis.

Both analyses of developing gastric ulcer though six months using the Fisher's exact test showed statistically significant lower rates with the PA32540 treatment than with EC aspirin 325 mg treatment.

Per this reviewer's request, the applicant performed an analysis on the cumulative proportion of subjects developing gastric ulcers, duodenal ulcer, gastric and/or duodenal ulcers throughout six Month, where ulcer is defined as of size greater than or equal to 5 mm.

The results revealed a statistically significantly lower rate with PA32540 treatment than with EC aspirin 325 mg treatment for developing gastric ulcer, and gastric and/or duodenal ulcer.

2. INTRODUCTION

2.1 Overview

PA8140 (aspirin 81mg/omeprazole 40 mg tables) and PA32540 (aspirin 325 mg/omeprazole 40 mg tablets) was developed by the applicant as a delivery formulation of PA tablets allows omeprazole to be immediately release while the release of aspirin from the core is delayed dependent on the pH value. The applicant developed PA tablets to ensure that subjects who require chronic aspirin therapy will always receive a preceding omeprazole 40 mg.

The applicant is seeking marketing approval for PA8140 and PA32540 for the following indication.

(b) (4)

2.2 Data Sources

The applicant submitted Special Protocol Assessment (SPA) under IND 78,747 S/N 007 on June 4, 2008. Statistical consultation was performed and documented. A non-agreement letters was issued on July 29, 2008.

The applicant also submitted Statistical Analysis Plan (SAP) for Studies PA32440-301 and PA32540-302 on September 1, 2011. Statistical Review and Evaluation was performed and documented on November 28, 2011. An advice letter was issued on November 29, 2011.

The comments to the applicant were:

- We recommend your primary analysis use a CMH test stratified by the three NSAID use strata used for the randomization (Cox-2, other NSAID, or no NSAID users). Your proposed CMH test can be used as a supportive analysis.
- Your primary analysis should be based on the ITT population defined as all randomized subjects. Your proposed ITT population is a modified ITT (mITT) population that can be used for a supportive or sensitivity analysis.
- Expand your sensitivity analyses on the primary efficacy endpoint to investigate the impact of missing data on the efficacy conclusions. These could include completed-case, observed-case, worst-case, and multiple imputation methods.

The applicant has submitted two phase 3 studies (PA32540-301 and PA32540-302) for the proposed indication:

These two studies were entitled as follows:

- Study PA32540-301: A 6-Month, Phase 3, Randomized, Double-Blinded, Parallel-Group, Controlled, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either PA32540 or Enteric-Coated Aspirin 325 mg in Subjects Who Are at Risk for Developing Aspirin 325 mg .

- Study PA32540-302: A 6-Month, Phase 3, Randomized, Double-Blinded, Parallel-Group, Controlled, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either PA32540 or Enteric-Coated Aspirin 325 mg in Subjects Who Are at Risk for Developing Aspirin 325 mg

This original submission of this NDA was submitted in eCTD dated March 25, 2013.

The electronic submission can be viewed through
\\cdsesub1\EVSPROD\NDA205103\205103.enx

The applicant submitted response on June 14, 2013, to this reviewer's Information Request dated May 31, 2013.

The applicant submitted response on October 18, 2013, to this reviewer's Information Requests dated October 4, 2013 and October 11, 2013.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study PA32540-301

3.1.1.1 Study Design

This study was a 6-month, phase 3, multi-center, randomized, double-blind, parallel-group, controlled trial to evaluate the incidence of gastric ulcers following the administration of either PA32540 or enteric coated (EC) aspirin 325 mg in subjects who are at risk for developing aspirin-associated ulcer.

The primary objective of this study is to demonstrate that PA32540 causes fewer gastric ulcers in subjects at risk for developing aspirin-associated gastric ulcers compared to EC aspirin 325 mg.

The secondary objectives were:

- To demonstrate that PA32540 causes fewer gastric and/or duodenal ulcers in subjects at risk for developing aspirin-associated ulcers compared to EC aspirin 325 mg;
- To compare between treatments, the proportion of subjects with "Treatment Success", defined as those subjects without gastric ulcers and without upper gastrointestinal (UGI) adverse events (AEs) leading to discontinuation;
- To compare between treatments, the proportion of subjects discontinuing the study due to UGI AEs;
- To compare between treatments, the proportion of subjects with heartburn resolution, defined as the answer "None" on the heartburn assessment question;
- To evaluate the overall safety of PA32540 as compared to EC aspirin 325 mg.

The study began with a screening period followed by a double-blind treatment period. After all entrance criteria were satisfied, subjects were randomized to either PA32540 or EC aspirin 325 mg, taken orally, once daily.

Randomization was stratified based on chronic non-steroidal anti-inflammatory drugs (NSAIDs) use at baseline. Eligible subjects were stratified into three groups: 1) non-specific NSAID users; 2) Cox-2 users; and, 3) subjects not currently on NSAIDs or Cox-2.Subjects taking NSAIDs were instructed to continue their prescribed NSAID therapy and report any changes to the

Investigator. Chronic NSAID use was defined as at least five days/week per prescribed dosage. Subjects were asked to report NSAID use monthly to site staff.

Subjects returned at one month (Visit 4) and three months (Visit 5) for safety assessments, an endoscopy and additional study drug. Also during each visit, subjects were asked about adverse events, NSAID use, and heartburn symptoms. If an UGI ulcer was detected, study drug would be discontinued, and the subject would be discontinued from the study and placed on appropriate medication, such as PPI, for treatment of the ulcer. Interim endoscopies could be performed if clinically indicated.

Subjects completing six months of therapy returned for a final visit at which final visit procedures, including an endoscopy would be performed.

The main criteria for inclusion were:

1. Male or non-pregnant, non-breastfeeding females who have been on daily aspirin 325 mg for at least three months and who are expected to use daily aspirin 325 mg for at least six months (daily is defined as "at least five days per week"):
   and, who are
   - 55 years of age and older;

   or
   - 18 - 54 years of age and have a history of a documented gastric or duodenal ulcer within the past five years.

2. Aspirin use should be for the secondary prevention of cardiovascular or cerebrovascular events as defined as follows:
   Have been diagnosed with or have had a history of
   - MI (myocardial infarction that has been confirmed or suspected),
   - Ischemic stroke,
   - TIA (transient ischemic attack),

   or have established, clinically significant coronary and other atherosclerotic vascular disease (meaning at high risk for surgical intervention or for MI, TIA, stroke, if left untreated), including:
   - Angina (stable or unstable),
   - Peripheral arterial disease,
   - Atherosclerotic aortic disease,
   - Carotid artery disease,

   or have had
   - CABG (coronary artery bypass graft),
   - PCI (percutaneous coronary intervention with or without stent),
   - Carotid endarterectomy.

The main criteria for exclusion were:

1. Baseline endoscopy showing any gastric, esophageal or duodenal ulcer at least 3 mm in diameter with depth;

2. Positive test result for *H. pylori* at screening;
3. Have had a revascularization procedure (i.e., CABG, PTCA or carotid endarterectomy) less than six months prior to screening;
4. Unstable hypertension as judged by the Investigator;
5. Uncontrolled diabetes mellitus as judged by the Investigator;
6. Unstable cardio- or cerebrovascular disease such that it would endanger the subject if they participated in the trial;
7. Clinically significant valvular disease;
8. Congestive heart failure or other cardiovascular symptoms according to New York Heart Association (NYHA) Functional Classification III or IV;
9. History of serious UGI event, such as bleeding, perforation, or obstruction;
10. Gastrointestinal disorder or surgery leading to impaired drug absorption;
11. Presence of chronic or uncontrolled acute medical illness, e.g. gastrointestinal disorder (esophageal stricture, severe esophagitis, long-segment Barrett's esophagus, signs and symptoms of gastric outlet obstruction), thyroid disorder and/or infection that would endanger a subject if they were to participate in the study;
12. History of alcoholism or drug addiction within a year prior to enrollment in the study
13. Severe hepatic dysfunction (i.e., cirrhosis or portal hypertension);
14. Blood coagulation disorder, including use of systemic anticoagulants such as warfarin or other vitamin K antagonists.

Efficacy was assessed by gastroduodenal endoscopy at Screening (Visit 2), Visit 4 (Day 30), Visit 5 (Day 90 and Final Visit (Day 180) and by heartburn assessment at Baseline (Visit 3), Visit 4, Visit 5 and Final Visit.

The actual assessment dates were used to define the "study day" on which assessments occurred relative to the randomization date. Visit windows for efficacy analyses were based on the actual study days outlined in the table below.

Visit Windows

Visit	Planned Visit Day	Visit Window Based on Actual Study Day (Day – Day)
1 Month	30 ± 6	1-36
3 Months	90 ± 12	37-108
6 Months	180 ± 12	≥109

The endoscopic assessment date was used to calculate the window for the subjects categorized as 'Gastric Ulcer' or 'Maintained Gastric Ulcer-Free'; the window for subjects categorized as 'Discontinued Gastric Ulcer-Free' was calculated from the date of randomization to the date of withdrawal (the last date the subject was seen at the investigator site for study assessments).

The gastroduodenal ulcer analysis followed the same data handling rules as those for the gastric ulcer analysis.

Study drug should be discontinued for a given subject if the Investigator determines that continuing might result in a significant safety risk for that subject. The following circumstances also required study drug discontinuation:

- Upper gastrointestinal ulceration
- Pregnancy
- A confirmed > 2.0g/dL decrease in hemoglobin

Subjects, who discontinued study drug before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit would be performed.

A subject was considered to have completed the study if either one of the following criteria is met:

- Completion of six months of study drug treatment and the six month endoscopy
- Endoscopic confirmation of a gastric ulcer at any time during study drug treatment, including at the six month visit

Note that subjects with duodenal or esophageal ulcers detected at any time during study drug treatment were not considered completers.

3.1.1.2 Pre-specified Analysis

The primary efficacy variable was the cumulative incidence of gastric ulcers at any time throughout six months of treatment.

An ulcer was defined as a mucosal break of at least 3 mm in diameter (measured by e.g., close application of open endoscopic biopsy forceps) with depth. Endoscopies were performed at Screening Visit 2 prior to randomization and at one, three and six months during the treatment period. The applicant claimed effort was made to have the same endoscopist performing all endoscopies for a given subject.

The secondary efficacy variable was the cumulative incidence of gastric and /or duodenal ulcers at any time throughout the six months of treatment. A duodenal ulcer was defined as a mucosal break of at least 3 mm in diameter with depth.

The tolerability endpoints were:

- Proportion of subjects with “Treatment Success”, defined as those subjects without gastric
- ulcers and without UGI AEs leading to discontinuation;
- Incidence of subjects discontinuing the study due to UGI AEs at any time throughout six months of treatment;
- Incidence of subjects with heartburn resolution, defined as the answer “None” at the post-baseline heartburn symptom assessment. At baseline and one, three and six months all

subjects were asked the following question regarding heartburn symptoms within the seven days prior to the visit:

- Over the last seven days, please rate your heartburn symptoms as

None: No symptoms;

Mild: Awareness of symptom, but easily tolerated;

Moderate: Discomforting symptom sufficient to cause interference with normal activities (including sleep);

Severe: Incapacitating symptom, with inability to perform normal activities (including sleep);

Heartburn definition - A burning feeling rising from the stomach or lower part of the chest towards the neck.

