CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205103Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

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Application Number	NDA 205103
Priority or Standard	Standard
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Division / Office	Division of Gastroenterology and Inborn Errors Products
Reviewer Name	Zana H. Marks, MD, MPH
Review Completion Date	December 16, 2013
Established Name	Aspirin/omeprazole
(Proposed) Trade Name	YOSPRALA
Therapeutic Class	
Applicant	POZEN
Formulation	Oral tablet
Dosing Regimen	ECASA (325 mg) and Omeprazole (40mg) once a day
Proposed Indications	(b) (4)
Intended Population(s)	Adults 18 years and above

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to support the recommendation of marketing approval for Yosprala (enteric coated aspirin 325 mg/omeprazole 40 mg) for the indication of preventing recurrent cerebrovascular and cardiovascular events, in subjects at risk of developing aspirin-associated gastric ulcers.

1.2 Risk Benefit Assessment

The geriatric population is increasing and as such there are more individuals with cardiovascular and cerebrovascular disease requiring daily antiplatelet therapy such as aspirin. Aspirin produces its antithrombotic effect by irreversible acetylation of a serine residue in platelet cyclooxygenase-1 (COX-1), which blocks thromboxane A_2 production for the life of the platelet, preventing platelet aggregation. Low dose aspirin, commonly defined as 75-325 mg daily, is now widely used for primary and secondary prevention of cardiovascular (CV) disease.[1]

However, aspirin has been shown to cause a two to three fold increase in the risk of dose related peptic ulcer bleeding.[2] Aspirin is thought to cause mucosal damage by both topical irritant effects on the epithelium and systemic effects related to the suppression of mucosal prostaglandin synthesis. This suppression reduces mucosal defenses such as mucus and bicarbonate secretion, blood flow, epithelial cell turnover and repair and mucosal immunocyte function.

Aspirin therapy has become an integral part in the primary and secondary prevention of cardiovascular disease. It has been associated with a significantly lower risk of cardiovascular events, such as myocardial infarction, stroke or vascular death. Even at low doses (<100mg) aspirin may be associated with gastrointestinal adverse events[3]. These are more prevalent in patients who are at increased risk, such as older patients, those with a previous history of ulcer disease or a GI bleed, steroid or anticoagulation medication use, or *H. pylori* infection. The GI effects of low dose aspirin (LDA) range

[1] Hirata, Yoshikazu et al Incidence of gastrointestinal bleeding in patients with cardiovascular disease: buffered aspirin versus enteric coated aspirin; Scandanavian Journal of Gastroenterology, 2011;46:803-809
[2] Laine, L. Review article: Gastrointestinal bleeding with low dose aspirin-what's the risk?;Ailment Pharmacol Ther 2006;24(6):897-908
[3] *ibid*

from dyspeptic symptoms and heartburn to serious peptic ulcer complications with bleeding and perforation. The risk of gastrointestinal bleeding after a year of aspirin use is more than twice that of non-users. Enteric coated and buffered formulations have not been shown to lessen the potential for untoward GI events with aspirin use.[4]

Gastrointestinal bleeding may occur without warning and may lead to discontinuation of LDA therapy. Development of symptoms such as dyspepsia or heartburn may also result in discontinuing LDA therapy. This is troublesome because discontinuing the aspirin may be associated with an increased risk for serious cardiovascular events to occur. Having patients continue on aspirin therapy is key to the management of cardiovascular disease.[5]

The benefits of aspirin therapy must be balanced against the increased risk for GI adverse events such as dyspepsia and bleeding associated with the use of aspirin. Therefore concomitant gastroprotection with a proton pump inhibitor (PPI) is recommended for cardiovascular patients who require continuous low dose aspirin therapy and are at increased risk for gastrointestinal injury.[6]

All drugs have both benefit and risk. Treatment must be based on whether the potential benefit outweighs the risk of harm. The benefit of aspirin in the treatment of cardiovascular disease is well documented as is the risk of GI bleeding associated with its use. The challenge to healthcare providers is to determine the risk/benefit balance for individual patients.

The expert consensus document developed by the American College of Cardiology Foundation (ACCF), the American College of Gastroenterology (ACG) and the American Heart Association (AHA) recommend proton pump inhibitors be co-prescribed with antiplatelet therapy such as aspirin to reduce the increased risk of GI complications. The need for GI protection increases with the number of risk factors for severe bleeding, the strongest and most consistent risk factor being a previous upper GI bleed (UGIB).

Patients with coronary artery disease and prior UGIB are at a greater risk of cardiovascular events and GI bleeds, so concomitant aspirin and PPI therapy may provide an acceptable balance of risk and benefit. This is also evident in stable patients

[4] Hirata, Yoshikazu et al Incidence of gastrointestinal bleeding in patients with cardiovascular disease: buffered aspirin versus enteric coated aspirin; Scandinavian Journal of Gastroenterology, 2011;46:803-809

[5] Scheinman, J; Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low dose acetylsalicylic acid: a randomized, controlled trial (OBERON);Heart 2011;97:797-802

[6] Harrington, R et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the GI risks of antiplatelet therapy and NSAID use. Am J Gastroenterl 2010;105:2533-49

undergoing coronary revascularization who may have had a GI bleed previously. If a coronary stent is placed to treat the patient, the risk/benefit also may favor the concomitant use of antiplatelet therapy and a PPI.

The other factors that increase the risk of GI bleeding with antiplatelet therapy such as advanced age, concomitant use of coumadin, steroids, NSAIDs; or *H. pylori* infection may be mitigated with the combined use of aspirin and PPI therapy.

The use of Yosprala Tablets containing enteric coated aspirin 325 mg and omeprazole 40 mg would presumably reduce the undesired gastrointestinal effects often associated with long term aspirin use. The addition of the omeprazole to the aspirin may result in improving adherence to the aspirin therapy by eliminating upper GI adverse events often associated with aspirin use such as dyspepsia and heartburn. Increased compliance with this medication would enhance therapeutic goals while improving the overall risk benefit profile for aspirin in patients being treated for the secondary prevention of cardiovascular and cerebrovascular disease who are at risk for developing gastric ulcers.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

As of 2005, all prescription NSAIDs have been required to include a Box Warning and Medication Guide as parts of the product label due to the risk of cardiovascular and gastrointestinal adverse events. Aspirin, an NSAID, is in a class of drugs called salicylates that have a known risk of gastrointestinal adverse events associated with chronic or long term use, even at low doses. Therefore a Medication Guide is necessary to communicate these risks. A REMS is not recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The sponsor requested a full waiver from the requirement to conduct studies with Yosprala in patients from birth to 18 years of age because the proposed indication in the pediatric population is rare, therefore the incidence of aspirin associated gastric ulcers would also expected to be rare.. The Pediatric Review Committee convened on September 25, 2013 and the waiver request was agreed upon.

2 Introduction and Regulatory Background

2.1 Product Information

Yosprala Tablets are a multilayer tablet consisting of an enteric-coated aspirin core (ECASA 325 mg), and an immediate release (IR) omeprazole 40 mg film coat. This

allows for the sequential release, first of omeprazole in the stomach (b) (4) followed by the release of aspirin (b) (4) Yosprala Tablets are intended for oral administration on a once daily regimen to provide the benefits of aspirin with the upper gastrointestinal (UGI) protection of the Proton Pump Inhibitor (PPI; omeprazole).

Omeprazole is a proton pump inhibitor that inhibits the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell. The labeled indications include:

- Treatment in adults of duodenal ulcer and gastric ulcer
- Treatment in adults and children of gastroesophageal reflux disease (GERD) and maintenance of healing of erosive esophagitis

The safety and effectiveness of omeprazole in pediatric patients < 1 year of age have not been established.

Omeprazole currently does not have an indication for the prevention of gastric or duodenal ulcers.

Aspirin is acetylsalicylic acid and is chemically known as benzoic acid, 2-(acetyloxy). Aspirin irreversibly inhibits platelet COX-1. Aspirin is available by prescription and over the counter (OTC). The professional labeling for aspirin in the Monograph (21CFR343.80) includes the following indications which are all secondary prevention of cardiovascular event indications. The dose is in parentheses:

- Reduction of the combined risk of death and non-fatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli (50-325 mg once a day, continued indefinitely),

- Reduction of risk of vascular mortality in patients with a suspected acute MI (160-162.5 mg once a day for 30 days),

- Reduction of combined risk of death and non-fatal MI in patients with previous MI or unstable angina pectoris (75-325 mg once a day, continued indefinitely), and

- Reduction of combined risk of MI and sudden death in patients with chronic stable angina pectoris (75-325 mg once a day, continued indefinitely).

Aspirin is also indicated for use in revascularization procedures when there is a preexisting condition for which aspirin is already indicated. For CABG, 325 mg daily is started post- procedure and continue for 1 year. For PTCA, 325 mg is administered pre-surgery, and the maintenance dose post-surgery is 160-325 mg daily, continued indefinitely. For carotid endarterectomy, the dose ranges from 80 mg once daily to 650 mg twice daily, continued indefinitely.

Patients in the studies submitted in support of this application used Omeprazole in an immediate release formulation at 40mg combined in a single tablet with delayed release aspirin at 325 mg.

Structural Formulas

Figure 1 Aspirin

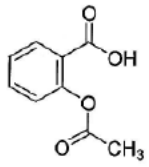
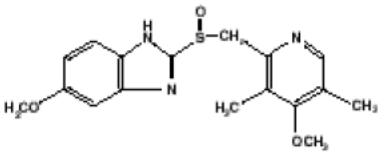


Figure 2 Omeprazole



Molecular Formula

The empirical formula of aspirin is $C_9H_8O_4$. The empirical formula of omeprazole is $C_{17}H_{19}N_3O_3S$.

Molecular Weight

The molecular weight of aspirin is 180.16. The molecular weight of omeprazole is 345.4.

2.2 Tables of Currently Available Treatments for Proposed Indications

There is no FDA approved drug for the proposed indication (b) (4)

[redacted]

2.3 Availability of Proposed Active Ingredient in the United States

Prilosec® (Omeprazole) is currently approved for use in adult and pediatric (greater than one year of age) patients for various indications. Primarily it is used to treat duodenal and gastric ulcers in adults. It is also used to treat gastroesophageal reflux disease (GERD) and maintenance of healing of erosive esophagitis in adults and children.

Aspirin is available by prescription and over the counter (OTC).

2.4 Important Safety Issues With Consideration to Related Drugs

PPIs are widely used and have generally been found to be safe and well-tolerated. Current PPI labeling includes the following warnings and precautions:

- Symptomatic response does not preclude the presence of gastric malignancy
- Atrophic gastritis has been noted with long-term therapy
- PPI therapy may be associated with the increased risk of *Clostridium difficile* associated diarrhea.
- Avoid concomitant use of Prilosec with clopidogrel
- Bone fracture: Long term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine.
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs.
- Avoid concomitant use of Prilosec® with St. John's Wort or rifampin due to the potential reduction in omeprazole concentrations
- Interactions with diagnostic investigations for Neuroendocrine Tumors: Increase in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased Chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors.

Additionally, prescribers should be warned against concomitant use of certain antiretroviral drugs and drugs for which the gastric pH may affect bioavailability. See individual product labeling for further details.

Aspirin is also widely used and patients who consume three or more alcoholic drinks everyday should be counseled regarding the bleeding risks involved with chronic, heavy alcohol use while taking aspirin. Low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited and acquired bleeding disorders. Some of the possible major gastrointestinal side effects with aspirin use include stomach pain, heartburn, nausea, vomiting, and frank GI bleeding. Although minor upper GI symptoms such as dyspepsia are common and may occur at any time during therapy with aspirin use, physicians should be vigilant for signs

of ulceration and bleeding, even in the absence of previous GI symptoms. Aspirin should be avoided in patients with severe renal failure and severe hepatic insufficiency. For more information please see the professional labeling for aspirin in the Monograph (21CFR343.80).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development program for PA32540 Tablets (delayed release aspirin, 325 mg/immediate release omeprazole, 40 mg) was discussed with the Agency at a number of meetings and included a Special Protocol Assessment. The discussions and development took place under IND 78,747 (submitted December 19, 2007).