The intent-to-treat (ITT) population consisted of all randomized subjects who received at least one dose of study drug and had no ulcer detected by endoscopy at screening. Subjects who had ulcers detected on the screen endoscopy or did not take any medication were excluded from the modified intent-to-treat (mITT) population. All efficacy analyses were performed using the ITT population. Following the ITT principle, subjects were analyzed according to the treatment they are assigned to at randomization.

All subjects in the ITT population who did not violate the protocol in any major way that would impact the evaluation of efficacy constituted the per protocol (PP) population. Subjects who were excluded from the PP population were identified prior to the unblinding of the treatment code and the reason for exclusion was documented.

The safety population consisted of all randomized subjects who receive at least one dose of study drug.

For the baseline characteristics, qualitative data, such as, gender, race, age group, and history of gastric or duodenal ulcer will be presented in frequency tables. Quantitative data will be summarized by means of quantitative descriptive statistics (n, mean, median, standard deviation, minimum, and maximum).

The primary analysis population was conducted on the Intent-to-Treat (ITT). The primary efficacy endpoint was analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by NSAID use [Yes (COX-2 or other)/ No] at randomization. No centers were pooled for analysis purposes, as the analysis of the primary endpoint was not adjusted for center differences.

The ITT population was also used for analyses of secondary key and tolerability endpoints.

The treatment comparisons were performed for the following key secondary efficacy and tolerability endpoints in a sequential order as shown below:

1. The proportion of subjects with observed gastric and/or duodenal ulcer
2. The proportion of subjects with "Treatment Success", defined as those subjects without gastric ulcers and without UGI adverse events leading to discontinuation
3. The proportion of subjects discontinuing the study due to UGI AEs
4. The proportion of subjects with heartburn resolution, defined as the answer "None" on the heartburn assessment question; heartburn results were be tabulated by the baseline severity for each treatment group

Since the comparisons of the key secondary efficacy and tolerability endpoints were in sequential order, the hierarchical fixed-sequence testing approach was used to adjust for multiple comparisons. These endpoints were be tested in the specified sequence above with the rule that once a p-value exceeded 0.05, endpoints further down in the sequence would not be claimed for statistical significance.

Comparison between the treatment groups for the key secondary and the tolerability endpoints were performed using a CMH test, stratified by NSAID use at randomization.

The analyses for primary and key secondary endpoints were repeated using the Per-Protocol (PP population as a supportive analysis. In addition, supporting analyses of the primary endpoint, using other covariates and various censoring methods, was conducted to demonstrate sensitivity of the primary analysis.

The determination of the sample size was based on the assumption that 13% of subjects treated with EC aspirin 325 mg would have a gastric ulcer over the six months study duration compared to 5% of subjects treated with PA32540. The Fisher's exact test, with a two-sided significance level of 5% and 86% power required 250 subjects per treatment arm to detect the difference between EC aspirin 325 mg and PA32540. The applicant stated this sample size provided adequate power to test each of the key secondary and tolerability endpoints.

3.1.1.3. Applicant's Analysis

A total of 847 subjects were screened for the study at 91 centers. Of these, 317 subjects were screening failures and not selected for the study; the primary reasons of the screening failures were not meeting the inclusion/exclusion criteria, ulcer detected at screening endoscopy, positive *H. pylori* test, withdrawn consent, or laboratory test results.

A total of 530 subjects (265 per treatment group) were randomized to study drug at 78 centers, and were included in the ITT population. The majority of the study centers enrolled less than 10 subjects (58 of 78 centers). No center enrolled more than 5.8 % (31subjects) of total population. The first subject was randomized on 10 November 2009 and the last subject completed the study on 30 January 2012.

3.1.1.3.1 Patient Disposition

Approximately 82% of the subjects in the PA32540 group and 75% of the subjects in the EC aspirin 325 group completed the study (i.e., completed 6 months of treatment and had a 6-month endoscopy or developed gastric ulcer). In both treatment groups, the primary reason for study withdrawal was AEs. Subject disposition of this study is given in the table below.

Table 1 Study Disposition
Study PA32540-301

	PA32540 N = 265	EC-Aspirin 325 mg N = 265
Subjects randomized	265 (100%)	265 (100%)
Subjects completed [1]	218 (82.3%)	198 (74.7%)
Subjects withdrawn prior to completion	47 (17.7%)	67 (25.3%)
Adverse event	18 (6.8%)	33 (12.5%)
Withdrew consent	10 (3.8%)	10 (3.8%)
Lost to follow-up	3 (1.1%)	3 (1.1%)
Other [2]	16 (6.0%)	21 (7.9%)

Source: Table 14.1.1, Listing 16.2.1.
[1] Completed 6 months of treatment and had 6-month endoscopy or developed gastric ulcer prior to 6 months.
[2] Includes violations of inclusion/exclusion criteria, proscribed medications, clinically significant changes in laboratory values, protocol non-compliance, and site closure; 8 or fewer subjects were included in these categories.

3.1.1.3.2 Analysis Population

One subject (2301) was randomized to PA32540, but was dispatched the wrong medication kit/material and actually received EC aspirin 325 mg; this subject completed the study. All of the efficacy data for this subject were included in the ITT and mITT analyses for his randomized treatment (PA32540). However, efficacy data for this subject were excluded from the PP efficacy analyses, and his safety data were excluded from the PA32540 group and included in the EC aspirin 325 mg group.

Three subjects (one in the PA32540 group and two in the EC aspirin 325 mg group) were excluded from the mITT population, because two subjects (one in each group) had ulcers detected on the screening endoscopy and one subject in the EC aspirin 325 mg group did not take any study medication.

Approximately 97% of the subjects in each treatment group were included in the PP population (seven subjects in the PA32540 group and nine subjects in the EC aspirin 325 mg group were excluded). Use of a proscribed concomitant medication was the primary reason for exclusion from this population.

3.1.1.3.3 Treatment Group Comparability

A summary of the demographic and other baseline characteristics, ulcer history and NSAID use at randomization, cardiovascular and cerebrovascular histories, co-morbidities, and clopidogrel use at randomization, by treatment groups are presented in Appendix Tables 1 to 3.

As seen from Appendix Table 1, in the PA32540 and EC aspirin 325 mg treatment groups of the ITT population, subjects were predominantly male (71% and 72%, respectively), White (93% and 86%, respectively), and of Non-Hispanic/Latino origin (91% and 93%, respectively). Overall, subjects ranged in age from 41 to 88 years, and the median age was 66 years in both treatment groups.

As seen from Appendix Table 2, approximately 5% of the subjects in each treatment group reported an ulcer occurrence within the previous five years prior to study enrollment. When subjects were queried as to the occurrence of an ulcer at any time in their past, more subjects reported a history of gastric ulcers than duodenal ulcers. In both treatment groups, less than 10% of the subjects were taking an NSAID at the time of randomization.

As seen from Appendix Table 3, the administration of aspirin as secondary prevention was used predominantly in patient with histories of cardiac disorders (89% for PA32540 and 82% for EC aspirin 325 mg) rather than neurological disorders (21% for PA32540 and 24% for EC aspirin 325 mg); coronary artery disease was the primary cardiac history (69% for PA32540 and 64% for EC aspirin 325 mg), followed by MI (43% for PA32540 and 38% for EC aspirin 325 mg). With the exception of stroke, the distribution of cardiac and neurological histories was comparable in the two treatment groups. Strokes were slightly more prevalent among EC aspirin 325 mg subjects than among PA32540 subjects (17% vs. 11%).

Approximately 22% of the subjects randomized to PA32540 and 20% of the subjects randomized to EC aspirin 325 mg were taking clopidogrel at the time of randomization.

3.1.1.3.4 Applicant's Analysis of the Primary Efficacy Endpoint

Results of the analysis on the cumulative proportion of subjects who developed gastric ulcers are summarized in the table below.

Table 2 Analysis of Cumulative Proportion (n, %) of Subjects Developed Gastric Ulcers through 1, 3, and 6 Months
ITT Populatio5n
Study PA32540-301

Timepoint Ulcer Status	PA32540 N = 265	EC-Aspirin 325 mg N = 265	p-Value [1]
0-1 Month			
Gastric ulcer	3 (1.1%)	10 (3.8%)	0.046
95% CI	(0.2% – 3.3%)	(1.8% – 6.8%)	
Gastric ulcer-free	262(98.9%)	255(96.2%)	
Maintained [2]	242(91.3%)	230(86.8%)	
Discontinued	20 (7.5%)	25 (9.4%)	
0-3 Months			
Gastric ulcer	8 (3.0%)	18 (6.8%)	0.044
95% CI	(1.3% – 5.9%)	(4.1% – 10.5%)	
Gastric ulcer-free	257(97.0%)	247(93.2%)	
Maintained [2]	216(81.5%)	197(74.3%)	
Discontinued	41(15.5%)	50(18.9%)	
0-6 Months			
Gastric ulcer	10 (3.8%)	23 (8.7%)	0.020
95% CI	(1.8% – 6.8%)	(5.6% – 12.7%)	
Gastric ulcer-free	255(96.2%)	242(91.3%)	
Maintained [2]	208(78.5%)	175(66.0%)	
Discontinued	47(17.7%)	67(25.3%)	

Source: Tables 14.2.1.1 (0-6 months) and 14.2.1.4 (0-1 and 0-3 months).
[1] P-value for ulcer occurrence from CMH test stratified by NSAID use (use=COX-2, other NSAID, or use=no) at time of randomization.
[2] Maintained=continued in study.

As shown in the table above, the cumulative proportion of ITT subjects who developed gastric ulcers through six months was statistically significantly lower with the PA32540 treatment than with the EC aspirin 325 mg treatment.

Results of the analysis on the cumulative proportion of subjects who developed gastric ulcers in the mITT and PP populations are summarized in Appendix Tables 4 and 5.

As seen from Appendix Tables 4 and 5, similar findings were observed in the mITT and PP populations. Incidences of gastric ulcers through six months of treatment were statistically significantly lower in the PA32540 group than in the EC aspirin group for both the mITT population and the PP population.

3.1.1.3.4.1 Sensitivity Analyses

To confirm the robustness of the primary analysis results, the applicant performed the following three sensitivity analyses (FDA's comments ion the statistical analysis plan (SAP) in the advice letter dated November 29, 2011) on the primary endpoint:

- "Completed-Case" analysis: analysis of the subgroup of Completers (defined as either 6 months of study treatment with a 6-month endoscopy or presence of gastric ulcer confirmed by endoscopy prior to 6 months).
- "Observed-Case" analysis: analysis of the subgroup of Completers and subjects who withdrew prematurely but had at least one post-baseline endoscopy (last endoscopy during the study was used in this analysis).
- "Worst-Case" analysis: analysis of the ITT population in which subjects who discontinued without the final endoscopy were imputed to have a gastric ulcer, unless an ulcer-free endoscopy occurred within a 14-day window of the last dose of study drug.

The results of sensitivity analyses on the primary endpoint are summarized below.

Table 3 Sensitivity Analyses on Cumulative Proportion of Subjects Developed Gastric Ulcers through 6 Months ITT Population Study PA32540-301

	PA32540 N = 265		EC-Aspirin 325 mg N = 265		p-Value [1]
Gastric Ulcer Through 0-6 Months	N	n (%)	N	n (%)	
Completed-Case Analysis [2]	218		198		
Gastric Ulcer		10 (4.6%)		23(11.6%)	0.008
Gastric Ulcer-Free		208(95.4%)		175(88.4%)	
Observed-Case Analysis [3]	255		250		
Gastric Ulcer		10 (3.9%)		23 (9.2%)	0.017
Gastric Ulcer-Free		245(96.1%)		227(90.8%)	
Worst-Case Analysis [4]	265		265		
Gastric Ulcer		35(13.2%)		48(18.1%)	0.120
Gastric Ulcer-Free		230(86.8%)		217(81.9%)	

Source: Tables 14.2.1.7 (completed-case), 14.2.1.8 (observed-case), and 14.2.1.9 (worst-case).
[1] P-value for ulcer occurrence from CMH test stratified by NSAID use (use=COX-2, other NSAID, or use=no).
[2] Completed 6 months of treatment and had 6-month endoscopy or developed gastric ulcer prior to 6 months.
[3] Completed subjects (footnote 2) and premature withdrawals who had at least 1 post-baseline endoscopy (last endoscopy used in analysis).
[4] Discontinued subjects without final endoscopy imputed to have gastric ulcer unless ulcer-free endoscopy occurred within 14-day window of last dose of study drug.

As seen from the table above, incidences of gastric ulcers were consistently lower (between approximately 5-7 percent points%) in the PA32540 group than in the EC aspirin 325 mg group,

When the worst-case analysis (which assumed the development of gastric ulcers when no final information was available) was applied, the absolute incidence rate of gastric ulcers remained approximately 5 percentage points lower in the PA32540 group than in the EC aspirin 325 mg group, but the treatment difference between treatment groups failed to achieve statistical significance.

3.1.1.3.5 Applicant's Analyses of the Secondary Efficacy Endpoint

3.1.1.3.5.1 Gastric and/or Duodenal Ulcer

Results of the analysis on the cumulative proportion of subjects who developed gastric ulcers and/or duodenal ulcer are summarized in the table below.

Table 4 Analysis of Cumulative Proportion of Subjects Develop Gastric and/or Duodenal Ulcers at 1, 3, and 6 Months
ITT Population
Study PA32540-301

	PA32540 N = 265	EC-Aspirin 325 mg N = 265	p-Value [1]
	n (%)	n (%)	
0-1 Month			
Gastric/duodenal ulcer	3 (1.1%)	14 (5.3%)	0.007
95% CI	(0.2% – 3.3%)	(2.9% – 8.7%)	
Gastric/duodenal ulcer-free	262(98.9%)	251(94.7%)	
Maintained [2]	242(91.3%)	229(86.4%)	
Discontinued	20 (7.5%)	22 (8.3%)	
0-3 Months			
Gastric/duodenal ulcer	9 (3.4%)	25 (9.4%)	0.005
95% CI	(1.6% – 6.3%)	(6.2% – 13.6%)	
Gastric/duodenal ulcer-free	256(96.6%)	240(90.6%)	
Maintained [2]	216(81.5%)	196(74.0%)	
Discontinued	40(15.1%)	44(16.6%)	
0-6 Months			
Gastric/duodenal ulcer	11 (4.2%)	31(11.7%)	0.002
95% CI	(2.1% – 7.3%)	(8.1% – 16.2%)	
Gastric/duodenal ulcer-free	254(95.8%)	234(88.3%)	
Maintained [2]	208(78.5%)	174(65.7%)	
Discontinued	46(17.4%)	60(22.6%)	

Source: Table 14.2.3.1 (0-6 months) and Table 14.2.3.4 (0-1 and 0-3 months).
[1] P-value for ulcer occurrence from CMH test stratified by NSAID use (use=COX-2, other NSAID, or use=no) at

As seen from the table above, the cumulative proportion of the ITT subjects developing gastric and/or duodenal ulcers through six months was statistically significantly lower with the PA32540 treatment than with the EC aspirin 325 mg treatment.

3.1.1.3.6 Applicant's Analyses of the Tolerability Endpoints

3.1.1.3.6.1 Treatment Success

Subjects who did not develop a gastric ulcer and were not withdrawn from the study due to the pre-specified UGI AEs were considered having treatment successes.

Results of analysis of proportion of subjects with treatment success are given in the table below.

Table 5 Analysis of Proportion of Subjects with Treatment Success
ITT Population
Study PA32540-301

	PA32540 N = 265	EC-Aspirin 325 mg N = 265	p-Value [1]
Treatment Success [2]	249 (94.0%)	220 (83.0%)	<0.001
95% Confidence interval	(90.4% – 96.5%)	(77.9% – 87.3%)	

Source: Table 14.2.4.1.
[1] p-value for treatment success is from CMH test stratified by NSAID use (use=COX-2, other NSAID, or use=no) at randomization.
[2] No gastric ulcer and no withdrawal due to pre-specified UGI adverse event. Subjects who were not dosed or had gastric ulcers at Screening were considered treatment successes in this analysis.

As seen from the table above, in the ITT population, a statistically significantly larger proportion of subjects in the PA32540 group were considered having treatment successes compared to those in the EC aspirin 325 mg group.

3.1.1.3.6.2 Discontinuation due to Pre-specified UGI AEs

Results of analysis on the proportion of subjects discontinued due to pre-specified UGI AEs are given in the table below.

Table 6 Proportion of Subjects Discontinued due to Pre-Specified UGI AEs
ITT Population
Study PA32540-301

	PA32540 N = 265	EC-Aspirin 325 mg N = 265	p-Value [1]
	n (%)	n (%)	
Number of UGI Events Leading to Discontinuation	6	22	
Number of Subjects Discontinuing Due to UGI Events	6(2.3%)	22(8.3%)	0.002
Specific UGI Events			
Abdominal pain upper	2(0.8%)	1(0.4%)	
Dyspepsia	2(0.8%)	8(3.0%)	
Duodenal ulcer	1(0.4%)	6(2.3%)	
Gastritis	1(0.4%)	0	
Duodenal ulcer haemorrhage	0	1(0.4%)	
Erosive oesophagitis	0	1(0.4%)	
Gastritis haemorrhagic	0	1(0.4%)	
Gastrooesophageal reflux disease	0	3(1.1%)	
Oesophageal ulcer	0	1(0.4%)	

Source: Table 14.2.5.1.
[1] p-value is from CMH test stratified by NSAID use (use=COX-2, other NSAID, or use=no) at randomization.

As seen from the table above, the proportion of ITT subjects discontinued study participation due to development of a pre-specified UGI AEs was statistically significantly lower in the PA32540 group than in the EC aspirin 325 mg group. Incidences of dyspepsia, and duodenal ulcer leading to study drug discontinuation were lower among subjects in the PA32540 group than among subjects in the EC aspirin 325 mg group.

3.1.1.4 Reviewer's Comments and Evaluation

3.1.1.4.1 Analysis of Primary Efficacy Endpoint

3.1.1.4.1.1 Cumulative Proportion of Subjects Developing Gastric Ulcer through 6 Month

In this study, if an upper gastric intestine (UGI) ulcer was detected, the subject would be discontinued from the study. Interim endoscopies could be performed if clinically indicated. The applicant's pre-specific analysis of the primary endpoint using cumulative proportion of subjects developing gastric ulcer through six month is the same as LOCF analysis of this endpoint.

3.1.1.4.1.2 Crude Rate and Modified Crude Rate

This reviewer performed analyses of the crude rate and the modified crude rate using Fisher's exact test, the more conservative statistical method for 2 x 2 data. In the crude rate analysis, the subjects who were withdrawn prior to the study completion were assumed to be non-responders. This turns out to be the same as the primary analysis. For the modified crude rate analysis, the subjects who were withdrawn prior to completion of the study were excluded from the analysis. This turns out to be the same as the completed-case analysis.

Table 7 Analysis of Crude Rate and Modified Crude Rate of Subjects Developed Gastric Ulcer through Month 6
Study PA32540-301

Analysis	Treatment	No of patients	Developing Gastric Ulcer	Difference	p-value	95% CI
Crude Rate	PA32540	265	10 (3.8%)	-4.9%	0.0296	(-9.3%, -0.6%)
	EC Aspirin 325 mg	265	23 (8.7%)			
Modified Crude Rate	PA32540	218	10 (4.6%)	-7.0%	0.0104	(-12.7%, -1.3%)
	EC Aspirin 325 mg	198	23 (11.6%)			

P-values were obtained using Fisher's exact test..
Compiled by this reviewer.

As shown in the table above, the crude rate and modified crude rate of developed gastric ulcer though s months was lower with PA32540 treatment than with EC aspirin 325 mg treatment.

3.1.1.4.1.3 Subgroup Analyses

Results of the subgroup analyses on the proportion of subjects developed gastric ulcer throughout six months are summarized in the table below.

Table 8 Subgroup Analyses of Cumulative Proportion of Subjects Developed Gastric Ulcers through 6 Month
ITT Population
Protocol PA32540-301

Subgroup	PA32540	EC ASA 325 mg	Difference	95% C. I.
Gender				
Male	8/188 (4.3%)	15/190 (7.9%)	-3.6%	(-8.9%, 1.3%)
Female	2/77 (2.6%)	8/75 (10.7%)	-8.1%	(-17.6%, -0.1%)
Age				
<65	5/103 (4.9%)	8/117 (6.8%)	-1.9%	(-8.8%, 4.9%)
≥65	5/162 (3.1%)	15/148 (10.1%)	-7.0%	(-13.3%, -1.2%)
Race				
White	9/245 (3.7%)	20/228 (8.8%)	-5.1%	(-9.9%, -0.6%)
Black	1/19 (5.3%)	2/31 (6.5%)	-1.2%	(-17.6%, 19.9%)
Other	0/1 (0.0%)	1/6 (16.7%)	-16.7%	(-64.3%, 86.0%)

Ulcer History				
Yes	3/13 (23.1%)	0/13 (0.0%)	23.1%	(-4.7%, 53.8%)
No	7/252 (2.8%)	23/252 (9.1%)	-6.3%	(-10.9%, -1.9%)
NSAID Use				
Yes	0/20 (0.0%)	3/24 (12.5%)	-12.5%	(-32.4%, 5.1%)
No	10/245 (4.1%)	20/241 (8.3%)	-4.2%	(-8.8%, 0.1%)

Compiled by this reviewer from Tables 14.2.2.3-14.2.2.6

As seen from table above, for all subgroup analyses, the outcome in the PA32540 group was more favorable than in the EC aspirin 325 mg group; however, due to the small number of subjects in many of the subgroups (NSAID use at randomization, ulcer history within five years prior to randomization, non-White race), no clinically meaningful findings can be drawn from these results.

3.1.1.4.1.4 Sensitivity Analyses

The applicant's "observed-case" analysis and "worst-case" analysis were not commonly defined. In the applicant's "observed-case analysis", subjects who withdrew prematurely but had at least one post-baseline endoscopy were included. In the applicant's "worst-case" analysis, subjects who discontinued without the final endoscopy were imputed as having gastric ulcer, unless an ulcer-free endoscopy occurred within 14-day window of the last dose of study drug.

This reviewer requested the applicant performed the following sensitivity analyses for primary efficacy endpoint or this study

a. Observed case: exclude subjects from the analysis at a specific time point if the subjects had insufficient data at that time point.

b. Worst-cases:
   (1) subjects with missing observations at any of the time points of the analysis were considered non-responders;
   (2) subjects receiving EC aspirin 325 mg with missing observations at any of the time points of the analysis were considered responders, and subjects receiving PA32540 with missing observations at any of the time points of the analysis were considered non-responders.

The study primary endpoint was the cumulative observed ulcer rate over a 6 month period. Three post-baseline endoscopies were planned during the 6 month period. In this "observed case" analysis, the applicant had excluded patients with any missing post-baseline endoscopy data and calculated the observed ulcer rate over the duration of the study.

The result from the "observed case" analysis is given in Appendix Table 6.