August 8, 2007 (Meeting Minutes)
The Agency agreed to the elements required for a 505(b)(2) submission. The agreed reference listed drugs (RLDs) are Ecotrin® (Enteric Coated Aspirin; GSK) and Prilosec® Delayed Release Capsules (AstraZeneca). The demonstration of improved GI safety relative to EC aspirin alone is considered sufficient justification for development of this combination product relative to the requirements of 21CFR300.50.

To satisfy the requirements of 21CFR320.25 (g)(1), comparative bioavailability of aspirin and omeprazole from PA32540 to the RLDs administered concurrently would be required.

To support the aspirin component of PA32540, the Agency agreed that bioequivalence of PA32540 to the RLD reference listed drug Ecotrin was acceptable.

October 24, 2008 (Meeting Minutes)
POZEN agreed to support their rationale for use of salicylic acid rather than acetylsalicylic acid as the analyte for demonstrating bioequivalence. Due to the short half-life of acetylsalicylic acid, the Agency had originally agreed to the use of salicylic acid and also recommended collecting acetylsalicylic acid levels to estimate systemic exposure.

May 25, 2011 (Meeting Minutes)
A Type C meeting convened to discuss alternative PA presentations; the Agency noted that acetylsalicylic acid should be the analyte of choice for aspirin products. In response, POZEN provided data and justification for adequacy in the context of having demonstrated bioequivalence to the RLD based on salicylic acid as previously agreed with the Agency.

(b

December 12, 2011 (Advice Letter) and February 28, 2012 (Meeting Minutes)
Written advice and a Type A meeting concluded that bioequivalence to the RLD should be based on acetylsalicylic acid as analyte and it was recommended that POZEN use a reference scaled bioequivalence approach specified in the guidance for progesterone.

Study Design/Efficacy

August 8, 2007 (Meeting Minutes)
The two efficacy studies PA32540-301 and PA32540-302 each enrolled subjects with established cardiovascular disease who were: 1) age 18 to 54 (18 to 60 in PA32540-302) with history of a documented uncomplicated gastric or duodenal ulcer within the past 5 years or 2) age ≥ 55 years (>60 years in PA32540-302) regardless of prior history of ulcer as age alone is acceptable as a risk factor to develop aspirin-associated UGI damage.

July 29, 2008 (SPA Advice Letter)
For studies PA32540-301 and PA32540-302, the 1:1 ratio for randomization to either PA32540 or EC-aspirin 325 mg included a specified stratification for NSAID use

The primary endpoint to support product approval was the cumulative incidence of subjects developing GU confirmed by endoscopy through 6-months of treatment with PA32540 relative to the EC-aspirin control.

The definition of GU, both for the purposes of patient inclusion/exclusion and assessment of response, was a mucosal break ≥ 3 mm in diameter with depth.

The adequacy of the proposed extent of exposure in the Phase 3 efficacy and the open-label, long-term safety studies was confirmed with the Agency.

October 24, 2008 (Meeting Minutes)
ECASA 325 mg was accepted as the comparator arm in this population and studies were of 6-month duration to adequately assess durability of the risk reduction.

Exclusion criteria included subjects on aspirin at doses other than 325 mg/day, and subjects with uncontrolled cardiovascular or cerebrovascular disease.

The adequacy of the proposed extent of exposure in the Phase 3 efficacy and the open-label, long-term safety studies was confirmed with the Agency.

March 12, 2008 (Advice Letter); July 29, 2008 (SPA Advice Letter); and October 24, 2008 (Meeting Minutes)
The design of the efficacy studies, including the choice of aspirin 325 mg as a clinically relevant dose, were agreed to by the Agency following an initial response after the IND

filing (Advice Letter; July 29,2008), a clinical special protocol assessment and a Type A meeting based on the SPA.

February 18, 2009 (Advice Letter)
The Agency confirmed the use of endoscopically observed gastric ulcers as the primary endpoint in the controlled studies.

November 29, 2011(Advice Letter)
Details of the efficacy studies were initially discussed as part of the SPA (July 29, 2008) and confirmed following submission of the final statistical analysis plans for the studies.

The primary endpoint to support product approval was the cumulative incidence of subjects developing GU confirmed by endoscopy through 6-months of treatment with PA32540 relative to the EC-aspirin control.

February 28, 2012 (Meeting Minutes)
In response to the Agency's advice to include a lower aspirin dose strength (i.e., 81mg) POZEN submitted data in this application supporting the therapeutic equivalence of PA8140 to ECASA 81 mg and a scientific rationale for the need for PPI treatment to reduce the UGI damage caused by ECASA 81 mg.

Chemistry, Manufacturing and Controls

September 29, 2009 (SPA Advice Letter)
The production lots of PA32540 Tablets supporting this application were manufactured from (b) (4) tablet batches and (b) (4) based upon the Agency's response to a Special Protocol Assessment of the stability protocol.

This submission includes 24-month stability data with the statistical analysis package for PA32540 Tablet. A (b) (4) design was implemented for PA32540 Tablets packaged in four container/tablet count HDPE bottle configurations. The dissolution testing used for the definitive stability studies supporting the NDA and intended for release of commercial batches, is performed in two stages in accordance with Agency recommendation.

Nonclinical Development
August 8, 2007 (Meeting Minutes)

The Agency agreed in a July 9, 2007 Pre-IND meeting that POZEN could file a 505(b)2 application relying on FDA's previous findings of safety and publically available information on the toxicology of aspirin and omeprazole to meet the nonclinical assessment requirements as part of the new drug application.

No new nonclinical pharmacology, pharmacokinetic or toxicology studies have been conducted by POZEN with PA32540 or PA8140 Tablets.

2.6 Other Relevant Background Information

Not applicable

3 Ethics and Good Clinical Practices

Per the sponsor, all studies were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, as well as described in the Code of Federal Regulations, Title 21, and Part 50 (21CFR50)

3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was organized appropriately and easily navigable.

3.2 Compliance with Good Clinical Practices

According to the applicant, all studies were conducted in accordance with the US Code of federal Regulations (CFR) governing the protection of human patients (21CFR 312). All studies were also conducted in accordance with US Title 21 CFR on Good Clinical Practices (GCPs), which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration.

The following sites were identified for inspection. Site Site 0776, investigator Dr. Sabine Hazan-Steinberg and Site 0671, investigator Neal Secrist. The sites were selected primarily because they had the largest number of enrollees per study (Study PA3245-301 and Study PA3245-302). Many sites had 15 or less subjects enrolled. Sites 0776 and 0671 were inspected and determined NAI by Dr. Khairy Malek Division of Good Clinical Practice Compliance/ Office of Scientific Investigations/ Office of Compliance/CDER.

3.3 Financial Disclosures

For studies PA32540-301 and PA32540-302 the Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement

with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no significant efficacy or safety issues related to the review of this product.

4.2 Clinical Microbiology

Clinical Microbiology considerations do not apply to this application, because it is not intended as an antimicrobial product.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical pharmacology, pharmacokinetic or toxicology studies have been conducted by POZEN with PA32540 or PA8140 Tablets.

4.4 Clinical Pharmacology

The Clinical Pharmacology reviewer has stated there is no PK data for the PA8140 formulation. No clinical studies were conducted for this formulation as well. Note that at the time of finalization of this review, the sponsor had initiated PK studies to demonstrate BE between the omeprazole component of PA32540 and PA8140 in order to support approval of the PA8140 dose.

Please see the Clinical Pharmacology review by Dr. Dilara Jappar and the Biopharmaceutical Review by Dr. Banu Zolnik for a detailed discussion of the pharmacokinetic and pharmacodynamic profile of Yosprala (PA32540) Tablets.

4.4.1 Mechanism of Action

PA32540 Tablets consist of an immediate release omeprazole layer surrounding an enteric coated aspirin core resulting in the coordinated release of the active ingredients. This allows for the sequential release, first of omeprazole in the stomach (b) (4)

(b) (4) followed by the release of aspirin (b) (4)

4.4.2 Pharmacodynamics

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the $[H^+/K^+]$-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclooxygenase (COX-1) via acetylation and prevents formation of the platelet aggregating factor thromboxane A2 in a dose-independent manner. Because platelets cannot generate new COX, the effects of aspirin last for the duration of the life cycle of the platelet (approximately 10 days).

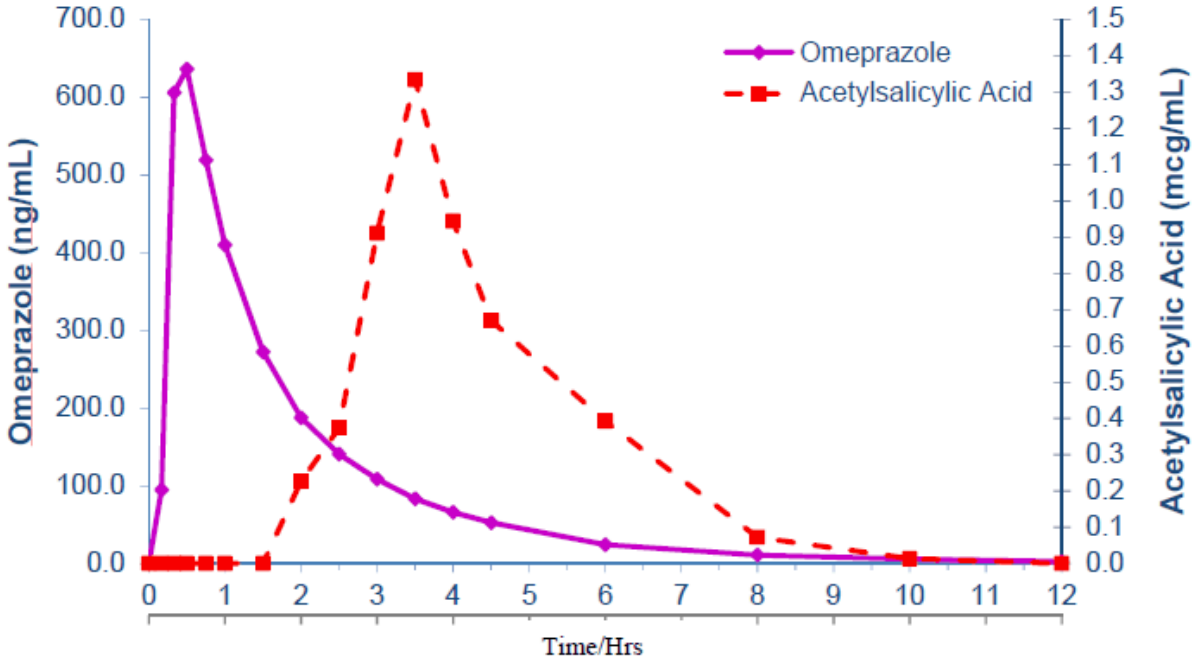
Measurable inhibition of platelet function occurs within 60 minutes of aspirin administration and is associated with prolongation of bleeding time. After a single dose of aspirin, platelet COX activity recovers by approximately 10% per day as a function of platelet turnover. A single low dose of aspirin can, therefore, effectively suppress both serum and urinary thromboxane B2 by 95% for about 5 days or indefinitely if taken daily.

4.4.3 Pharmacokinetics

The cardioprotective activity of aspirin is attributed to aspirin (acetylsalicylic acid), and not salicylic acid. Aspirin is hydrolyzed to form salicylic acid. Therefore, salicylic acid was treated as secondary analyte in the PK review. The plasma exposure profiles of acetylsalicylic acid or salicylic acid and omeprazole following Yosprala (PA32540) Tablets administration is consistent with the sequential delivery design of the tablet, i.e., peak omeprazole levels precede peak aspirin levels The profile is consistent with the designed tablet release characteristics and supports the intended pharmacodynamic effect of early availability of the gastro-protective component prior to systemic exposure to the mucosal insult. Comparative data for Figure 3 and Figure 4 is provided from the bioequivalence study PA32540-104, as omeprazole levels were not determined in the formal acetylsalicylic acid bioequivalence study (PA32540-115); the acetylsalicylic acid

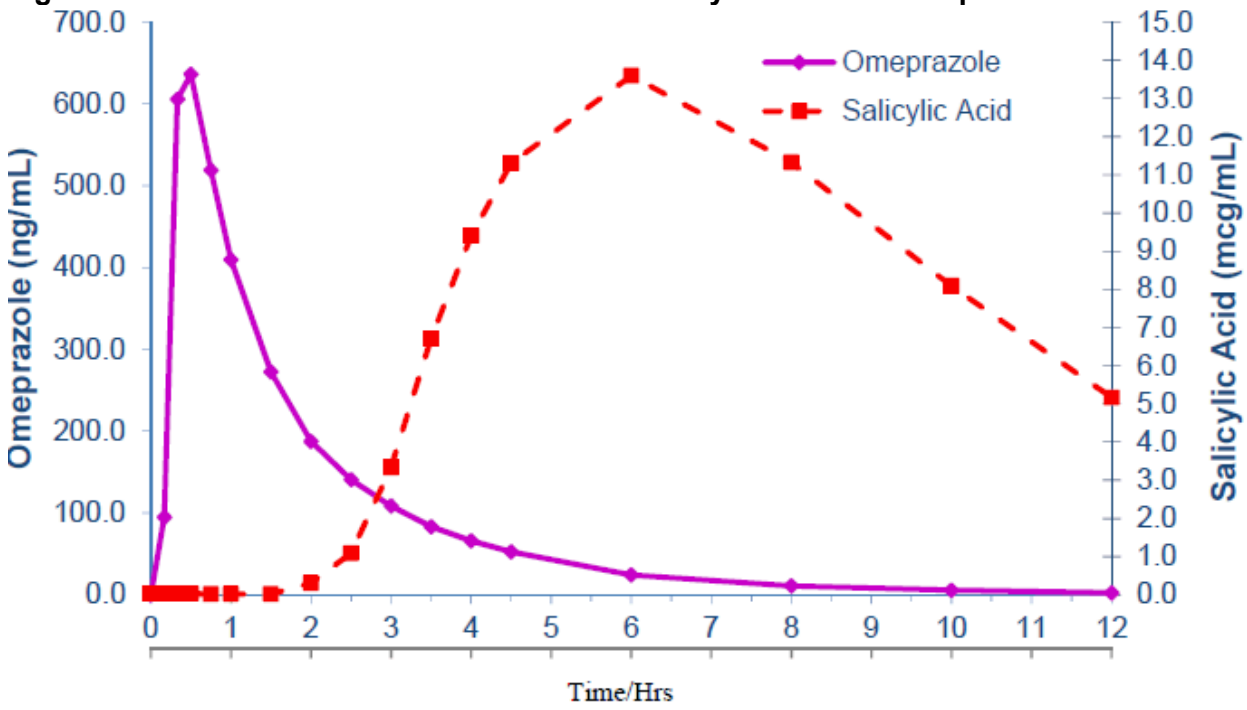
profile from Study PA32540-115 was consistent with that displayed in Figure 3 (Study PA32540-115 Figure 2,Treatment A).

Figure 3 Pharmacokinetic Profile of PA32540 - Acetylsalicylic acid and Omeprazole



Source: Applicant, CSR. Figure 14 Summary of Biopharmaceutics and associated Analytical Methods. Page 98

Figure 4 Pharmacokinetic Profile of PA32540-Salicylic acid and Omeprazole



Source: Applicant, CSR. Figure 14 Summary of Biopharmaceutics and associated Analytical Methods. Page 98

This was observed similarly in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

Reviewer's comments: The pharmacokinetics of Yosprala tablets has not been determined in subjects with renal impairment or hepatic insufficiency. However based on individual PK data for aspirin and omeprazole supplied in the submission, with regards to labeling Yosprala should be avoided in patients with severe renal /hepatic insufficiency. Also no data exists on the pharmacokinetics of Yosprala Tablets in patients over age 65 or of different ethnicities. However data on aspirin and omeprazole do not suggest that dosage adjustment based on gender or race is warranted.

5 Sources of Clinical Data

The clinical development program for PA32540 was designed to support the proposed indication for preventing recurrent cerebrovascular and cardiovascular events, in subjects at risk of developing aspirin-associated gastric ulcers. The cardiovascular indications are supported in the current application by demonstration of a bridge for PA32540 to the currently marketed product enteric-coated aspirin (EC-aspirin) 325 mg (Ecotrin 325 mg). PA8140 Tablets are bioequivalent to EC-aspirin 81 mg (Ecotrin 81 mg), meet applicable USP monograph (b) (4) The goal of the clinical efficacy studies was to demonstrate the efficacy of the IR omeprazole 40 mg component as assessed by the incidence of gastric ulcers comparing PA32540 to EC-aspirin 325 mg. A description of all studies is presented in Table 1.

Data from eight phase 1 trials provide a description of the clinical pharmacology of ECASA and IR-omeprazole 40 mg in PA tablets. A total of 506 healthy volunteers participated in the studies conducted. Five studies assessing UGI damage were conducted at the same institution. The subject populations were similar across the studies.

Gastroduodenal injury was determined by endoscopic examination using the same blinded endoscopist. Gastric and duodenal bulb lesions were scored using the Lanza (1988) method: 0 = no visible lesions; 1 = 1 hemorrhage or erosion; 2 = 2-10 hemorrhages or erosions; 3 = 11-25 hemorrhages or erosions; 4 = >25 hemorrhages or erosions or an ulcer. An ulcer was defined as a mucosal break of at least 3 mm in diameter with depth.[7]

Five studies assessing UGI damage were conducted in the same institution, using a similar subject population and the same individual who was blinded to study treatment performed all endoscopies. Studies PA325-101, PA325-102 and PA325-106 evaluated in healthy volunteers the incidence of aspirin-associated UGI injury (Grade 3 or 4 Lanza scores) following 27 days of once daily dosing with PA32520 (ECASA 325 mg and IR-omeprazole 20 mg), PA32540 (ECASA 325 mg and IR-omeprazole 40 mg), and two doses of ECASA 81 mg and 325 mg. Two other two-week UGI endoscopy studies (PA32540-109 and PA08140-101) compared the incidence of UGI damage (Grades 3 or 4 and Grade 0 Lanza scores) of once daily dosing with PA Tablets administered with or without celecoxib and EC-aspirin administered with celecoxib.

[7] Lanza FL, Aspinall RL, Swabb EA et al. (1988) Double-Blind, Placebo-Controlled Endoscopic Comparison of the Mucosal Protective Effects of Misoprostol Versus Cimetidine on Tolmetin-Induced Mucosal Injury to the Stomach and Duodenum. Gastroenterology; 95:289-294.

The gastroprotective effects of the chosen IR-omeprazole strength, 40 mg (when combined with ASA 325mg) was confirmed in the pivotal efficacy and safety studies (PA32540-301 and PA32540-302).

Study PA32540-112 compared, in healthy volunteers, the effects of PA32540 versus ECASA 325 mg administered with EC-omeprazole 40 mg once daily for 7 days on intragastric pH (measured as the percent time of pH > 4.0 over 24 hours).

Two additional clinical pharmacology studies (PA32540-110 and PA32540-111) assessed the effect of PA32540 or ECASA dosed concurrently or separately (10 hours apart) for 7 days, on the *ex vivo* platelet aggregation inhibition due to clopidogrel.

Two identical, adequate and well-controlled studies PA32540-301 and PA32540-302 were conducted to confirm the efficacy of the IR omeprazole 40 mg component of PA32540 in the reduction of gastric ulcer incidence (primary endpoint) compared with EC-aspirin 325 mg QD for 6 months.

These phase 3 clinical trials were randomized, multi-center, double-blind, parallel group, active controlled trials and included mandatory UGI endoscopies at baseline and Months 1, 3 and 6 or early termination. Both studies evaluated differences in several secondary endpoints including, incidence of gastric and/or duodenal ulcers; proportion of subjects completing treatment without gastric ulcers or discontinuation due to pre-specified UGI adverse events ("Treatment Success"); discontinuations due to pre-specified UGI adverse events; and subjects with no heartburn at final visit ("Heartburn Resolution"). Pre-specified UGI adverse events including dyspepsia, nausea, and upper abdominal pain and vomiting were evaluated in the 12 month open-label safety study.

Studies PA32540-301 and PA32540-302 showed a clinically and statistically significant lower incidence of gastric ulcers in subjects who took PA32540 compared with those who took ECASA 325 mg on a daily basis for 6 months. In addition, both studies demonstrated significant differences favoring PA32540 in all secondary endpoints. No phase 3 studies were conducted with PA8140 but since it contains the same 40 mg dose of IR omeprazole as PA32540, the Sponsor reasoned a similar benefit would be expected compared to EC-aspirin 81 mg.

A 12-month open-label safety study, PA32540-303, was conducted in order to evaluate the long term safety of PA32540. This study also provided supportive efficacy data in terms of UGI tolerability.

The two phase 3 efficacy studies PA32540-301 and PA32540-302 will be reviewed for this NDA application.

5.1 Tables of Studies/Clinical Trials

Table 1 Tabular Description of All Clinical Trials

Study ID	Objective	Primary Endpoint	Design	Treatment Duration	Test Article	N
PA8140-101	Gastroduodenal mucosal damage	Proportion Grade ¾ Lanza scores	R, PG, AC, Single blind	13 days	PA8140 PA8140 + celecoxib ECASA 81 mg +celecoxib	N= 30 N= 30 N= 30
PA8140-102	Bioavailability and Pharmacokinetics	Plasma levels of acetylsalicylic acid	OL ,R 3-way Crossover	3 single dose periods (3 tablets) of 8 hours duration	PA8140 ECASA 81mg ECASA 81mg	N=27
PA325-101	Gastroduodenal mucosal damage	Proportion Grade ¾ Lanza scores	R, PG, AC, Single blind	27 days	PA32520 ECASA 325 mg	N= 40 N= 40
PA325-102	Gastroduodenal mucosal damage	Proportion Grade ¾ Lanza scores	R, PG, AC, Single blind	27 days	PA32520 ECASA 81 mg	N= 41 N= 39

Study ID	Objective	Primary Endpoint	Design	Treatment Duration	Test Article	N
PA32540-104	Bioavailability and Pharmacokinetics	Plasma levels of acetylsalicylic acid	OL ,R 3-way Crossover	3 single doses of 72 hours duration	PA32540 ASA component of PA32540 ECASA	N= 36
PA32540-105	Food Effect	Plasma levels	OL ,R , 3-way Crossover, Food effect	3 single dose periods	PA32540 5 min after meal 60 min prior to meal 4 hour fast	N=24
PA32540-106	Gastroduodenal mucosal damage	Proportion Grade ¾ Lanza scores	R, PG, AC, Single blind	27 days	PA32540 ECASA 325 mg	N= 40 N= 40
PA32540-109	Gastroduodenal mucosal damage	Proportion Grade ¾ Lanza scores	R, PG, AC, Single blind	13 days	PA32540 PA32540+celecoxib ECASA 325 mg +celecoxib	N= 41 N= 39

Study ID	Objective	Primary Endpoint	Design	Treatment Duration	Test Article	N
PA32540-110	Inhibition of platelet aggregation	%IPA using Chronolog ADP agonist	OL ,R AC,Crossover	Three 7-day treatments	Clopidogrel/ECASA 325mg qd Clopidogrel/PA32540 PA32540 in A.M./Clopidogrel 10 hrs. apart	N= 30
PA32540-111	Inhibition of platelet aggregation	%IPA using Chronolog ADP agonist	OL ,R AC, Crossover	Two 7-day treatments	PA32540 + Clopidogrel 10hrs apart ECASA 81mg qd + EC coated omeprazole 40mg + Clopidogrel	N=30
PA32540-112	PD Effect on intragastric pH	Intragastric pH percent time >	OL ,R, AC, 2-way Crossover	Two 7-day treatments	PA32540 EC omeprazole40mg/ECASA 325mg	N=26
PA32540-113	PK/Relative Bioavailability	Plasma levels of omeprazole and salicylic acid	OL ,R, AC, 4-way Crossover	4 single dose treatments	PA32540 EC omeprazole40mg/ECASA 325mg ECASA 325 mg alone EC omeprazole 40mg alone	N= 36
PA32540-115	PK/Relative Bioavailability	Plasma levels of acetylsalicylic acid	OL ,R, AC, 3-way Crossover	3 single dose periods of 12 hours duration	PA32540 ECASA 325 mg alone EC omeprazole 40mg alone	N= 42

Study ID	Objective	Primary Endpoint	Design	Treatment Duration	Test Article	N
PA32540-301	Reduction of risk of Gastric Ulcers	Cumulative incidence of subjects with gastric ulcers by endoscopy throughout 6 months of treatment	R,DB, PG, AC	6 months	PA32540 ECASA 325mg	N= 265 N= 265
PA32540-302	Reduction of risk of Gastric Ulcers	Cumulative incidence of subjects with gastric ulcers by endoscopy throughout 6 months of treatment	R,DB, PG, AC	6 months	PA32540 ECASA 325 mg	N= 259 N=260
PA32540-303	Long term safety of PA32540 in at risk patients	Adverse events	OL	12 months	PA32540	N= 380

Source: NDA 205103; Module 2.7.3 Summary of Clinical Efficacy. 16-20.