As seen from Appendix Table 6, the treatment difference obtained from the "observed case" analysis was similar to that from the applicant's "observed case" analysis (-5.8% vs. -5.2%).

The result from the "worst-case 1" analysis is given in Appendix Table 7.

As seen from Appendix Table 7, the treatment difference obtained from the "worst-case 1" analysis was similar to that from the applicant's "worst-case" analysis (-5.6% vs. -4.9%).

For the "worst-case 2" analysis, the applicant stated:

> This analysis does not provide a valid sensitivity analysis of the dataset. Missing observations (endoscopies) were seen in 70 subjects in study 301 or about 13% of all subjects and was similar between PA32540 and EC ASA. The incidence of subjects with missing observations exceeds the observed ulcer rate (6.2%). Importantly the missing data is NOT due to loss-to-follow up which constituted a small number of subjects (1%). The most common reason for missing observations (endoscopies) was adverse events (38%) and subject withdrawal of consent (23%). Subjects enrolled in the study were elderly (mean age of about 66 years) with significant co-morbidities. Under many of the medical conditions the subjects experienced during the study, an invasive protocol-mandated procedure (endoscopy) was not considered clinically appropriate.

Per this reviewer's request, the applicant performed analysis on the cumulative proportion of subjects developed gastric ulcers, duodenal ulcer, gastric and/or duodenal ulcers through six Month, where ulcer is defined as of size greater than or equal to 5 mm.

The results from this analysis are given Appendix Tables 8 and 9 to for gastric ulcer, and gastric and/or duodenal ulcer, respectively.

As shown from Appendix Tables 8 and 9, the cumulative proportion of subjects developed gastric ulcer, and gastric and/or duodenal ulcer through six months, where ulcer is defined as of sized greater than or equal to 5 mm was statistically significantly lower with the PA32540 treatment than with the EC aspirin 325 mg treatment.

3.1.2 Study PA32540-302

3.1.2.1 Study Design

The study design of this study was identical to that of PA32540-301.

3.1.2.2 Applicant's Analysis

A total of 779 subjects were screened at 80 centers. Of these, 260 subjects were screening failures and not selected for the study; the primary reasons of the screening failures were not meeting the inclusion/exclusion criteria, ulcer detected at Screening endoscopy, positive *H. pylori* test, consent withdrawn, or abnormal laboratory test results.

A total of 519 subjects were randomized to treatment (259 to PA32540 and 260 to EC aspirin 325 mg) at 75 centers, and were included in the ITT population. No center enrolled more than 4.2% (22 subjects) of the total study population. The first subject was randomized on October 27 2009 and the last subject completed the study on January 25, 2012.

3.1.2.2.1 Patient Disposition

Approximately 78% of the subjects completed the study (i.e., completed six months of treatment and had a final 6-month endoscopy or had an endoscopically-confirmed gastric ulcer prior to six months of therapy). The most frequent reasons for early study withdrawal in both treatment groups were AEs (7% for PA32540 and 10% for EC aspirin 325 mg) and withdrawal of consent.

The subject disposition for all randomized subjects is given below.

Table 9 Subject Disposition – All Randomized Subjects – PA32540-302

	PA32540 n=259	EC-Aspirin 325 mg n=260
	Number of Subjects (%)	
Subjects randomized	259 (100%)	260 (100%)
Subjects completed[1]	206 (79.5%)	198 (76.2%)
Subjects withdrawn prior to completion	53 (20.5%)	62 (23.8%)
Adverse Event	17 (6.6%)	26 (10.0%)
Withdrew Consent	16 (6.2%)	14 (5.4%)
Lost to follow-up	1 (0.4%)	4 (1.5%)
Other[2]	19 (7.3%)	18 (6.9%)

Source: Table 14.1.1, Listing 16.2.1
[1]Completed 6 months of treatment and had 6-month endoscopy or developed endoscopically-confirmed gastric ulcer prior to 6 months.
[2]Includes violations of inclusion/exclusion criteria, endoscopy not performed, required prohibited medications, outside visit window, and other reasons. Seven or fewer subjects were included in these categories.

3.1.2.2.2 Analysis Population

In the opinion of the Investigators, 17 subjects in the PA32540 group and 12 subjects in the EC aspirin 325 mg group had major protocol violations; the primary violations were not meeting the inclusion/exclusion criteria and use of disallowed medications. Two of these subjects had screening creatinine clearance values that did not meet the original protocol criterion (<50 mL/min) and they were enrolled prior to the removal of creatinine clearance limitations in protocol Amendment 2. Another four subjects were taking high doses of fish oils or omega-3 fatty acids (>3000 mg/day) at screening, but they agreed to lower their dose to less than 3000 mg/day during the study. One subject, who was 56 years of age without a documented ulcer history in the past 5 years, was enrolled prior to the protocol Amendment 2, which reduced the age requirement for documented histories from 60 years or younger to 54 years or younger. One subject who took disallowed medications for two days during a hospital stay, which was more than six weeks prior to the endoscopy, was not considered a major protocol violator by the applicant. Six subjects were permitted to continue in the study after consultation with the applicant. The remaining subjects not meeting inclusion/exclusion criteria or using prohibited medications were discontinued from the study.

Three subjects (two in the PA32540 group and one in the EC aspirin 325 mg group) did not take any study drug, and therefore were not included in either the mITT or the safety populations. Three subjects (4322, 4579 and 4628) were randomized to PA32540, but dispensed the wrong medication kits and actually received EC aspirin 325 mg. There were also three subjects (4507, 4582 and 4586) randomized to EC aspirin 325 mg, but dispensed the wrong medication kits, and actually received PA32540. Efficacy and tolerability data for these subjects were included in the ITT and mITT analyses according to their randomized treatment. However, the efficacy and tolerability data for these subjects were excluded from the PP analyses. Safety data for these subjects were evaluated based on the treatment actually received.

The study populations are summarized in the table below.

Table 10 Data Sets Analyzed – PA32540-302

Data Set	PA32540 N = 259	EC-Aspirin 325 mg N = 260
	Number of Subjects (%)	
ITT Population	259 (100%)	260 (100%)
mITT Population	257 (99.2%)	259 (99.6%)
Did not take any study drug[1]	2	1
Per Protocol (PP) Population	248 (95.8%)	253 (97.3%)
Reasons for Exclusion[2]		
Did not take any study drug	2 (0.8%)	1 (0.4%)
Disallowed medication taken	5 (1.9%)	3 (1.2%)
Compliance <70%	2 (0.8%)	0
Received study drug different from randomization[3]	3 (1.2%)	3 (1.2%)
Safety Population[3]	257 (99.2%)	259 (99.6%)
Did not take study drug[1]	2	1

Source: Table 14.1.1, 14.1.3.1, 14.1.3.2.1
[1] These subjects did not take study drug and were not included in either the mITT or Safety populations.
[2] These violations may have occurred at enrollment and/or during the study. Subjects may have had more than one violation. Subject 3004 was not included due to disallowed medication use and non-compliance (Table 14.1.3.2.2).
[3] Three subjects randomized to PA32540 (subjects 4322, 4579, and 4628) and 3 subjects randomized to EC-aspirin 325 mg (subjects 4507, 4582, 4586) received incorrect study medication kits (Listing 16.2.6, Table 14.1.1). While these subjects were not included in the PP population, they were included in the Safety population, according to their actual treatment (e.g., those subjects randomized to PA32540 but who received EC-aspirin 325 mg were analyzed in the Safety population of subjects who took EC-aspirin 325 mg).

3.1.2.2.3 Treatment Group Comparability

A summary of the demographic and other baseline characteristics, ulcer history and NSAID use at randomization, cardiovascular and cerebrovascular histories, co-morbidities, and clopidogrel use at randomization, by treatment groups are presented in Appendix Tables 10 to 12.

As seen from Appendix Table 10, demographic characteristics of the ITT population were similar for the two treatment groups, except there were more black subjects (12%) in the PA32540 group compared to the EC aspirin 325 mg group (4%). In both treatment groups, subjects were predominantly male (approximately 70%), white (>85%), and of non-Hispanic/Latino ethnicity (approximately 92%). The mean age of the study population was approximately 66 years, and more than 50% were ≥65 years, and approximately 13% were ≥75 years.

As seem from Appendix Table 11, a history of ulcer occurrence within the five years prior to study enrollment was slightly higher in the EC aspirin 325 mg group than the PA32540 group (7% vs. 5%). Approximately 10% of subjects in each treatment group were taking NSAIDs at the time of randomization.

As seen from Appendix Table 12, the administration of aspirin as secondary prevention was used predominantly in patient with histories of cardiac disorders (90% for PA32540 and 84% for EC aspirin 325 mg) rather than neurological disorders (18% for PA32540 and 19% for EC aspirin 325 mg); coronary artery disease was the primary cardiac history (67% for PA32540 and 63% for EC aspirin 325 mg), followed by MI (38% for both treatment groups). More subjects in the PA32540 group had a history of angina (28% for PA32540 and 22% for EC aspirin 325 mg).

A similar percentage of subjects in both treatment groups were taking clopidogrel at the time of randomization (21% for PA32540 and 22% for EC aspirin 325 mg).

In addition to current co-morbid cardiovascular conditions, >90% of the study population had comorbid gastrointestinal and endocrine disorders. A history of diabetes was higher in the PA32540 group (39% vs. 31% for EC aspirin 325 mg group).

3.1.2.2.4 Applicant's Analysis of Primary Efficacy Endpoint

Results of the analysis on the cumulative proportion of subjects who developed gastric ulcers are summarized in the table below.

Table 11 Analysis of Cumulative Proportion (n, %) of Subjects Developed Gastric Ulcers through 1, 3, and 6 Months
ITT Population
Study PA32540-302

Time period	PA32540 N = 259	EC-Aspirin 325 mg N = 260	P-value[1]
	n (%)	n (%)	
0-1 Month			
Gastric ulcer	1 (0.4%)	8 (3.1%)	0.019[2]
95% CI	(0.0% - 2.1%)	(1.3% - 6.0%)	
Gastric ulcer-free	258 (99.6%)	252 (96.9%)	
Maintained[3]	243 (93.8%)	231 (88.8%)	
Discontinued	15 (5.8%)	21 (8.1%)	
0-3 Months			
Gastric ulcer	1 (0.4%)	17 (6.5%)	<0.001
95% CI	(0.0% - 2.1%)	(3.9% – 10.3%)	
Gastric ulcer-free	258 (99.6%)	243 (93.5%)	
Maintained[3]	218 (84.2%)	199 (76.5%)	
Discontinued	40 (15.4%)	44 (16.9%)	
0-6 Months			
Gastric ulcer	7 (2.7%)	22 (8.5%)	0.005
95% CI	(1.1% - 5.5%)	(5.4% - 12.5%)	
Gastric ulcer-free	252 (97.3%)	238 (91.5%)	
Maintained[3]	199 (76.8%)	176 (67.7%)	
Discontinued	53 (20.5%)	62 (23.8%)	

Source: Tables 14.2.1.1 (0-6 months) and 14.2.1.4 (0-1 and 0-3 months).
[1]P-value for ulcer occurrence is from a CMH test stratified by NSAID use at time of randomization (use=COX-2, other NSAID, or use=no).
[2]Mantel-Fleiss criteria was <5 when stratified by NSAID use with 3 strata, so only 2 strata (NSAID use=Yes/No) were used.
[3]Maintained=continued in study.

As seen from the table above, the cumulative proportion of subjects developing gastric ulcers Throughout six months was significantly lower with the PA32540 vs. the EC aspirin 325 mg.