5.2 Review Strategy

In this application, the efficacy and safety data for the drug were generated from two clinical efficacy and safety trials, PA32540-301 and PA32540-302. These two clinical trials will be reviewed in section 5.3 and the comparative summary of efficacy and safety will be discussed in sections 6 and 7 respectively.

5.3 Discussion of Individual Studies/Clinical Trials

Efficacy and safety data from two studies PA32540-301 and PA32540-302 were evaluated for the proposed indication of preventing recurrent cerebrovascular and cardiovascular events, in subjects at risk of developing aspirin-associated gastric ulcers

5.3.1 Study PA32540-301 and PA32540-302

Study PA32540-301 was a 6-month, phase 3, randomized, double –blind, parallel group, controlled, multicenter 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-associated ulcers. The study was conducted at 78 investigative sites in the US.

Study Period
10 November 2009 to 30 January 2012

Study Objectives

Primary Objective: To demonstrate that PA32540 caused fewer gastric ulcers in subjects at risk for developing aspirin–associated ulcers compared to enteric coated aspirin (ECASA) 325 mg.

Secondary Objectives:

- To demonstrate that PA32540 caused fewer gastric and/or duodenal ulcers in subjects at risk for developing aspirin associated ulcers compared to ECASA 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 leading to discontinuation

- To compare between treatments the proportion of subjects discontinuing the study due to UGI adverse events

- 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.

Study Design

Study PA32540-301 was a randomized double-blind, parallel-group, multicenter, 6-month study that was conducted at 78 investigative sites in the US. Eligible subjects were randomized into the two treatment groups, PA32540 (N=265) and ECASA 325 mg (N=265)

Screening procedures were performed up to 21 days before randomization. There were 2 Screening Visits (Visits 1 and 2), which were separated by no more than 14 days. Screening endoscopies were performed at Visit 2; if these endoscopies revealed any gastric, esophageal or duodenal ulcers ≥ 3 mm in diameter with depth, subjects were not randomized to study drug. If endoscopic results were available at Visit 2, randomization may have occurred on the same day otherwise, randomization occurred within 7 days of Visit 2 (Visit 3).

Subjects who fulfilled the inclusion and no exclusion criteria were stratified into 3 groups based on concomitant NSAID use (non-specific NSID use, cyclooxygenase-2 (COX-2) inhibitor use, and no NSAID use), and randomized within each of these groups to the study drug. Subjects taking NSAIDs continued their prescribed NSAID therapy throughout the study. Study drug administration began the day after randomization with subjects taking single daily doses of either PA32540 or EC-aspirin 325 mg for up to 6

months. Study medication was taken in the morning, approximately 1 hour prior to the first meal of the day. NSAIDs were taken at least 2.5 hours after PA32540 or EC-aspirin.

Subjects returned to the clinical research unit 1 month (Visit 4), 3 months (Visit 5), and 6 months (Final Visit) after the initiation of study drug for endoscopies, heartburn assessments, and safety assessments. Interim endoscopies were performed if clinically indicated. If a gastric, duodenal or esophageal ulcer was detected at Visits 4 or 5 or at any time during the trial, study drug was discontinued, and the subject was withdrawn from the study and placed on appropriate ulcer treatment.

In between clinic visits, subjects were contacted monthly by telephone. During each clinic visit and telephone interview, adverse events and concomitant medication use (including NSAID use) were assessed.

Subjects were considered to have completed the study if they completed 6 months of treatment and had a 6-month endoscopy, or if the primary endpoint (gastric ulcer confirmed by endoscopy) had been reached prior to 6 months.

Screening Visit 1

Once a written informed consent was obtained, subjects were assigned screening numbers and underwent the screening procedures listed below:

- Review of inclusion /exclusion criteria
- Medical history - As part of the medical history assessment, study site staff inquired about the subject's status with regard to heartburn, stomach pain/discomfort. The study Medical Monitor was consulted if there was any uncertainty regarding eligibility.
- Review of concomitant medications
- Urine pregnancy tests for women of child-bearing potential
- Vital signs (seated blood pressure [BP], heart rate measured after subject had been seated for at least 5 minutes)
- Physical Examination
- 12-Lead electrocardiograms (ECGs) - The Investigator (or designee) performed a 12-lead ECG to determine eligibility for study participation. The original ECG trace was signed by the Investigator and retained at the site as source documentation.
- Collection of clinical laboratory samples for hematology and chemistry analyses
- Collection of a stool sample for the H. pylori stool antigen test
- Recording of serious adverse events (SAEs).

Screening Visit 2
Screening Visit 2 was conducted within 14 days of the first screening visit and was scheduled after safety laboratory test results were known. Subjects who were eligible underwent the following assessments:

- Final review of inclusion/exclusion criteria
- Medical history updated
- Concomitant medications reviewed;
- Endoscopic examination of the UGI tract. If these endoscopies revealed any gastric, esophageal or duodenal ulcers ≥ 3 mm in diameter with depth, subjects were not randomized to study drug. Endoscopic abnormalities were documented in the subject's medical history
- Recording of SAEs.

Visit 3 Baseline/ Randomization
Visit 3 and Screening Visit 2 were combined if endoscopy results were available. If not, a separate visit occurred when the endoscopy results were available. Visit 3 was to occur within 7 calendar days of Screening Visit 2. The following study procedures were performed:

- Review of endoscopy results
- SAEs recorded
- Medical history updated to include baseline endoscopic findings
- Vital Signs
- Clinical laboratory samples collected for hematology and chemistry analyses ONLY if the visit date was greater than 14 days from Screening Visit 1
- Heartburn assessment
- Review of concomitant medications (not necessary if Visit 3 was combined with Screening Visit 2)
- Randomization and dispensing of study drug and review medication dosing, i.e., once daily on an empty stomach about 1 hour prior to the first meal.

Subjects were given the study drug at this visit and were instructed to take the first dose of study drug in the morning of the following day.

Visit 4 (Day 30+/- 6 days) and Visit 5 (Day 90+/- 12 days)
This treatment period was conducted on an outpatient basis. Subjects returned to the research unit at 30 days (Visit 4), 90 days (Visit 5)), and 6 months (Final visit), or an early termination. At Visits 4 and 5 the following procedures were performed:

- Endoscopy
- Recording of serious and non-serious adverse events;
- Review of concomitant medication;
- Study drug accountability and dispensing;
- Collection of clinical laboratory samples for hematology and chemistry analyses;

- Heartburn assessment – prior to endoscopy
- Urine pregnancy tests for women of child-bearing potential;
- Vital signs

At Visit 4 the study drug was dispensed in sufficient quantities to last until Visit 5 where the drug was dispensed in an amount that would last until the final visit (Visit 6).

Subjects were contacted by telephone in between study visits to discuss study drug dosing, adverse events, and concomitant medication use.

If an endoscopically confirmed gastric duodenal or esophageal ulcer was detected at Visits 4 or 5, the study drug was discontinued and the subject was withdrawn from the study and placed on the appropriate ulcer treatment. Duodenal and esophageal ulcers were considered adverse events but gastric ulcers were not. Interim endoscopies were performed if clinically indicated.

Final Visit (Day 180 +/- 12 days) or Early Termination
The following procedures were performed at study completion or at the final assessment following early termination. Investigators made every reasonable effort to perform endoscopy and other end-of-study assessments on subjects who discontinued the study prematurely:

- Endoscopy)
- Recording of serious and non-serious adverse events
- Review of concomitant medication
- Study drug accountability
- Collection of clinical laboratory samples for hematology and chemistry analyses
- Heartburn assessment – prior to endoscopy;
- Urine pregnancy tests for women of child-bearing potential
- Physical examination
- Vital signs

Study Population

Selection of Trial Population for Studies PA32540-301 and PA32540-302
Subjects who were candidates for participation in the study were screened for inclusion/exclusion criteria before enrollment into the study. The inclusion criteria differed slightly between the two studies with regards to age and prior CV history. Subjects were eligible for inclusion in these studies if the following criteria applied:

1) Males or non-pregnant, non-breastfeeding females who had been on daily (at least 5 days per week) aspirin 325 mg for at least 3 months (6 months in Study PA32540-301), AND, who were:

- 55 years of age and older (>60 in PA32540-301)
- 18-54 years of age (18 to 60 in PA32540-301) with a history of a documented gastric or duodenal ulcer within the past 5 years.

Study PA32540-302 required that subject were expected to use daily aspirin 325 mg for at least 6 months.

2) Study PA325-301 enrolled subjects currently on 325 mg aspirin for secondary prevention of cardio- or cerebrovascular events for at least three months prior to enrollment, including subjects who have undergone coronary revascularization or carotid endarterectomy at least six months prior to enrollment.

   Study PA32540-302 enrolled subjects receiving aspirin for the secondary prevention of the following cardiovascular or cerebrovascular events:

   Diagnosis or history of:
   - Confirmed or suspected myocardial infarction (MI);
   - Ischemic stroke; or
   - Transient ischemic attack (TIA).

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

   Or history of:
   - Coronary artery bypass graft (CABG);
   - Percutaneous coronary intervention (PCI) with or without stent; or
   - Carotid endarterectomy.

3) Female subjects were eligible if they were of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) or were of childbearing potential, and had a negative pregnancy test at Screening and at least one of the following applied or was agreed to by the subject:
   - Female sterilization or sterilization of male partner;
   - Use of hormonal contraception by oral route, implant, injectable, or vaginal ring;
   - Use of any intrauterine device with published data showing that the lowest expected failure rate was less than 1% per year;

- Use of double-barrier method (2 physical barriers or 1 physical barrier plus spermicide);
- Use of any other contraceptive method with published data showing that the lowest expected failure rate was less than 1% per year.

4) Ability to understand and comply with study procedures required and ability and willingness to provide written informed consent prior to any study procedures being performed.

A subject was not eligible for inclusion if one or more of the following criteria applied:

- Baseline endoscopy showed any gastric, esophageal or duodenal ulcer at least 3 mm in diameter with depth;
- Positive test result for *H. pylori* at Screening
- Had a revascularization procedure (i.e., CABG, Percutaneous Transluminal Coronary Angioplasty, or carotid endarterectomy) less than 6 months prior to Screening
- Unstable hypertension as judged by the Investigator
- Uncontrolled diabetes mellitus as judged by the Investigator
- Unstable cardio- or cerebrovascular disease that would endanger the subject if they participated in the trial
- Clinically significant valvular disease;
- Congestive heart failure (CHF) or other Class III or IV cardiovascular symptoms according to New York Heart Association (NYHA) Functional Classification;
- History of hypersensitivity to omeprazole or other proton pump inhibitors;
- History of allergic reaction or intolerance to aspirin and/or a history of aspirin-induced symptoms of asthma, rhinitis, and/or nasal polyps
- History of serious UGI event, such as bleeding, perforation, or obstruction
- GI disorder or surgery leading to impaired drug absorption
- Presence of chronic or uncontrolled acute medical illness, e.g. GI disorder (esophageal stricture, severe esophagitis, long-segment Barrett's esophagus, signs and symptoms of gastric outlet obstruction), thyroid disorder and/or infection that would have endangered a subject if they were to participate in the study
- Schizophrenia, uncontrolled bipolar disorder, or severe depression;
- History of alcoholism or drug addiction within a year prior to enrollment in the study
- Severe hepatic dysfunction (i.e., cirrhosis or portal hypertension)
- Blood coagulation disorder, including use of systemic anticoagulants such as warfarin or other vitamin K antagonists
- Any condition that, in the opinion of the Investigator, may have either put the subject at risk or influenced the results of the study

- Use of any excluded concomitant medication
- Screening laboratory alanine transaminases (ALT) or aspartate transaminases (AST) value greater than 2 times the upper limit of normal
- Renal failure or requirement for dialysis. In addition, any clinically significant renal disease that, in the opinion of the Investigator, may have endangered the subject if he/she participated in the study
- Other than noted specifically, any screening laboratory value that was clinically significant in the Investigator's opinion and would have endangered a subject if the subject participated in the study
- Use of an investigational treatment within 4 weeks prior to Screening;
- History of malignancy, treated or untreated, within the past 5 years, with the exception of successfully treated basal cell or squamous cell carcinoma of the skin
- Previous participation in another PA32540 clinical research study
- Subjects who were employees of the research facility, immediately related to the Principal Investigator, or were in some way under the supervision of the Principal Investigator.