Results of the analysis on the cumulative proportion of subjects who developed gastric ulcers in the mITT and PP populations are summarized in Appendix Tables 14 and 15.

As seen from Appendix Tables 14 and 15, similar findings were observed in the mITT and PP populations. Incidences of gastric ulcers through six months of treatment were statistically significantly lower in the PA32540 group than in the EC aspirin group in both mITT population and the PP population.

3.1.2.2.4.1 Sensitivity Analyses

Results of the three sensitivity analyses (Completed-Case, Observed-Case, and Worst-Case on) are given in the table below.

Table 12 Sensitivity Analyses on Cumulative Proportion of Subjects Developed Gastric Ulcers through 6 Months
ITT Population
Study PA32540-302

Gastric Ulcer through 0-6 Months	PA32540 N = 259		EC-Aspirin 325 mg N = 260		P-value[1]
	N	n (%)	N	n (%)	
Completed-Case Analysis[2]	206		198		
Gastric Ulcer		7 (3.4%)		22 (11.1%)	0.003
Gastric Ulcer-Free		199 (96.6%)		176 (88.9%)	
Observed-Case Analysis[3]	248		248		
Gastric Ulcer		7 (2.8%)		22 (8.9%)	0.005
Gastric Ulcer-Free		241 (97.2%)		226 (91.1%)	
Worst-Case Analysis[4]	259		260		
Gastric Ulcer		32 (12.4%)		45 (17.3%)	0.113
Gastric Ulcer-Free		227 (87.6%)		215 (82.7%)	

Source: Tables 14.2.1.7 (completed-case), 14.2.1.8 (observed-case), and 14.2.1.9 (worst-case).
[1] P-value for ulcer occurrence is from a CMH test stratified by NSAID use (use=COX-2, other NSAID, or use=no) at time of randomization.
[2] Completed 6 months of treatment and had 6-month endoscopy or developed endoscopically-confirmed gastric ulcer prior to 6 months.
[3] Completed subjects (footnote 2) and premature withdrawals who had at least 1 post-baseline endoscopy (last endoscopy used in analysis).
[4] Discontinued subjects without final endoscopy imputed to have gastric ulcer, unless an ulcer-free endoscopy occurred within 14-day window of last dose of study drug.

As seen from the table above, in all three sensitivity analyses, the absolute incidences of gastric ulcers were consistently lower (between approximately 5-8 percentage points lower) in the PA32540 group than in the EC aspirin 325 mg group. When the worst-case analysis (which assumed the development of gastric ulcers when no final information was available) was applied, the absolute incidence of gastric ulcers remained approximately 5 percentage points lower in the PA32540 group than in the EC aspirin 325 mg group, but the difference between treatment groups did not achieve statistical significance. The consistently lower (5-8 percent points) absolute incidence of gastric ulcers with PA32540 observed in all 3 sensitivity analyses support the primary positive outcome of this study.

3.1.2.2.5 Applicant's Analyses of Secondary Efficacy Endpoint

3.1.2.2.5.1 Gastric and/or Duodenal Ulcer

Results of the analysis on the cumulative proportion of subjects who developed gastric ulcers and/or duodenal ulcer are summarized in the table below.

Table 13 Analysis of Cumulative Proportion of Subjects Develop Gastric and/or Duodenal Ulcers at 1, 3, and 6 Months
ITT Population
Study PA32540-302

Time Period	PA32540 N = 259 n (%)	EC-Aspirin 325 mg N = 260 n (%)	P-value[1]
0-1 Months			
Gastric / duodenal ulcer	1 (0.4%)	13 (5.0%)	0.002
95% CI	(0.0% - 2.1%)	(2.7% - 8.4%)	
Gastric / duodenal ulcer-free	258 (99.6%)	247 (95.0%)	
Maintained[2]	243 (93.8%)	229 (88.1%)	
Discontinued	15 (5.8%)	18 (6.9%)	
0-3 Months			
Gastric / duodenal ulcer	1 (0.4%)	22 (8.5%)	<0.001
95% CI	(0.0% - 2.1%)	(5.4% - 12.5%)	
Gastric / duodenal ulcer-free	258 (99.6%)	238 (91.5%)	
Maintained[2]	218 (84.2%)	199 (76.5%)	
Discontinued	40 (15.4%)	39 (15.0%)	
0-6 Months			
Gastric / duodenal ulcer	7 (2.7%)	30 (11.5%)	<0.001
95% CI	(1.1% - 5.5%)	(7.9 - 16.1%)	
Gastric / duodenal ulcer-free	252 (97.3%)	230 (88.5%)	
Maintained[2]	199 (76.8%)	173 (66.5%)	
Discontinued	53 (20.5%)	57 (21.9%)	

Source: Table 14.2.3.1 (0-6 months) and Table 14.2.3.4 (0-1 and 0-3 months).
[1] P-value for ulcer occurrence from CMH test stratified by NSAID use (use=COX-2, other NSAID, or use=no) at time of randomization.
[2] Maintained=continued in study.

As seen from the table above, the cumulative proportion of ITT subjects developed gastric and/or duodenal ulcers through six months was statistically significantly lower with the PA32540 treatment than with the EC aspirin 325 mg treatment.

3.1.2.2.6 Applicant's Analyses of Tolerability Endpoints

3.1.2.2.6.1 Treatment Success

Subjects who did not develop a gastric ulcer and were not withdrawn from the study due to the pre-specified UGI AEs were considered having treatment successes.

Results of the analysis on the proportion of subjects with treatment success are given in the table below.

Table 14 Analysis of Proportion of Subjects with Treatment Success
ITT Population
Study PA32540-302

	PA32540 N = 259	EC-Aspirin 325 mg N = 260	P-value[1]
Treatment Success[2]	250 (96.5%)	217 (83.5%)	<0.001
95% CI	(93.5% - 98.4%)	(78.4% - 87.8%)	

Source: Table 14.2.4.1
[1]P-value from CMH test stratified by NSAID use (use=COX-2, other NSAID, or use=no) at time of randomization.
[2] Treatment success was defined as no gastric ulcer and no withdrawal due to a pre-specified UGI adverse event. Subjects not dosed were considered treatment successes in this analysis.

As seen from the table above, in the ITT population, a statistically significantly larger proportion of subjects in the PA32540 group were considered having treatment successes compared to those in the EC aspirin 325 mg group.

3.1.2.2.6.2 Discontinuation due to Pre-specified UGI AEs

Results of analysis of proportion of subjects discontinued due to pre-specified UGI AEs are given in the table below.

Table 15 Proportion of Subjects Discontinuing due to Pre-Specified UGI AEs
ITT Population
Study PA32540-302

	PA32540 N = 259	EC-Aspirin 325 mg N = 260	P-value[1]
Number of UGI Events Leading to Discontinuation	2	21	
	Number of subjects (%)		
Subjects Discontinuing Due to UGI Events	2 (0.8%)	21 (8.1%)	<0.001
Specific UGI Events			
Abdominal pain	1 (0.4%)	0	
Gastritis erosive	1 (0.4%)	0	
Dyspepsia	0	8 (3.1%)	
Duodenal ulcer	0	4 (1.5%)	
Oesophagitis	0	4 (1.5%)	
Oesophageal ulcer	0	2 (0.8%)	
Duodenitis	0	1 (0.4%)	
Erosive oesophagitis	0	1 (0.4%)	
Gastrointestinal erosion	0	1 (0.4%)	

Source: Table 14.2.5.1.
[1] P-value from CMH test stratified by NSAID use (use=COX-2, other NSAID, or use=no) at time of randomization.

As seen from the table above, the proportion of ITT subjects discontinued study participation due to the development of a pre-specified UGI AEs was statistically significantly lower in the PA32540 group than in the EC aspirin 325 mg group. More subjects who took EC aspirin 325 mg compared with those who took PA32540 discontinued due to dyspepsia.

3.1.2.3 Reviewer's Comments and Evaluation

3.1.2.3.1 Analysis of Primary Efficacy Endpoint

3.1.2.3.1.1 Crude Rate and Modified Crude Rate

This reviewer performed analyses of the crude rate and the modified crude rate using Fisher's exact test.

Table 16 Analysis of Crude Rate and Modified Crude Rate of Developed Gastric Ulcer through 6 Months
Study PA32540-302

Analysis	Treatment	No of patients	Developing Gastric Ulcer	Difference	p-value	95% CI
Crude Rate	PA32540	259	7 (2.7%)	-5.8%	0.0065	(-10.1%, -1.5%)
	EC Aspirin 325 mg	260	22 (8.5%)			
Modified Crude Rate	PA32540	206	7 (3.4%)	-7.7%	0.0033	(13.3%, -2.0%)
	EC Aspirin 325 mg	198	22 (11.1%)			

P-values were obtained using Fisher's exact test.
Compiled by this reviewer.

As shown in the table above, the crude rate and modified crude rate of developing gastric ulcer though six months was lower with PA32540 treatment than with EC aspirin 325 mg treatment.

3.1.2.3.1.2 Subgroup Analyses

Results of the subgroup analyses on the proportion of subjects developed gastric ulcer throughout 6 months are summarized in Table below.

Table 17 Subgroup Analyses of Cumulative Proportion of Subjects Developed Gastric Ulcers through 6 Month
ITT Population
Protocol PA32540-302

Subgroup	PA32540	EC ASA 325 mg	Difference	95% C. I.
Gender				
Male	5/187 (2.7%)	15/184 (8.2%)	-5.5%	(-10.6%, -0.9%)
Female	2/72 (2.8%)	7/76 (9.2%)	-6.4%	(-15.6%, 1.6%)
Age				
<65	5/111 (4.5%)	9/118 (7.6%)	-3.1%	(-10.1%, 3.4%)
≥65	2/148 (1.4%)	13/142 (9.2%)	-7.8%	(-13.8%, -2.8%)
Race				
White	5/225 (2.2%)	22/245 (9.0%)	-6.8%	(-11.3%, -2.2%)
Black	2/30 (6.7%)	0/11 (0.0%)	6.7%	(-21.8%, 22.6%)
Other	0/4 (0.0%)	0/4 (16.7%)	0.0%	(-60.2%, 60.2%)
Ulcer History				
Yes	1/12 (8.3%)	2/19 (10.5%)	-2.2%	(-26.9%, 25.7%)
No	6/247 (2.4%)	20/241 (8.3%)	-5.9%	(-10.3%, -1.7%)
NSAID Use				
Yes	2/24 (8.3%)	2/25 (8.0%)	0.3%	(-19.6%, 19.6%)
No	5/235 (2.1%)	20/235 (8.5%)	-6.4%	(-10.9%, -2.0%)

Compiled by this reviewer from Tables 14.2.2.1-14.2.2.7

As seen from the table above, for all subgroup analyses, the outcome in the PA32540 group was more favorable than in the EC aspirin 325 mg group; however, due to the low number of subjects in many of the subgroups (i.e., NSAID use at randomization, ulcer history within five years prior to randomization, non-White race), no clinically meaningful findings can be drawn from these results.

3.1.2.3.1.3 Sensitivity Analyses

As for Study PA32540-301, this reviewer requested the applicant to perform "observed case", worst-case 1, and worst case 2 analyses for the primary efficacy endpoint of this study

The result from the "observed-case" analysis is given in Appendix Table 15.

As seen from Appendix Table 15, the treatment difference obtained from the "observed case" analysis was similar to that from the applicant's "observed-case" analysis (-6.5% vs. -6.1%).