Reviewer Comment: The Inclusion and Exclusion criteria appear appropriate for the studies. The patient population selected for each study appears clinically similar.

Treatments

Subjects were randomized to receive single daily doses of PA32540 or ECASA 325 mg for up to 6 months. At Visits 3, 4, and 5, subjects were provided sufficient quantities of study medication to allow for outpatient dosing until the next visit. Subjects were instructed to return all unused study drug from the prior visit at Visit 4, Visit 5, and the Final Visit. All study drug dispensed to the subject was recorded in the eCRF and accountability logs.

Subjects were randomized 1:1 to receive to receive either PA32540 or EC-aspirin 325mg, stratified into 3 groups based on their chronic (at least 5 days per week) NSAID use at the time of randomization: 1) non-specific NSAID use; 2) COX-2 inhibitor use; and, 3) no NSAID use. Within each of these strata, subjects were randomized to receive either PA32540 or EC-aspirin 325 mg in accordance with the randomization schedule. The randomization schedule was produced by a third party under the supervision of POZEN. Once a randomization number was assigned to a subject, it was not re-assigned to any other subject.

Study drug administration was initiated the day following randomization and was taken on a daily basis for up to 6 months; the last dose was taken the day prior to the Final Visit. Study drug was taken in the morning approximately 1 hour before

breakfast (or the first meal of the day); tablets were consumed on an empty stomach with water, and were swallowed whole and not chewed, broken, or crushed.

Treatment Compliance was assessed by the Investigator and/or study personnel at each visit using pill counts and information provided by the subject. This information was entered on the eCRF. All empty bottles and unused study drug were maintained at the clinical site for reconciliation (accountability) by the clinical monitor.

Blinding

Subjects, investigators, study site staff, persons performing the assessments, POZEN staff and data analysts were blind to the identity of the treatment from the time of randomization until database lock using the following methods: (1) Randomization data were kept strictly confidential until the time of unblinding, and were only accessible by the third party individual not involved in the study; and (2) the identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labeling, schedule of administration, and appearance (e.g., the comparator EC-aspirin 325 mg tablet was indistinguishable from the PA32540 tablet with regard to size, shape and color).

Prior and Concomitant Therapy

Concomitant chronic (at least 5 days/week) NSAID use including COX-2 inhibitors was allowed in both Studies PA32540 -301 and PA32540-302. Subjects continued their prescribed NSAID therapy and reported any changes in therapy to the Investigator. NSAIDs were to be taken at least 2.5 hours after study medication.

Subjects enrolled in the study as non NSAID users were not to use NSAIDs. If incidental NSAID usage became necessary, their use was allowed for no more than 7 consecutive days and for no more than 3 periods during the study. Incidental NSAID use was to be discontinued 2 weeks prior to endoscopy assessment.

Restricted and Proscribed Medication

Aspirin may increase, decrease or change the effects of many drugs. Investigators were made aware that aspirin may increase the toxicity of certain medications such as methotrexate, and valproic acid. It may also decrease the efficacy of angiotensin-converting-enzyme (ACE) inhibitors, beta blockers, and some gout therapies such as probenecid and sulfinpyrazone; interact with diabetes and seizure medications; and result in decreased blood pressure, fainting or dizziness when administered with nitroglycerin.

Data also suggests that enteric coated PPIs such as Prilosec® that contain omeprazole may decrease the pharmacodynamic effect of clopidogrel on platelet aggregation. The decision to enroll subjects taking concomitant P2Y12 inhibitors such as cloidogrel was based on the Investigators judgement. Investigators

instructed subjects to notify the study site about any new concomitant medications taken after the start of the study drug and prior to study drug discontinuation.

The following medications were prohibited:

- PPIs, histamine-2 receptor antagonists or sucralfate from 14 days prior to the baseline endoscopy until the end of treatment
- Misoprostol-containing products, such as Cytotec® or Arthrotec®, from 14 days prior to the baseline endoscopy until the end of treatment
- Chronic corticosteroid therapy (i.e., exceeding prednisone 5 mg equivalent daily or more than prednisone 10 mg equivalent every other day) except the use of inhaled steroids for asthma
- Lithium
- Cholestyramine
- Anticoagulants (e.g., coumadin, warfarin, nutritional supplements having anticoagulant properties) from Screening to the end of treatment;
- Other investigational drug(s) within 4 weeks of Screening until the end of treatment.

5.3.2 Efficacy and Safety Measurements for Studies PA32540-301 and PA32540-302

The efficacy and safety assessments were identical for the two Phase 3 efficacy studies and are presented here. Table 2 lists the scheduled Study Assessments.

Table 2: Scheduled Study Assessments for Studies PA32540-301 and PA32540-302

	Screening [1]		Baseline/ Randomization [2]	Treatment		Final/Early Term
Visit	1	2	3	4 [3]	5 [3]	Final [4]
Day			0	30 ± 6	90 ± 12	180 ± 12
Month			0	1	3	6
Informed consent	X					
In/exclusion criteria	X	X				
Medical history	X	X	X [5]			
ECG	X					
Laboratory tests	X		X [6]	X	X	X
H. pylori test	X					
Pregnancy test [7]	X			X	X	X
Vital signs	X		X	X	X	X
Physical examination	X					X
Endoscopy		X		X	X	X
Randomization			X			
Study drug dispensed			X	X	X	
Study drug accountability				X	X	X
Concomitant Medications	X	X	X	X	X	X
Adverse events [8]	X	X	X	X	X	X
Heartburn assessment			X	X [9]	X [9]	X [9]

Source: NDA 205103 Section 9 5 1 page 35

[1] The time period between Screening Visit 1 and Screening Visit 2 did not exceed 14 days

[2] If endoscopy results were available at Screening Visit 2 and all inclusion/exclusion criteria were fulfilled, then randomization occurred on the same day as Screening Visit 2; otherwise, randomization occurred when endoscopy results became available Visit 3 was within 7 calendar days of Visit 2

[3] Monthly telephone contacts between Visits 4 and 5, and between Visit 5 and the Final Visit

[4] End-of-study assessments were performed at time of study discontinuation, or if the study endpoint had been reached, if possible

[5] Endoscopic findings at baseline were recorded as Medical History

[6] Only if screening results exceeded 14 days

[7] For women of childbearing potential

[8] SAEs were collected from the time of signed informed consent until 28 days after the last day of study participation Non-serious adverse events were collected from study drug initiation until the last day of study participation

[9] Heartburn was assessed prior to endoscopy, where applicable

Evaluation of Efficacy and Tolerability

Endoscopies

Endoscopies were performed at Screening Visit 2 (prior to randomization) and at 1, 3, and 6 months after the start of treatment. The same gastroenterologist performed the

endoscopies for a given subject when possible. Gastric and duodenal ulcers were recorded. An ulcer was defined as a mucosal break of at least 3 mm in diameter (measured by close application of open endoscopic biopsy forceps) with depth.

Detection of ulcers at Visits 4 or 5 resulted in the subject being withdrawn from the study and placed on appropriate ulcer treatment. The study drug was discontinued as well.

The primary efficacy endpoint was the proportion of subjects developing gastric ulcers throughout 6 months of study treatment. Duodenal and esophageal ulcers were considered adverse events and recorded as such.

Heartburn
Heartburn symptoms described as burning feeling rising from the stomach or lower part of the chest towards the neck were assessed at baseline (Visit 3, randomization) and at 1, 3, and 6 months following the initiation of treatment using the following:

Over the last 7 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)

Evaluation of Safety

Clinical Adverse Events
An adverse event (or adverse experience) was defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All adverse events occurring from the start of study medication administration through the Final Visit were recorded on the adverse event eCRF with the following information:

- the severity grade (mild, moderate, severe)
- relationship to the study drug (not related, unlikely related, possibly related, or
- duration (start and end dates or if continuing at final exam)
- whether it constitutes an SAE

The occurrence of adverse events was sought by non-directive questioning of the subject at each visit during the study. Adverse events were also detected when they were volunteered by the subject during or between visits or through physical

examination, laboratory tests or other assessments. Medical conditions/diseases present before starting study drug were considered adverse events only if they worsened after starting study drug.

Abnormal laboratory values or test results constituted adverse events only if they induced clinical signs or symptoms were considered clinically significant or required therapy. Adverse event collection commenced upon study drug administration. All adverse events were treated appropriately. The action taken to treat the adverse event was recorded on the adverse event eCRF.

A detected adverse event was to be followed until its resolution or as long as medically indicated as deemed by the Investigator. Assessment was made at each visit (or more frequently, if necessary) of any changes in severity, relationship to the study medication, the interventions required to treat it, and outcome.

Gastric ulcers were not considered adverse events, however, duodenal and esophageal ulcers were.

Serious Adverse Events

An SAE was defined as an event that:

- was fatal or life-threatening;
- resulted in persistent or significant disability/incapacity;
- constituted a congenital anomaly or birth defect
- required inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization was for:
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- elective or pre-planned treatment for a pre-existing condition that was unrelated to the indication under study and had not worsened since the start of study drug;
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission;
- social reasons and respite care in the absence of any deterioration in the subject's general condition
- medically significant, i.e., defined as an event that jeopardized the subject or may have required medical or surgical intervention to prevent one of the outcomes listed above.

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject had signed informed consent and until 28 days after the subject had stopped study participation was reported to the study Medical Monitor within 24 hours of learning of its occurrence.

Information about all SAEs was collected and recorded on the Serious Adverse Event Report Form. The Investigator assessed the relationship to study drug, completed the SAE Report Form in English, and sent the completed, signed form by fax within 24 hours to the study Medical Monitor. The telephone and telefax numbers of the contact persons were provided to each site.

The Investigator was responsible for promptly notifying the IRB of all SAEs, including any significant follow-up information.

Clinical Evaluations

Physical examination
The investigator or qualified personnel performed a thorough physical examination at Screening Visit 1 and at the Final Visit (Day 180 or early discontinuation)

Vital Signs and Electrocardiogram (ECG)
Standard 12-lead ECGs were performed at Screening Visit 1. The PI was responsible for assessing the clinical significance of ECG abnormalities and providing comments on the eCRF. Subjects with significant abnormal findings were excluded from the study enrollment. Vital signs including heart rate, systolic and diastolic blood pressure were obtained after subjects had been sitting for at least 5 minutes at Screening Visit 1 and at Visits 3, 4, 5, and at the Final Visit.

Pregnancy
If any subject was found to be pregnant while on the study drug, the medication was to be stopped immediately and the pregnancy was to be reported to the Medical Monitor within 24 hours of knowledge of the occurrence. Investigators were required to complete a Pregnancy Notification form.

The pregnancy was to be followed to determine outcome, including spontaneous or voluntary discontinuation, and the presence of any congenital abnormalities, or maternal and/or newborn complications. Any maternal and/or newborn complications were assessed for a possible relationship to the POZEN study drug, and evaluated whether it should have been reported as an SAE.

Clinical Laboratory Tests
Data were collected for the following laboratory assessments at screening and all treatment visits:

- Creatinine, ALT, AST, alkaline phosphatase, total bilirubin and blood urea nitrogen (BUN)
- Complete blood count (CBC), including hemoglobin (Hgb), and hematocrit

A stool sample was collected for the *H. pylori* stool antigen test at Screening Visit 1

The Principle Investigator was responsible for assessing the clinical significance of all abnormal laboratory values and documenting this information on the eCRF. Abnormal laboratory tests that were judged to be possibly drug related or clinically significant abnormal laboratory tests of uncertain causality were repeated. A confirmed >2.0g/dl decrease in hemoglobin resulted in study drug discontinuation for that subject.

An increase in serum ALT and/or AST > 3x ULN was to be followed by a repeat evaluation of ALT, AST, total bilirubin and alkaline phosphatase within 2-3 days. These subjects were to be monitored closely. Abnormal laboratory values were not listed on the Adverse Events eCRF unless they induced clinical signs or symptoms, were considered clinically significant, required therapy or fulfilled any SAE criteria.

Study PA32540-301

Disposition of Subjects

In Study 32540-301 530 subjects (265 per treatment group) were randomized to study drug at 78 centers. The majority of the centers enrolled less than 10 subjects and no center enrolled more than 31 subjects. 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 adverse events which were listed primarily as gastritis, dyspepsia, and erosive gastritis.

Table 3: Subject Disposition

	PA 32540 N= 265 (%)	ECASA 325 mg N= 265 (%)
Subjects randomized	265 (100)	265 (100)
Subjects completed	218 (82)	198 (75)
Subjects withdrawn prior to completion	47 (18)	67 (25)
Adverse event	18 (7)	33 (13)
Withdrew consent	10 (4)	10 (4)
Lost to follow-up	3 (1)	3 (1)
Other	16 (6)	21 (8)

Source: Adapted from NDA 205103 Section 10.1 page 49.

Protocol Violations

There were very few protocol violations. Only 12 subjects in the PA32540 group and 18 subjects in the ECASA 325mg group had major protocol violations. The violations included not meeting the inclusion/exclusion criteria and use of disallowed medications. Five of these subjects had screening creatinine clearance values that did not meet the original protocol criterion and they were enrolled prior to the removal of creatinine clearance limitations in protocol amendment 2. Another 5 subjects were taking high doses of fish oils or omega -3 fatty acids at screening but agreed to lower the dose to

less than 3000mg/day during the study. One 60 year old subject was enrolled without a documented history of ulcer disease in the past five years. The subject was enrolled prior to the second protocol amendment, which reduced the age requirement for documented histories from 60 to 54 years or younger.

Table 4. Summary of Major Protocol Violations for Study PA32540-301 (All Randomized Subjects)

	PA32540 (N=265) (%)	ECASA 325 mg (N=265) (%)
Per protocol exclusion: No Yes	 253 (95) 12 (4)	 247(93) 18 (7)
Inclusion /Exclusion Criteria Not Met	6 (2)	11 (4)
Disallowed Medication taken	7 (3)	7 (3)
Other Violations	0	2 (0.8)

Source: CSR Table 14.1.3.3; page 1
These violations may have occurred at enrollment and/or during the study. Subjects may have had more than one violation.

Data Sets Analyzed

The analysis populations included the following:

Intent–to-Treat (ITT) Population: The ITT population consisted of all randomized subjects.

Modified Intent-to-Treat (mITT) Population: The mITT population consisted of all randomized subjects who received at least one dose of study drug and had no ulcer detected by endoscopy at screening visit

Per Protocol (PP) Population: All subjects in the ITT population who did not violate the protocol in any major way that would impact the evaluation of efficacy and had at least 70% overall treatment compliance comprised the PP population.

Safety Population: All randomized subjects who received at least one dose of study drug comprised the safety population.

A total of 265 subjects were randomized to each treatment and were included in the ITT population.

Three subjects (1 in the PA32540 group and 2 in the ECASA 325 mg group) were excluded from the mITT population; 2 subjects (1 in each group) had ulcers detected on the screening endoscopy and 1 subject in the ECASA 325 mg group did not take any study medication.

Approximately 97% of the subjects in each treatment group were included in the PP population (only 7 subjects in the PA32540 group and 9 subjects in the ECASA 325 mg

group were excluded). Use of a proscribed concomitant medication was the primary reason for exclusion from this population.

For the safety population, as mentioned above, the subject who did not take any study medication was excluded from the ECASA 325 mg group, and the subject who was administered the incorrect study drug was excluded from the PA32540 safety group and included in the ECASA 325 mg group. Therefore, the safety population included 264 subjects in the PA32540 group and 265 subjects in the ECASA 325 mg group.

Table 5: Data Sets Analyzed for Study PA32540-301

Data Set	PA32540	ECASA 325 mg
ITT Population	265 (100)	265 (100)
mITT Population	264 (99)	263 (99)
Reasons for Exclusion		
Ulcer at screening	1	1
Did not take study drug	0	1
Per Protocol Population	258 (97)	256 (97)
Reason for Exclusion[1]		
Ulcer at screening	1	1
Did not take study drug	0	1
Disallowed medication taken	4	7
Compliance <70%	1	1
Received study drug different from randomization	1	0
Safety Population[2]	264 (99)	265 (100)
Did not take study drug	0	1

Source: Reproduced from CSR PA32540-301; Table 6; Page 52.
1 Subject 2269 in the EC-aspirin 325 mg group had more than 1 reason for exclusion.
2 Subject 2301 received the incorrect medication kit (randomized to PA32540 but received EC-aspirin 325 mg [Listing 16 2.6]); subject was excluded from PA32540 safety population and included in EC-aspirin 325 mg safety population, increasing the N in the EC-aspirin 325 mg safety population from 264 to 265.

Subject Demographics for Study PA32540-301

Subjects were predominantly male, white and of non-Hispanic/Latino origin. Subjects ranged in age from 41-88 years of age, with the median age being 66 years in both treatment groups. Approximately 85% of subjects were between 55 and 74 years of age. Table 6 below presents the demographic summary for ITT subjects.

Table 6: Demographics and Other Baseline Characteristics- ITT Population

	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.

Demographics, baseline characteristics, NSAID use at randomization, and ulcer histories in the mITT and PP populations were similar to those in the ITT population. Therefore NSAID use in the ITT population will be described in Table 7 below:

Table 7: Ulcer History and NSAID Use at Randomization Study PA32540-301

	PA32540 N=265	ECASA 325 mg N=265
Gastric or Duodenal Ulcer within the Previous 5 years	13 (5)	13 (5)
History of Most Recent Ulcer at Any Time		
Gastric	14 (5)	29 (11)
Duodenal	4 (2)	3 (1)
Both	2 (0.8)	0
None	245 (93)	233 (88)
NSAIDs or COX-2 Inhibitor Use at Randomization		
None	245 (93)	241 (91)
COX-2 Inhibitor or other NSAID[1]	20 (8)	24 (9)
COX-2 inhibitor	1 (5)	1 (4)
Other NSAID	19 (95)	23 (96)

Source: Reproduced from CSR PA32540-301; Table 8; Page 54.
[1]Percentages for NSAID type are based on total number of NSAID users

At baseline, all but 4 subjects (2 subjects in each treatment group) were taking aspirin 325 mg for secondary prevention of the cardiovascular or cerebrovascular conditions. Other medical conditions for which aspirin 325 mg was prescribed included cardiac valve disease, atrial enlargement, atrial fibrillation, and diabetes mellitus.

The administration of aspirin as secondary prevention was used predominantly for histories of cardiac disorders (89% for PA32540 and 82% for ECASA 325 mg) rather than neurological disorders (21% for PA32540 and 24% for ECASA 325 mg); coronary artery disease was the primary cardiac history (69% for PA32540 and 64% for ECASA 325 mg), followed by MI (43% for PA32540 and 38% for ECASA 325 mg).

With the exception of stroke, the distribution of cardiac and neurological histories was comparable in the 2 treatment groups. Strokes were slightly more prevalent among ECASA 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 ECASA 325 mg were taking clopidogrel at the time of randomization. Body systems with the highest incidences of co-morbid medical conditions were cardiovascular, endocrine, and GI system disorders (>93% of the subjects in each treatment group), followed by musculoskeletal/connective tissue, immune, and nervous system disorders (approximately50-60% of the subjects in each group). In addition, approximately 40% of the subjects in each group reported a history of diabetes.

The co- morbid medical conditions in addition to clopidogrel use are depicted In Table 8 below:

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Table 8: Cardiovascular and Cerebrovascular Histories, Co-Morbidities, and Clopidogrel Use at Randomization-ITT Population

	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: CSR 32540-301; Table 9; page 55

Concomitant Medications

The majority of the subjects in the safety population took concomitant medications. In both groups, more than 75% of the subjects took lipid modifying agents, more than 50% of the subjects took beta blocking agents, and more than 25% of the subjects took ACE inhibitors, blood glucose lowering drugs, antithrombotic agents, or multivitamins. The use of clopidogrel was similar for both treatment groups ECASA 325mg (21%) and PA32540 (23%).

The use of concomitant medications for peptic ulcer, GERD, and antacids coincided with higher incidences of UGI adverse events, and discontinuations due to UGI adverse events. Fewer subjects on PA32540 (5.7%) used peptic ulcer and GERD medications than those on ECASA 325 mg (12.1%). Proton pump inhibitors and H2 receptor antagonists were mostly employed for treatment of UGI ulcer or GERD after subjects stopped study drug intake (in case endoscopy occurred prior to the last Visit). Antacids were used more frequently by subjects taking ECASA 325 mg (11%) than those taking PA32540 (5%). Both chronic and incidental NSAIDs were used by a similar number of subjects in both treatment groups ECASA 325 mg (19%) and PA32540 (17%).

Table 9 shows the drug classes in which 10% or more of subjects in either treatment group took a concomitant medication.

Table 9: Concomitant Medication Use by Class taken by ≥ 10% of Subjects in Either Treatment Group Safety Population Study PA32540-301

Drug Class	PA32540 N = 264	EC-Aspirin 325 mg N = 265
All drug classes	263 (99.6%)	263 (99.2%)
Lipid modifying agents	226 (85.6%)	211 (79.6%)
Beta blocking agents	169 (64.0%)	135 (50.9%)
ACE inhibitors	126 (47.7%)	104 (39.2%)
Blood glucose lowering drugs, excl. insulin	87 (33.0%)	81 (30.6%)
Antithrombotic agents	78 (29.5%)	78 (29.4%)
Multivitamins, combinations	68 (25.8%)	85 (32.1%)
Antidepressants	63 (23.9%)	64 (24.2%)
Selective calc. channel block. w/mainly vascular. eff.	60 (22.7%)	52 (19.6%)
Vasodilators used in cardiac diseases	60 (22.7%)	63 (23.8%)
Antiinflammatory/antirheumatic prod., non-steroids	46 (17.4%)	51 (19.2%)
Other analgesics and antipyretics	44 (16.7%)	48 (18.1%)
High-ceiling diuretics	41 (15.5%)	39 (14.7%)
Insulins and analogues	38 (14.4%)	31 (11.7%)
Opioids	36 (13.6%)	45 (17.0%)
Angiotensin II antagonists	35 (13.3%)	28 (10.6%)
Drugs used in benign prostatic hypertrophy	34 (12.9%)	21 (7.9%)
Adrenergics, inhalants	31 (11.7%)	29 (10.9%)
Antihistamines for systemic use	31 (11.7%)	33 (12.5%)
Vitamin A and D, incl. combinations of the two	31 (11.7%)	33 (12.5%)
Thyroid preparations	29 (11.0%)	37 (14.0%)
Calcium	26 (9.8%)	38 (14.3%)
Low-ceiling diuretics, thiazides	24 (9.1%)	32 (12.1%)
Anxiolytics	23 (8.7%)	32 (12.1%)
Potassium	21 (8.0%)	30 (11.3%)
All other therapeutic products	19 (7.2%)	27 (10.2%)
Unspecified herbal	19 (7.2%)	31 (11.7%)
Laxatives	17 (6.4%)	28 (10.6%)
Drugs for peptic ulcer and GORD	15 (5.7%)	32 (12.1%)
Antacids	14 (5.3%)	29 (10.9%)

Source: CSR PA32540-301 Table 10; page 57

Reviewer comments-The prevalence of each of these drug classes was not unexpected. The population is primarily > 55 years with underlying cardiovascular disease.

Prohibited Medications

A total of 30 subjects (11 in the PA32540 group and 19 in the ECASA 325 mg group) took aspirin-containing products (ASA, Alka Seltzer, Asasantin, and/or Vanquish) during the course of the study. The majority of these subjects took only a few doses at a time period that would not have impacted the study outcome, and were included in the ITT, mITT and PP efficacy analyses.