The result from the "worst case 1" analysis is given in Appendix Table 16.

As seen from Appendix Table 16, the treatment difference obtained from the "worst-case 1" analysis was similar to that from the applicant's "worst-case" analysis (-5.0% vs. -4.9%)

For the "worst-case 2" analysis, the applicant stated:

> This analysis does not provide a valid sensitivity analysis of the dataset. Missing observations (endoscopies) were seen in 68 subjects in this study or about 13% of all subjects and was similar between PA32540 and EC ASA. The incidence of subjects with missing observations exceeds the observed ulcer rate (5.6%). Importantly the missing data is NOT due to loss-to-follow up which constituted a small number of subjects (1%). The most common reason for missing observations (endoscopies) was adverse events (31%) and subject withdrawal of consent (37%). Subjects enrolled in the study were elderly (mean age of about 66 years) with significant co-morbidities. Under many of the medical conditions the subjects experienced during the study, an invasive protocol-mandated procedure (endoscopy) was not considered clinically appropriate.

Per this reviewer's request, the applicant performed analysis on the cumulative proportion of subjects developed gastric ulcers, duodenal ulcer, gastric and/or duodenal ulcers through six Month, where ulcer is defined as of size greater than or equal to 5 mm.

The results from this analysis are given in Appendix Tables17and18 for developed gastric ulcer, duodenal ulcer, and gastric and/or duodenal ulcer, respectively.

As seen from Appendix Tables 17 and 18, the cumulative proportions of subjects developed gastric ulcer, duodenal ulcer, and gastric and through 6 months, where ulcer is defined as of sized greater than or equal to 5 mm were statistically significantly lower with the PA32540 treatment than with EC aspirin 325 mg treatment.

3.2 Evaluation of Safety

3.2.1 Study PA32540-301

Overall exposures to PA32540 were comparable to those to EC aspirin 325 mg. Subjects received a median of 175.0 doses of PA32540 and 173.0 doses of EC aspirin 325 mg over the course of the study.

A summary of AEs by treatment group is presented in the table below.

Table 18 Overview of Adverse Events – Safety Population
Study PA32540-301

	PA32540 N = 264	EC-Aspirin 325 mg N = 265
Any adverse event	193 (73.1%)	224 (84.5%)
Most severe adverse event		
Mild	99 (37.5%)	92 (34.7%)
Moderate	70 (26.5%)	103 (38.9%)
Severe	24 (9.1%)	29 (10.9%)
Treatment-related adverse event	90 (34.1%)	159 (60.0%)
Withdrawn due to adverse event	18 (6.8%)	33 (12.5%)
Any SAE	16 (6.1%)	24 (9.1%)
Deaths	0	1(0.4%)

Source: Tables 14.3.1.1 (any event), 14.3.1.2 (related events), 14.3.1.3 (severity), 14.3.2.1 (SAEs), 14.3.3 (leading to discontinuation), Listing 16.2.13.

As seen from the table above, in the PA32540 and EC aspirin 325 mg groups, the proportions of subjects having at least one AE considered to be related to the study medication, having an AE leading to study discontinuation, and having an SAE were lower in the PA32540 group than in the EC aspirin 325 mg group. One death was reported (sudden cardiac death in the EC aspirin 325 mg group); this was not considered related to the study medication.

3.2.2 Study PA32540-302

The median duration of exposure was similar in both treatment groups (178.0 for PA32540 and 177.0 for EC aspirin 325 mg), but more subjects treated with PA32540 (86%) remained on study drug for >108 days than subjects treated with EC aspirin 325 mg (77%).

An overview of AEs is shown in the table below.

Table 19 Table Overview of AE – Safety Population
Study PA32540-302

	PA32540 N = 257	EC-Aspirin 325 mg N = 259
	Number of Subjects (%)	
Any treatment-emergent adverse event	178 (69.3)	211 (81.5)
Most severe treatment-emergent adverse event		
Mild	99 (38.5%)	111 (42.9%)
Moderate	64 (24.9%)	76 (29.3%)
Severe	15 (5.8%)	24 (9.3%)
Treatment-related, treatment-emergent adverse events	67 (26.1%)	105 (40.5%)
Withdrawals due to treatment-emergent adverse events	17 (6.6%)	26 (10.0%)
Any SAE	23 (8.9%)	17 (6.6%)
Deaths	2 (0.8%)	1 (0.4%)

Source: Tables 14.3.1.1 (any event), 14.3.1.2 (related events), 14.3.1.3 (severity), 14.3.2.1 (SAEs), 14.3.3 (leading to discontinuation); Listing 16.2.13.

As seen from the table above, overall, more subjects who took EC aspirin 325 mg had at least one treatment-emergent AE compared with those who took PA32540; and in more EC aspirin 325 mg subjects, the events were treatment-related. While most events with both treatments were of mild severity, subjects in the EC aspirin 325 mg group had more moderate or severe events than those in the PA32540 group. Discontinuations due to AEs were also higher in the EC aspirin 325 mg group. More subjects who took PA32540 experienced at least one SAE compared to those who took EC aspirin 325 mg. There were three deaths reported during the study, two in subjects who took PA32540 and one in a subject who took in the EC aspirin 325 mg.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATION

4.1 Gender, Race, and Age

4.1.1 Study PA32540-301

Table 20 Subgroup Analyses of Cumulative Proportion of Subjects Developing Gastric Ulcers through 6 Month - Protocol PA32540-301

ITT Population
Protocol PA32540-301

Subgroup	PA32540	EC ASA 325 mg	Difference	95% C. I.
Gender				
Male	8/188 (4.3%)	15/190 (7.9%)	-3.6%	(-8.9%, 1.3%)
Female	2/77 (2.6%)	8/75 (10.7%)	-8.1%	(-17.6%, -0.1%)
Age				
<65	5/103 (4.9%)	8/117 (6.8%)	-1.9%	(-8.8%, 4.9%)
≥65	5/162 (3.1%)	15/148 (10.1%)	-7.0%	(-13.3%, -1.2%)
Race				
White	9/245 (3.7%)	20/228 (8.8%)	-5.1%	(-9.9%, -0.6%)
Black	1/19 (5.3%)	2/31 (6.5%)	-1.2%	(-17.6%, 19.9%)
Other	0/1 (0.0%)	1/6 (16.7%)	-16.7%	(-64.3%, 86.0%)

Compiled by this reviewer from Tables 14.2.2.3-14.2.2.6

As seen from Table above, in all of the subgroup analyses, the outcome in the PA32540 group was more favorable than in the EC aspirin 325 mg group; however, due to the low number of subjects in many of the subgroups (non-White races), no clinically meaningful findings can be drawn from these data.

4.1.2 Study PA32540-302

Table 21 Subgroup Analyses of Cumulative Proportion of Subjects Developing Gastric Ulcers through 6 Month - Protocol PA32540-302

ITT Population
Protocol PA32540-302

Subgroup	PA32540	EC ASA 325 mg	Difference	95% C. I.
Gender				
Male	5/187 (2.7%)	15/184 (8.2%)	-5.5%	(-10.6%, -0.9%)
Female	2/72 (2.8%)	7/76 (9.2%)	-6.4%	(-15.6%, 1.6%)
Age				
<65	5/111 (4.5%)	9/118 (7.6%)	-3.1%	(-10.1%, 3.4%)
≥65	2/148 (1.4%)	13/142 (9.2%)	-7.8%	(-13.8%, -2.8%)
Race				

White	5/225 (2.2%)	22/245 (9.0%)	-6.8%	(-11.3%, -2.2%)
Black	2/30 (6.7%)	0/11 (0.0%)	6.7%	(-21.8%, 22.6%)
Other	0/4 (0.0%)	0/4 (16.7%)	0.0%	(-60.2%, 60.2%)

Compiled by this reviewer from Tables 14.2.2.1-14.2.2.7

As seen from the table above, in all of the subgroup analyses, the outcome in the PA32540 group was more favorable than in the EC aspirin 325 mg group; however, due to the low number of subjects in many of the subgroups (non-White races), no clinically meaningful findings can be drawn from these data.

4.2 Other Special/Subgroup Population

4.2.1 Study PA32540-301

Table 22 Subgroup Analyses of Cumulative Proportion of Subjects Developing Gastric Ulcers through 6 Month - Protocol PA32540-301
ITT Population
Protocol PA32540-301

Subgroup	PA32540	EC ASA 325 mg	Difference	95% C. I.
Ulcer History				
Yes	3/13 (23.1%)	0/13 (0.0%)	23.1%	(-4.7%, 53.8%)
No	7/252 (2.8%)	23/252 (9.1%)	-6.3%	(-10.9%, -1.9%)
NSAID Use				
Yes	0/20 (0.0%)	3/24 (12.5%)	-12.5%	(-32.4%, 5.1%)
No	10/245 (4.1%)	20/241 (8.3%)	-4.2%	(-8.8%, 0.1%)

Compiled by this reviewer from Tables 14.2.2.3-14.2.2.6

As seen from the table above, in all of the subgroup analyses, the outcome in the PA32540 group was more favorable than in the EC aspirin 325 mg group; however, due to the low number of subjects in many of the subgroups (NSAID use at randomization, ulcer history within 5 years prior to randomization), no clinically meaningful findings can be drawn from these data.

4.2.2 Study PA32540-302

Table 23 Table Subgroup Analyses of Cumulative Proportion of Subjects Developing Gastric Ulcers through 6 Month - Protocol PA32540-302
ITT Population
Protocol PA32540-302

Subgroup	PA32540	EC ASA 325 mg	Difference	95% C. I.
Ulcer History				
Yes	1/12 (8.3%)	2/19 (10.5%)	-2.2%	(-26.9%, 25.7%)
No	6/247 (2.4%)	20/241 (8.3%)	-5.9%	(-10.3%, -1.7%)
NSAID Use				
Yes	2/24 (8.3%)	2/25 (8.0%)	0.3%	(-19.6%, 19.6%)
No	5/235 (2.1%)	20/235 (8.5%)	-6.4%	(-10.9%, -2.0%)

Compiled by this reviewer from Tables 14.2.2.1-14.2.2.7

As seen from the table above, in all of the subgroup analyses, the outcome in the PA32540 group was more favorable than in the EC aspirin 325 mg group; however, due to the low number of subjects in many of the subgroups (NSAID use at randomization, ulcer history within 5 years prior to randomization), no clinically meaningful findings can be drawn from these data.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Two studies, Studies PA32540-301 and PA32540-302, were conducted to evaluate PA32540 as compared to EC aspirin 325 mg for the proposed indication.

In both studies, if an UGI ulcer was detected, the subject would be discontinued from the study. Interim endoscopies could be performed if clinically indicated. Ulcer was pre-specified as of size of greater than or equal to 3mm.

This reviewer performed analyses of the crude rate and the modified crude rate using the Fisher's exact test. For the crude rate analysis, the subjects who were withdrawn prior to completion of the study were considered non-responders. This turns out to be the same as the primary analysis. For the modified crude rate analysis, the subjects who were withdrawn prior to completion of the study were excluded from the analysis. This turns out to be the same as the completed-case analysis.

Both analyses of developing gastric ulcer though six months using the Fisher's exact test showed statistically significant lower rates with the PA32540 treatment than with EC aspirin 325 mg treatment.

Per this reviewer's request, the applicant performed analysis on the cumulative proportion of subjects developed gastric ulcers, duodenal ulcer, gastric and/or duodenal ulcers through 6 Month, where ulcer is defined as of size greater than or equal to 5 mm.

The results revealed a statistically significantly lower rate with PA32540 treatment than with EC aspirin 325 mg treatment for developing gastric ulcer, and gastric and/or duodenal ulcer.

5.2 Conclusion and Recommendations

Two studies, Studies PA32540-301 and PA32540-302, were conducted to evaluate PA32540 as compared to enteric-coated (EC)-aspirin 325 mg to support the proposed indication:

In both Studies PA32540-301 and PA32540-302, the cumulative proportion of subjects developing gastric ulcers throughout six months was significantly lower with PA32540 vs. EC aspirin 325 mg. The treatment differences were 5% in Study PA32540-301 and 6% in Study PA32540-302.

But, both studies failed to achieve statistical significance for a conservative method (worst-case analysis) with p=0.120 and 0.113 for Study PA32540-301, Study PA32540-302, respectively.

6. APPENDEX

Table 1Demographics and Other Baseline Characteristics – ITT Population

Study PA32540-301

	PA32540 N = 265	EC-Aspirin 325 mg N = 265
Gender (n [%])		
Male	188 (70.9%)	190 (71.7%)
Female	77(29.1%)	75(28.3%)
Race (n [%])		
White	245 (92.5%)	228 (86.0%)
Black/African American	19 (7.2%)	31(11.7%)
Asian	0	4 (1.5%)
American Indian/Alaskan Native	0	2 (0.8%)
Other	1 (0.4%)	0
Ethnicity (n [%])		
Not Hispanic or Latino	241 (90.9%)	246(92.8%)
Hispanic or Latino	24 (9.1%)	19 (7.2%)
Age (years)		
Mean (SD)	66.3 (7.2)	65.8 (6.7)
Median	66.0	66.0
Range	41 – 88	51 – 88
Age Group (n [%])		
<65 years	103 (38.9%)	117 (44.2%)
<55 years	3 (1.1%)	3 (1.1%)
55-64 years	100 (37.7%)	114 (43.0%)
≥65 years	162 (61.1%)	148 (55.8%)
65-74 years	124 (46.8%)	118 (44.5%)
≥75 years	38(14.3%)	30 (11.3%)
BMI (kg/m^2), mean (SD)	31.0 (6.3)	31.1 (6.0)

Source: Table 14.1.4.1.
SD = standard deviation.

Table 2 Ulcer History and NSAID Use at Randomization – ITT Population

Study PA32540-301

	PA32540 N = 265	**EC-Aspirin 325 mg N = 265**
Gastric or Duodenal Ulcer within Previous 5 Years	13 (4.9%)	13 (4.9%)
History of Most Recent Ulcer at Any Time		
Gastric	14 (5.3%)	29 (10.9%)
Duodenal	4 (1.5%)	3 (1.1%)
Both	2 (0.8%)	0
None	245 (92.5%)	233 (87.9%)
NSAID or COX-2 Inhibitor Use at Randomization		
None	245 (92.5%)	241 (90.9%)
COX-2 Inhibitor or Other NSAID [1]	20 (7.5%)	24(9.1%)
COX-2 inhibitor	1 (5.0%)	1 (4.2%)
Other NSAID	19 (95.0%)	23 (95.8%)

Source: Table 14.1.5.1.

[1] Percentages for NSAID type are based on total number of NSAID users.

Table 3 Cardiovascular and Cerebrovascular Histories, co-Morbidities, and Clopidogrel Use at Randomization – ITT Population

Study PA32540-301

	PA32540 N = 265	EC-Aspirin 325 mg N = 265
Any Cardiovascular or Cerebrovascular History for Secondary Prevention		
Yes	263 (99.2%)	263(99.2%)
No	2 (0.8%)	2 (0.8%)
Cardiac History for Secondary Prevention	236 (89.1%)	218 (82.3%)
Coronary artery disease	183 (69.1%)	169 (63.8%)
Myocardial infarction	115 (43.4%)	100 (37.7%)
Stent(s) placement	102 (38.5%)	72 (27.2%)
Coronary artery bypass graft	77 (29.1%)	84 (31.7%)
Angina	68 (25.7%)	61 (23.0%)
Angioplasty, catheterization, PCI, or angiography	65 (24.5%)	53 (20.0%)
Ischemic cardiomyopathy	10(3.8%)	13(4.9%)
Neurological History for Secondary Prevention	56 (21.1%)	64 (24.2%)
Stroke	30 (11.3%)	45 (17.0%)
Transient ischemic attack	26 (9.8%)	25 (9.4%)
Cerebral or cerebrovascular disease	5 (1.9%)	2 (0.8%)
Any peripheral artery disease	40 (15.1%)	32 (12.1%)
Co-Morbidities in ≥40% of Subjects		
Endocrine disorders	255 (96.2%)	248 (93.6%)
History of Diabetes	112 (42.3%)	107 (40.4%)
Gastrointestinal disorders	253 (95.5%)	249 (94.0%)
Musculoskeletal and connective tissue disorders	164 (61.9%)	181 (68.3%)
Immune system disorders	149 (56.2%)	126 (47.5%)
Nervous system disorders	124 (46.8%)	140 (52.8%)
Respiratory, thoracic and mediastinal disorders	96 (36.2%)	109 (41.1%)
Clopidogrel Use at Randomization	58 (21.9%)	54 (20.4%)

Source: Tables 14.1.5.1 (diabetes), 14.1.6.1(co-morbidities), and 14.1.6.3 (cardio- and cerebro-vascular histories); Listings 16.2.6 and 16.2.8 (clopidogrel use).

Table 4 Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers through 6 Months – Modified Intent-to-Treat Population

Study PA32540-301

POZEN, Inc.
Protocol: PA32540-301

Table 14.2.1.2
Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers Throughout 6 Months
Modified Intent-to-Treat Population

	PA32540 (N=264)	EC-ASA 325mg (N=263)	P-Value[1]
0 - 6 Months			
Gastric Ulcer	10 (3.8%)	23 (8.7%)	0.019
95% Confidence Interval	(1.8%- 6.9%)	(5.6%-12.8%)	
Gastric Ulcer-Free	254 (96.2%)	240 (91.3%)	
Maintained Gastric Ulcer-Free	208 (78.8%)	175 (66.5%)	
Discontinued Gastric Ulcer-Free	46 (17.4%)	65 (24.7%)	

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

Table 5 Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers through 6 Months – Per Protocol Population

Study PA32540-301

POZEN, Inc.
Protocol: PA32540-301

Table 14.2.1.3
Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers Throughout 6 Months
Per Protocol Population

	PA32540 (N=258)	EC-ASA 325mg (N=256)	P-Value[1]
0 - 6 Months			
Gastric Ulcer	10 (3.9%)	23 (9.0%)	0.019
95% Confidence Interval	(1.9%- 7.0%)	(5.8%-13.2%)	
Gastric Ulcer-Free	248 (96.1%)	233 (91.0%)	
Maintained Gastric Ulcer-Free	205 (79.5%)	175 (68.4%)	
Discontinued Gastric Ulcer-Free	43 (16.7%)	58 (22.7%)	

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

Table 6 Sensitivity Analyses - Observed-Case Analysis

Study PA32540-301

POZEN, Inc.
Protocol: PA32540-301

Table STAT-IR1.a
Sensitivity Observed-Case Analysis
of Cumulative Proportion of Subjects Developing Gastric Ulcers Throughout 6 Months
Intent-to-Treat Population

	PA32540 (N=230)	EC-ASA 325mg (N=227)	P-Value[1]
0 - 6 Months			
Gastric Ulcer	10 (4.3%)	23 (10.1%)	0.017
95% Confidence Interval	(2.1%- 7.9%)	(6.5%-14.8%)	
Gastric Ulcer-Free	220 (95.7%)	204 (89.9%)	
Maintained Gastric Ulcer-Free	208 (90.4%)	174 (76.7%)	
Discontinued Gastric Ulcer-Free	12 (5.2%)	30 (13.2%)	

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

Table 7 Sensitivity Analysis- Worst-Case Analysis– Intent-to-Treat Population

Study PA32540-301

POZEN, Inc.
Protocol: PA32540-301

Table STAT-IR1.b.1
Sensitivity Analysis: Worst-Case Substitution for Missing Values
Subjects with Missing Scheduled Endoscopy are Assumed to have Gastric Ulcers
Cumulative Proportion of Subjects Developing Gastric Ulcers Throughout 6 Months
Intent-to-Treat Population

	PA32540 (N=265)	EC-ASA 325mg (N=265)	P-Value[1]
0 - 6 Months			
Gastric Ulcer	45 (17.0%)	60 (22.6%)	0.105
95% Confidence Interval	(12.7%-22.1%)	(17.7%-28.2%)	
Gastric Ulcer-Free	220 (83.0%)	205 (77.4%)	
Maintained Gastric Ulcer-Free	208 (78.5%)	174 (65.7%)	
Discontinued Gastric Ulcer-Free	12 (4.5%)	31 (11.7%)	

Subject 2599 (who did not take any study drug) is counted as ulcer-free in the EC-ASA 325mg group, since the screening endoscopy was negative.

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

Table 8 Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers of at Least 5 mm in Diameter through 6 Months – Intent-to-to-Treat Population

Study PA32540-301

POZEN, Inc.
Protocol: PA32540-301

Table STAT-IR2.1.1
Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers
of at Least 5 mm in diameter
Throughout 6 Months
Intent-to-Treat Population

	PA32540 (N=265)	EC-ASA 325mg (N=265)	P-Value[1]
0 - 6 Months			
Gastric Ulcer	4 (1.5%)	13 (4.9%)	0.026
95% Confidence Interval	(0.4%- 3.8%)	(2.6%- 8.2%)	
Gastric Ulcer-Free	261 (98.5%)	252 (95.1%)	
Maintained Gastric Ulcer-Free	214 (80.8%)	185 (69.8%)	
Discontinued Gastric Ulcer-Free	47 (17.7%)	67 (25.3%)	

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

Table 9 Analysis of Cumulative Proportio0n of Subjects Developing Gastric Ulcers and/or Duodenal Ulcers of at Least 5 mm in Diameter through 6 Months – Intent-to-to-Treat Population

Study PA32540-301

POZEN, Inc.
Protocol: PA32540-301

Table STAT-IR2.3.1
Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers and/or Duodenal Ulcers
of at Least 5 mm in diameter
Throughout 6 Months
Intent-to-Treat Population

	PA32540 (N=265)	EC-ASA 325mg (N=265)	P-Value[1]
0 - 6 Months			
Gastric and/or Duodenal Ulcer	5 (1.9%)	18 (6.8%)	0.006
95% Confidence Interval	(0.6%- 4.3%)	(4.1%-10.5%)	
Gastric and Duodenal Ulcer-Free	260 (98.1%)	247 (93.2%)	
Maintained Gastric and Duodenal Ulcer-Free	214 (80.8%)	184 (69.4%)	
Discontinued Gastric and Duodenal Ulcer-Free	46 (17.4%)	63 (23.8%)	

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

Table 10 Demographics and Other Baseline Characteristics – ITT Population

Study PA32540-302

	PA32540 N = 259	EC-Aspirin 325 mg N = 260
Gender (n [%])		
Male	187 (72.2%)	184 (70.8%)
Female	72 (27.8%)	76 (29.2%)
Race (n [%])		
White	225 (86.9%)	245 (94.2%)
Black/African American	30 (11.6%)	11 (4.2%)
Asian	2 (0.8%)	4 (1.5%)
Native Hawaiian/Other Pacific Islander	1 (0.4%)	0
Other	1 (0.4%)	0
Ethnicity (n [%])		
Not Hispanic or Latino	237 (91.5%)	238 (91.5%)
Hispanic or Latino	22 (8.5%)	22 (8.5%)
Age (years)		
Mean (SD)	66.2 (7.8)	65.6 (7.6)
Median	66.0	65.5
Range	41 - 87	39 - 86
Age Group (n [%])		
<65 years	111 (42.9%)	118 (45.4%)
<55 years	10 (3.9%)	10 (3.8%)
55-64 years	101 (39.0%)	108 (41.5%)
≥65 years	148 (57.1%)	142 (54.6%)
65-74 years	113 (43.6%)	109 (41.9%)
≥75 years	35 (13.5%)	33 (12.7%)
Body Mass Index (kg/m^2), mean (SD)	31.0 (5.4)	31.2 (6.0)

Source: Table 14.1.4.1.
SD= standard deviation.