Four subjects in the PA32540 group and 7 subjects in the ECASA 325 mg group took aspirin-containing products for 2 weeks or more, and/or antithrombotic agents, PPIs, or H2-receptor antagonists that may have affected the study outcome. All of these concomitant medications were considered to be major protocol violations by the sponsor and these subjects were excluded from the PP efficacy analyses.

Primary Efficacy Endpoint –Study PA32540-301

The cumulative proportion of ITT subjects who developed gastric ulcers through 6 months was statistically significantly lower with PA32540 treatment than with ECASA 325 mg treatment (3.8% vs 8.7%). A difference between treatment groups was observed as early as 1 month and was maintained throughout six months of therapy, however statistical testing for the 0-1 and 0-3 month timepoints was not prespecified (and therefore p-values are presented only for descriptive purposes). See Table 10.

Table 10: Analysis of Cumulative Proportion (n %) of Subjects Developing Gastric Ulcers through 1, 3, and 6 Months- ITT Population

Time point Ulcer Status	PA32540 N= 265	ECASA 325 mg N= 265	p-Value[1]
	N (%)	N (%)	
0-1 Month			
Gastric ulcer	3 (1.1%)	10 (3.5%)	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%)	18 (6.8%)	0.044
95% CI	(1.3%- 5.9%)	(4.1%- 10.5%)	
Gastric ulcer-free	257 (97%)	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 (25.35)	

Source: CSR PA32540-301 Table 11 Page 59.
1 P-value for ulcer occurrence from CMH test stratified by NSA D use (use=COX-2, other NSAID, or use=no) at time of randomization.
2 Maintained = continued in study.

Secondary Efficacy Endpoint

The prespecified secondary efficacy endpoint was the cumulative proportion of ITT subjects developing gastric and/or duodenal ulcers through 6 months of treatment. A duodenal ulcer was similarly defined as a mucosal break of at least 3 mm in diameter with depth. The presence of gastric and/or duodenal ulcers was statistically significantly lower with PA32540 treatment than with ECASA 325 mg (4.2% and 11.7% respectively). Although not a prespecified analysis, the difference between treatment groups was also observed at 1 and 3 months after the start of treatment (1.1% and 5.3% respectively at I month; and 3.4% and 9.4, respectively at 3 months).

Table 11: Analysis of Cumulative Proportion (n %) of Subjects Developing Gastric and/or Duodenal Ulcers through 1, 3, and 6 Months- ITT Population

Timepoint Ulcer Status	PA32540 N= 265	ECASA 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%)	
0-3 Months			
Gastric/duodenal ulcer	9 (3.4%)	25 (9.4%)	0.005
95% CI	(1.6%- 6.3%)	(6.2%- 13.6%)	
0-6 Months			
Gastric/duodenal ulcer	11 (4.2%)	31(11.7%)	0.002
95% CI	(2.1%- 7.3%)	(8.1% - 16.2%)	

Source: CSR PA32540-301 Adapted from table 13; page 61.
1 P-value for ulcer occurrence from CMH test stratified by NSA D use (use=COX-2, other NSAID, or use=no) at time of randomization.

Study Discontinuation due to Pre-specified UGI Adverse Events

The proportion of ITT subjects discontinuing study participation due to the development of a pre-specified UGI adverse event was statistically significantly lower in the PA32540 group than in the ECASA 325 mg group (2.3% vs 8.3%) Incidences of dyspepsia, duodenal ulcer, and GERD leading to study drug discontinuation were lower among subjects in the PA32540 group than among subjects in the ECASA 325 mg group.

Table 12: Proportion of Subjects Discontinuing due to Pre-Specified UGI Adverse Events Study PA32540-301 –ITT Population

	PA32540 N= 259	ECASA 325 mg N= 260	P-value[1]
Number of UGI Events Leading to Discontinuation	6	22	
	Number of Subjects (%)		
Subjects Discontinuing d/t UGI Events	6 (2.3)	22 (8.3)	0.002
Specific UGI Events			
Abdominal pain	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 hemorrhage	0	1 (0.4)	
Erosive esophagitis	0	1 (0.4)	
Hemorrhagic gastritis	0	1 (0.4)	
Gastroesophageal reflux disease	0	3 (1.1)	
Esophageal ulcer	0	1 (0.4)	

Source CSR PA32540-301 Table 15 page 63
1P-value from CMH test stratified by NSAID use (use=COX-2, other NSAID, or use=no) at randomization

Study PA32540-302

Disposition of Subjects

In Study 32540-302 519 subjects (259 to PA325 and 260 to ECASA 325mg) were randomized to treatment at 75 centers. No center enrolled more than 22 subjects. Approximately 78% of the subjects completed the study. (i.e., completed 6 months of treatment and had a 6-month endoscopy or had an endoscopically- confirmed gastric ulcer prior to 6 months of therapy). In both treatment groups, the primary reason for study withdrawal was adverse events which were listed primarily as gastritis, dyspepsia, and erosive gastritis and withdrawal of consent.

Table 13: Subject Disposition for Study PA32540-302- All Randomized Subjects

	PA 32540 N= 259 (%)	ECASA 325 mg N= 260 (%)
Subjects randomized	259 (100)	260 (100)
Subjects completed	206 (80)	198 (76)
Subjects withdrawn prior to completion	53 (20)	62 (24)
Adverse event	17 (7)	26 (10)
Withdrew consent	16 (6)	14 (5)
Lost to follow-up	1 (0.4)	4 (1.5)
Other	19 (7)	18 (7)

Source: Adapted from Table 5 CSR Study PA32540-302; page 48.

Protocol Violations

17 subjects in the PA32540 group and 12 subjects in the ECASA 325mg group had major protocol violations. The violations included 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 4 subjects were taking high doses of fish oils or omega -3 fatty acids at screening but agreed to lower the dose to less than 3000mg/day during the study. One 56 year old subject was enrolled without a documented history of ulcer disease in the past five years. The subject was enrolled prior to the second protocol amendment, which reduced the age requirement for documented histories from 60 to 54 years or younger. A subject who took disallowed medications for two days during a hospital stay which was more than 6 weeks prior to endoscopy was not considered a major protocol violator by the sponsor. Six subjects were permitted to continue in the study after consultation with the sponsor. The remaining subjects not meeting inclusion/exclusion criteria or using prohibited medications were discontinued from the study.

The sponsor excluded subjects from the PP analyses whose violations would have impacted the outcome of the study. The table below summarizes the major protocol violations for all randomized subjects in Study PA32540-302.

Table 14: Summary of Major Protocol Violations for Study PA32540-302-All Randomized Subjects

	PA32540 (N=265) (%)	ECASA 325 mg (N=265) (%)
Per protocol exclusion: No Yes	 242 (93) 17 (7)	 248(96) 12 (5)
Inclusion /Exclusion Criteria Not Met	12 (5)	8 (3)
Disallowed Medication taken	5 (2)	4 (2)
Other Violations	0	0

Source: CSR Table 14.1.3.3; page 1

These violations may have occurred at enrollment and/or during the study. Subjects may have had more than one violation.

Data Sets Analyzed

A total of 259 PA32540 subjects and 260 ECASA 325mg subjects were randomized and were included in the ITT population for study PA32540-302.

Three subjects (2 in the PA32540 group and 1 in the ECASA 325 mg group) did not take any study drug and were excluded from the mITT population or the safety populations;

Three subjects (4322, 4579, and 4628) were randomized to PA32540 but received the wrong medication kits which contained ECSASA 325 mg. There were also 3 subjects (4507, 4582, and 4586) who were randomized to receive ECSASA 325 mg but received PA32540 instead. Efficacy and tolerability data for these subjects were included in the ITT and mITT analyses based on their randomized treatment. The efficacy data for these subjects was not included in the PP analyses. Safety data for these subjects was based on the treatment they actually received.

The 4 study populations are summarized below in Table 14.

Table 15 Data Sets Analyzed Study PA32540-302

Data Set	PA32540 N (%)	ECASA 325 mg N (%)
ITT Population	259 (100)	260 (100)
mITT Population	257 (99)	259 (99)
Did not take study drug[1]	2	1
Per Protocol Population	248 (96)	253 (97)
Reason for Exclusion[2]		
Did not take study drug	2 (0.8)	1(0.4%)
Disallowed medication taken	5 (2)	3 (1%)
Compliance <70%	2 (0.8)	0
Received study drug different from randomization	3(1)	3 (1)
Safety Population[3]	264 (99)	265 (100)
Did not take study drug	2	1

Source: Reproduced from Table 6 CSR PA32540-302 page 51.
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).

Subject Demographics for Study PA32540-302

The demographic characteristics of the ITT population were similar between the two treatment groups. However, there were more African American subjects randomized to the PA32540 group (12%) than the ECASA 325 mg group (4%). In both groups subjects were predominately male (approximately 70%), white (> 85%) and of non-Hispanic/Latino origin (approximately 92%). The mean age of the study population was approximately 66 years. More than half were ≥ 65 years and 13% were greater than 75 years of age. Table 15 presents the demographic summary for ITT subjects.

Table 16: Demographics and Other Baseline Characteristics-ITT Population

	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 (Table 7) CSR PA32540-302 page 52

Reviewer's comments- The ITT population is very similar between studies PA32540-301 and PA32540-302 with regard to age, race, and gender. Subgroup analyses reveal no significant differences between the studies for the primary efficacy endpoint based on these factors.

Demographics, baseline characteristics, NSAID use at randomization, and ulcer histories were similar among the mITT, PP, and ITT populations. The ulcer history and NSAID use at randomization is summarized for the ITT population in Table 17.

Table 17: Ulcer History and NSAID use at randomization for Study PA32540-302-ITT Population

	PA32540 N= 259(%)	ECASA 325mg N= 260(%)
Gastric or Duodenal Ulcer within the Previous 5 years	12 (5)	19 (7)
History of Most Recent Ulcer at Any Time		
Gastric	22 (9)	27 (10)
Duodenal	9 (3.5)	4 (2)
Both	2 (0.8)	0
None	226 (87)	229 (88)
NSAIDs or COX-2 Inhibitor Use at Randomization		
None	235 (91)	235 (90)
COX-2 Inhibitor or other NSAID[1]	24 (9)	25 (10)
COX-2 inhibitor	2 (8)	4 (16)
Other NSAID	22 (92)	21 (84)

Source: Reproduced from CSR PA32540-302; Table 8; Page 53.
[1]Percentages for NSAID type are based on total number of NSAID users

Reviewer's comments: Very few subjects had a history of previous ulcer disease prior to randomization and one would expect that these individuals would be less likely to develop an ulcer during the 6 month treatment period. The infrequent use of NSAIDs and the lack of previous ulcer history decreased the overall risk for these subjects to develop an ulcer during the treatment period.

At baseline, all but 5 subjects (1 in the PA32540 group and 4 in the ECASA 325 mg group) were taking aspirin 325 mg for secondary prevention of the cardiovascular or cerebrovascular conditions. The one subject in the PA32540 group should not have been randomized since her only cardiac condition was a heart murmur. Medical conditions for which aspirin 325 mg was prescribed in the subjects who were randomized to ECASA 325 mg included atrial fibrillation, aortic stenosis, and mitral valve prolapse.

Aspirin use for secondary prevention was predominantly for cardiac-related disorders (90% for PA32540 and 84% for ECASA 325 mg) rather than neurological disorders (18% for PA32540 and 19% for ECASA 325 mg). The primary cardiac reason was coronary artery disease (67% for PA32540 and 63% for ECASA 325 mg), followed by myocardial infarction (38% for both treatment groups). More subjects in the PA32540 group had a history of angina (28% vs. 22% for EC-aspirin 325 mg) or cardiac interventions such as angioplasty or PCI (25% vs. 21% for ECASA 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). Additionally, >90%

of the study subjects had co morbid gastrointestinal and endocrine disorders. A history of diabetes was higher in the PA32540 group (39%vs 31% for ECASA). The co- morbid medical conditions in addition to clopidogrel use are depicted In Table 18 below:

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Table 18: Cardiovascular and cerebrovascular Histories, Co-Morbidities, and Clopidogrel Use at Randomization – ITT Population

	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: CSR PA32540-302 Table 9; page 54

Reviewer's comments: The study population was primarily elderly with a history of cardiovascular disease. Therefore the number and types of co-morbid illnesses does seem unusual. Abnormalities were also seen in the screening ECGs for most of the study subjects in both treatment groups. However, none of the abnormal ECGs were considered clinically significant by the Investigators.