Table 11 Ulcer History and NSAID Use at Randomization – ITT Population

Study PA32540-302

	PA32540 N = 259	EC-Aspirin 325 mg N = 260
Gastric or Duodenal Ulcer within Previous 5 Years	12 (4.6%)	19 (7.3%)
History of Most Recent Ulcer at Any Time		
Gastric	22 (8.5%)	27 (10.4%)
Duodenal	9 (3.5%)	4 (1.5%)
Both	2 (0.8%)	0
None	226 (87.3%)	229 (88.1%)
NSAID or COX-2 Inhibitor Use at Randomization		
None	235 (90.7%)	235 (90.4%)
COX-2 Inhibitor or other NSAID[1]	24 (9.3%)	25 (9.6%)
COX-2 Inhibitor	2 (8.3%)	4 (16.0%)
Other NSAID	22 (91.7%)	21 (84.0%)

Source: Table 14.1.5.1

[1] Percentages for NSAID type are based on total number of NSAID users.

Table 12 Cardiovascular and Cerebrovascular Histories, co-Morbidities, and Clopidogrel Use at Randomization – ITT Population

Study PA32540-302

	PA32540 N = 259	EC-Aspirin 325 mg N = 260
Any Cardiovascular History for Secondary Prevention		
Yes	258 (99.6%)	256 (98.5%)
No	1 (0.4%)	4 (1.5%)
Cardiac history for secondary prevention	232 (89.6%)	217 (83.5%)
Coronary artery disease	174 (67.2%)	164 (63.1%)
Myocardial infarction	99 (38.2%)	99 (38.1%)
Stent(s) placement	94 (36.3%)	97 (37.3%)
Angina	72 (27.8%)	58 (22.3%)
Coronary artery bypass graft	70 (27.0%)	83 (31.9%)
Angioplasty, catheterization, PCI, or angiography	64 (24.7%)	54 (20.8%)
Ischemic cardiomyopathy	14 (5.4%)	14 (5.4%)
Neurological history for secondary prevention	46 (17.8%)	49 (18.8%)
Stroke	25 (9.7%)	22 (8.5%)
Transient ischemic attack	19 (7.3%)	28 (10.8%)
Cerebral or cerebrovascular disease	8 (3.1%)	4 (1.5%)
Any peripheral artery disease	22 (8.5%)	29 (11.2%)
Co-morbidities in ≥40% of Subjects		
Endocrine disorders	246 (95.0%)	242 (93.1%)
History of diabetes	101 (39.0%)	81 (31.2%)
Gastrointestinal disorders	240 (92.7%)	240 (92.3%)
Musculoskeletal and connective tissue disorders	164 (63.3%)	169 (65.0%)
Immune system disorders	111 (42.9%)	118 (45.4%)
Nervous system disorders	93 (35.9%)	108 (41.5%)
Clopidogrel use at randomization	53 (20.5%)	56 (21.5%)

Source: Tables 14.1.5.1 (diabetes), 14.1.6.1(co-morbidities), and 14.1.6.3 (cardiovascular and cerebrovascular histories); Listings 16.2.6 and 16.2.8 (clopidogrel use).

Table 13 Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers through 6 Months – Modified Intent-to-Treat Population

Study PA32540-302

POZEN, Inc.
Protocol: PA32540-302

Table 14.2.1.2
Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers Throughout 6 Months
Modified Intent-to-Treat Population

	PA32540 (N=257)	EC-ASA 325mg (N=259)	P-Value[1]
0 - 6 Months			
Gastric Ulcer	7 (2.7%)	22 (8.5%)	0.005
95% Confidence Interval	(1.1%- 5.5%)	(5.4%-12.6%)	
Gastric Ulcer-Free	250 (97.3%)	237 (91.5%)	
Maintained Gastric Ulcer-Free	199 (77.4%)	176 (68.0%)	
Discontinued Gastric Ulcer-Free	51 (19.8%)	61 (23.6%)	

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

Table 14 Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers through 6 Months – Per Protocol Population

Study PA32540-302

POZEN, Inc.
Protocol: PA32540-302

Table 14.2.1.3
Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers Throughout 6 Months
Per Protocol Population

	PA32540 (N=248)	EC-ASA 325mg (N=253)	P-Value[1]
0 - 6 Months			
Gastric Ulcer	7 (2.8%)	22 (8.7%)	0.006
95% Confidence Interval	(1.1%- 5.7%)	(5.5%-12.9%)	
Gastric Ulcer-Free	241 (97.2%)	231 (91.3%)	
Maintained Gastric Ulcer-Free	196 (79.0%)	173 (68.4%)	
Discontinued Gastric Ulcer-Free	45 (18.1%)	58 (22.9%)	

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

Table 15 Sensitivity Analysis - Observed-Case Analysis

Study PA32540-302

POZEN, Inc.
Protocol: PA32540-302

Table STAT-IR1.a
Sensitivity Observed-Case Analysis
of Cumulative Proportion of Subjects Developing Gastric Ulcers Throughout 6 Months
Intent-to-Treat Population

	PA32540 (N=222)	EC-ASA 325mg (N=226)	P-Value[1]
0 - 6 Months			
Gastric Ulcer	7 (3.2%)	22 (9.7%)	0.005
95% Confidence Interval	(1.3%- 6.4%)	(6.2%-14.4%)	
Gastric Ulcer-Free	215 (96.8%)	204 (90.3%)	
Maintained Gastric Ulcer-Free	197 (88.7%)	176 (77.9%)	
Discontinued Gastric Ulcer-Free	18 (8.1%)	28 (12.4%)	

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

Table 16 Sensitivity Analysis - Worst-Case Analysis– Intent-to-Treat Population

Study PA32540-302

POZEN, Inc.
Protocol: PA32540-302

Table STAT-IR1.b.1
Sensitivity Analysis: Worst-Case Substitution for Missing Values
Subjects with Missing Scheduled Endoscopy are Assumed to have Gastric Ulcers
Cumulative Proportion of Subjects Developing Gastric Ulcers Throughout 6 Months
Intent-to-Treat Population

	PA32540 (N=259)	EC-ASA 325mg (N=260)	P-Value[1]
0 - 6 Months			
Gastric Ulcer	42 (16.2%)	55 (21.2%)	0.147
95% Confidence Interval	(11.9%-21.3%)	(16.4%-26.6%)	
Gastric Ulcer-Free	217 (83.8%)	205 (78.8%)	
Maintained Gastric Ulcer-Free	197 (76.1%)	176 (67.7%)	
Discontinued Gastric Ulcer-Free	20 (7.7%)	29 (11.2%)	

Subjects who did not take any study drug (4347/EC-ASA 325mg, 4578/PA32540, and 4631/PA32540) are counted as ulcer-free, since their screening endoscopies were negative.

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

Table 17 Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers of at Least 5 mm in Diameter through 6 Months – Intent-to-to-Treat Population

Study PA32540-302

POZEN, Inc.
Protocol: PA32540-302

Table STAT-IR2.1.1
Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers
of at Least 5 mm in diameter
Throughout 6 Months
Intent-to-Treat Population

	PA32540 (N=259)	EC-ASA 325mg (N=260)	P-Value[1]
0 - 6 Months			
Gastric Ulcer	3 (1.2%)	10 (3.8%)	0.049
95% Confidence Interval	(0.2%- 3.3%)	(1.9%- 7.0%)	
Gastric Ulcer-Free	256 (98.8%)	250 (96.2%)	
Maintained Gastric Ulcer-Free	203 (78.4%)	188 (72.3%)	
Discontinued Gastric Ulcer-Free	53 (20.5%)	62 (23.8%)	

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

Table 18 Analysis of Cumulative Proportio0n of Subjects Developing Gastric Ulcers and/or Duodenal Ulcers of at Least 5 mm in Diameter through 6 Months – Intent-to-to-Treat Population

Study PA32540-302

POZEN, Inc.
Protocol: PA32540-302

Table STAT-IR2.3.1
Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers and/or Duodenal Ulcers
of at Least 5 mm in diameter
Throughout 6 Months
Intent-to-Treat Population

	PA32540 (N=259)	EC-ASA 325mg (N=260)	P-Value[1]
0 - 6 Months			
Gastric and/or Duodenal Ulcer	3 (1.2%)	15 (5.8%)	0.004
95% Confidence Interval	(0.2%- 3.3%)	(3.3%- 9.3%)	
Gastric and Duodenal Ulcer-Free	256 (98.8%)	245 (94.2%)	
Maintained Gastric and Duodenal Ulcer-Free	203 (78.4%)	186 (71.5%)	
Discontinued Gastric and Duodenal Ulcer-Free	53 (20.5%)	59 (22.7%)	

[1] P-Value for ulcer occurrence is from a CMH test stratified by NSAID use=COX-2, other NSAID, or NSAID use=NO.

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/s/

MILTON C FAN
03/28/2014

FREDA COONER
03/28/2014
See Statistical Team Leader Memorandum

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number:205103

Applicant: POZEN Inc.

Stamp Date: 3/25/13

Drug Name: PA8140 and PA32540 (aspirin/ Omeprazole) Tablets

NDA/BLA Type: Efficacy

Indication: Use in the secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin-associated ulcers

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	Electronic 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			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			No conform to ADaM

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	No efficacy interim analysis was planned.
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			Complete-case, observed-case, and worst-case analyses

Background

PA8140 (aspirin 81mg/omeprazole 40 mg tables) and PA32540 (aspirin 325 mg/omeprazole 40 mg tablets) were developed by the sponsor as a delivery formulation of PA tablet, which allows omeprazole to be immediately released while the release of aspirin from the core is delayed dependent on pH. The sponsor developed PA tablets to ensure that subjects who require chronic aspirin therapy will always receive a preceding omeprazole 40 mg..

The sponsor has submitted two Phase III studies (PA32540-301 and PA32540-302) for the proposed indication:

These two studies were entitled as follows:

- Study PA32540-301: A 6-Month, Phase 3, Randomized, Double-Blinded, Parallel-Group, Controlled, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either PA32540 or Enteric-Coated Aspirin 325 mg in Subjects Who Are at Risk for Developing Aspirin 325 mg .

- Study PA32540-302: A 6-Month, Phase 3, Randomized, Double-Blinded, Parallel-Group, Controlled, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either PA32540 or Enteric-Coated Aspirin 325 mg in Subjects Who Are at Risk for Developing Aspirin 325 mg

All analysis datasets and study reports for this submission have been submitted in electronic Common Technical Document (eCTD) format to the EDR at: \\cdsesub1\EVSPROD\NDA205103\205103.enx.

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/s/

MILTON C FAN
05/21/2013

FREDA COONER
05/21/2013