Concomitant Medication Use for Study PA32540-302

All but 5 subjects in the PA32540 group and 2 subjects in the ECASA 325 mg group were taking concomitant medications. The drug classes in which 10% or more of the subjects in either treatment group took a concomitant medication are shown in Table 18. In both groups, more than 80% of the subjects were taking lipid-modifying agents, more than 55% beta-blockers, and more than 35% ACE inhibitors. Likewise, blood glucose lowering drugs, vasodilators for cardiac disease, antithrombotic agents, and multivitamins were being used by >20% of subjects in both treatment groups.

A similar percentage of subjects took clopidogrel during the treatment period (22% for PA32540 and 23% for ECASA 325 mg). The use of NSAIDs at any time during the treatment period was 18% for PA32540 and 20% for ECASA 325 mg.

Reviewer Comment: The prevalence of the classes of drugs used by study subjects was not unusual given their advanced age, underlying cardiovascular disease and other co-morbid conditions.

Prohibited Medications Study PA32540-302

A list of prohibited medications was discussed previously in Section 5.3.2. However, in general, gastroprotective agents such as PPIs, histamine -2-receptor antagonists, sucralfate and anticoagulants were prohibited. Subjects were to have discontinued their existing aspirin regimen while on the study drug.

A total of 26 subjects in the PA32540 group and 25 in the ECASA 325 mg group took aspirin/aspirin-containing products, NSAIDs, or PPI therapy during the course of the study. The majority of these subjects either took only a few doses during a period of time that would not have impacted the study outcome or began treatment after discontinuing from the study; the majority of these subjects were included in the ITT, mITT and PP analysis populations.

Five subjects who took PA32540 and 3 subjects who took EC-aspirin 325 mg were taking aspirin/aspirin-containing products and/or PPIs or anticoagulants that may have affected the study outcome. All of these concomitant medications were considered to be major protocol violations by the sponsor; these subjects were excluded from the PP analysis population.

Primary Efficacy Endpoint –Study PA32540-302

The cumulative proportion of ITT subjects who developed gastric ulcers through 6 months was statistically significantly lower with PA32540 treatment than with ECASA 325 mg treatment (2.7% vs 8.5%). A difference between treatment groups was observed as early as 1 month and was maintained throughout six months of therapy, however statistical testing for the 0-1 and 0-3 month timepoints was not prespecified (and therefore p-values are presented only for descriptive purposes). See Table 19.

Table 19: Analysis of the Cumulative Proportion (n, %) of Subjects Developing Gastric Ulcers through 1, 3, and 6 Months Study PA32540-302- ITT Population

Timepoint Ulcer Status	PA32540 N= 265	ECASA 325 mg N= 265	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[2]	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[2]	199 (76.8%)	176 (67.7%)	
Discontinued	53 (20.5%)	62 (23.8%)	

Source: CSR PA32540-302 Table 11 Page 58.
1 P-value for ulcer occurrence from CMH test stratified by NSA D use (use=COX-2, other NSAID, or use=no) at time of randomization.
2Mantel-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.

Secondary Efficacy Endpoint

The secondary efficacy endpoint was the cumulative proportion of ITT subjects developing gastric and/or duodenal ulcers through 6 months of treatment. The presence of gastric and/or duodenal ulcers was statistically significantly lower with PA32540 treatment than with ECASA 325 mg (2.7% and 11.5% respectively). Differences between treatment groups was also observed at 1 and 3 months after the start of treatment, however these were not prespecified efficacy analyses and p-values are provided for descriptive purposes.

Table 20: Analysis of Cumulative Proportion (n %) of Subjects Developing Gastric and/or Duodenal Ulcers through 1, 3, and 6 Months Study PA32540-302 - ITT Population

Timepoint Ulcer Status	PA32540 N= 259	ECASA 325 mg N= 260	p-Value[1]
	N (%)	N (%)	
0-1 Month			
Gastric/duodenal ulcer	1 (0.4%)	13 (5.0%)	0.002
95% CI	(0.0%- 2.1%)	(2.7%-8.4%)	
0-3 Months			
Gastric/duodenal ulcer	1 (0.4%)	22 (8.5%)	<0.001
95% CI	(0.0%- 2.1%)	(5.4%- 12.5%)	
0-6 Months			
Gastric/duodenal ulcer	7 (2.7%)	30(11.5%)	<0.001
95% CI	(1.1%- 5.5%)	(7.9% - 16.1%)	

Source: CSR PA32540-302 Adapted from table 13; page 61.
1Pvalue for ulcer occurrence from CMH test stratified by NSAID use (use=Cox-2, other NSAID, or use=no) at time of randomization

Study Discontinuation due to Pre-specified UGI Adverse Events

Study discontinuations due to pre-specified UGI adverse events including duodenal ulcers was lower in subjects treated with PA32540 (0.8%) compared to ECASA 325 mg (8.1%). Subjects taking ECASA 325mg discontinued more frequently than those taking PA32540 with complaints of dyspepsia (3.1% vs.0), duodenal ulcer (1.5% vs. 0), and esophagitis (1.5% vs.0).

Table 21: Proportion of Subjects Discontinuing due to Pre-Specified UGI Adverse Events Study PA32540-302 –ITT Population

	PA32540 N= 259	ECASA 325 mg N= 260	P-value[1]
Number of UGI Events Leading to Discontinuation	2	21	
	Number of Subjects (%)		
Subjects Discontinuing d/t 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)	
Esophagitis	0	4 (1.5)	
Esophageal ulcer	0	2 (0.8)	
Duodenitis	0	1 (0.4)	
Erosive esophagitis	0	1 (0.4)	
Gastrointestinal erosion	0	1 (0.4)	

Source: CSR PA32540-302 Table 15 page 63
1P-value from CMH test stratified by NSA D use (use=COX-2, other NSAID, or use=no) at time of randomization

Reviewer's comments: The number of upper gastrointestinal events was predictably low in the treatment arm as compared to the active comparator. In clinical practice it is not unusual to recommend a PPI to those patients who are taking low dose aspirin or an NSAID chronically.

6 Review of Efficacy

Efficacy Summary

The proposed indication for PA Tablets is [redacted] (b) (4)

6.1.1 Methods

POZEN has developed PA8140 and PA32540 Tablets, which consist of an EC-aspirin 81 mg and 325 mg core, respectively, and an outer layer of immediate-release (IR) omeprazole 40 mg. PA Tablets are designed to provide the cardio protective effects of aspirin while minimizing aspirin related UGI toxicity. The outer layer of IR omeprazole in the PA Tablets is available for instantaneous dissolution and allows the pharmacologic effect of omeprazole to take place rapidly after ingestion [redacted] (b) (4)

Studies PA32540-301 and PA32540-302 were designed to study a broad population of subjects at risk for cardiovascular events that required daily use of aspirin and who were at risk of GI toxicity from the use of chronic aspirin. Specifically, the diagnoses required for entry into the study included subjects with established cardiovascular disease (Table 22) and were presently taking daily aspirin 325 mg for 3 months and would require the use of daily aspirin 325 mg for the study period of 6 months.

These studies included subjects who were at risk for aspirin-associated gastric ulcer. Specifically, the inclusion criteria required that subjects be 55 years or older, if less than 55 years must have history of a documented, uncomplicated, gastric or duodenal ulcer within 5 years of the study enrollment. However, those with an active ulcer (≥ 3 mm diameter with depth) at screening were to be excluded. Additionally, subjects who were *H. pylori* positive were also excluded.

Table 22. Conditions Required for Inclusion in Studies PA32540-301 and PA32540-302

Cardiac or cerebrovascular ischemic events	• Confirmed or suspected Myocardial Infarction • Ischemic Stroke • Transient Ischemic Attack
OR have established coronary or vascular disease at high risk for surgical intervention or for major event if left untreated	• Angina (Stable or Unstable) • Peripheral Arterial Disease • Aortic Atherosclerotic Disease • Carotid Artery Disease
OR history of a revascularization procedure	• Coronary Artery bypass grafting • Percutaneous Coronary Intervention with or without stent • Carotid Endarterectomy

Source: CSR (ISE) page 29.

Assessment of the primary endpoint, endoscopic gastric ulcers was performed by endoscopists who were blinded to the study drug and used a standard definition for ulcers. An ulcer was described as a disruption in the gastric mucosa of at least 3mm in diameter with depth. Endoscopy training was performed by review of a video containing definition of ulcers and other lesions as well as providing actual visuals of ulcerations and other types of lesions. Study endoscopists were required to document their understanding of the video.

Endoscopies were conducted at baseline and at 1, 3 and 6 months of treatment or at early termination; additional symptom emergent endoscopies were only performed if clinically indicated (e.g., dyspeptic symptoms). Subjects with an endoscopically confirmed ulcer (gastric, duodenal or esophageal) were discontinued from the study. Duodenal and esophageal ulcers were considered adverse events. GUs were not recorded as adverse events but were the primary efficacy endpoint.
Subjects who had GU discovered by endoscopy were designated as study completers, and were required to exit from the study. Subjects with endoscopically detected duodenal ulcer (DU) or esophageal ulcers during the study period were also required to discontinue from the study but were not considered as study completers. Duodenal and esophageal ulcers were treated as adverse events (AEs) in these studies and are included in the number of pre-specified upper GI events.

Reviewer's comments: The primary endpoint used by POZEN in the Phase 3 UGI endoscopy studies was GU. This endpoint has been used for assessment of UGI injury associated with the use of non-steroidal anti-inflammatory agents and aspirin, and is believed to have a strong correlation with the incidence of UGI complications (GI bleeding, perforations and obstruction) A recently approved combination product VIMOVO® (naproxen and esomeprazole magnesium) delayed release tablets 375mg/20mg (NDA 22511 approve April 30, 2010) used this ulcer definition as the primary endpoint.

6.1.2 Demographics

The demographics for both studies PA32540-301 and PA32540-302 have been discussed previously in Section 5. For Study PA32540-301 the demographics were balanced between treatment groups. There were more males than females in each treatment group and there were more African Americans in the ECASA 325 mg than in the PA32540 treatment group. Other races were represented by 7 individuals. In each treatment group 4.9% had experienced a gastric or duodenal ulcer within 5 years of starting the study. However, 10.9% of the ECASA 325mg and 5.3% of PA32540 had reported a gastric or duodenal ulcer in the past. Concomitant NSAID use was reported as 7.5% and 9.1% by the PA32540 and ECASA 325mg respectively.

The medical histories of the treatment groups appeared balanced and consistent with the population studied. Subjects primarily reported conditions that were categorized as cardiovascular, gastrointestinal, or endocrine.

Similarly, the demographics for the ITT population for study PA32540-302 were balanced between the treatment groups. There were more males than females and there were more African Americans in the PA32540 treatment group than in the ECASA 325 mg treatment group. As in study PA32540-301, other races were significantly underrepresented (8 subjects).

The percentage of subjects having experienced a gastric or duodenal ulcer within five years of starting the differed 4.6% in the PA32540 treatment group compared to 7.3% in the ECASA 325mg group. However, 10.4% of the ECASA 325 mg and 8.5% of PA32540 had reported a gastric or duodenal ulcer in the past. Concomitant NSAID use was reported as 9.3% and 9.6% by the PA32540 treatment group and the ECASA 325 mg, respectively.

The medical histories of the treatment groups were balanced and consistent with the population under study reporting conditions that were primarily categorized as cardiovascular, gastrointestinal and endocrine.
Table 23 below depicts the baseline demographics in the combined analysis. The demographics were balanced with White males being the predominate group. Races other than AA or white were underrepresented and not included in the table. More subjects in the ECASA 325mg group had experienced a gastric or duodenal ulcer within 5 years of starting the study. More subjects in the ECASA 325mg treatment group reported concomitant NSAID use as well.

Table 23 Demographics in the ITT Population from Studies PA32540-301 and PA32540-302

	PA32540 N=524	ECASA 325 mg N=525
Gender		
Male	375 (72%)	374 (71%)
Female	149 (28%)	151 (29%)
Race		
White	470 (90%)	473 (90%)
African American	49 (9%)	42 (8%)
Age		
Median	66	66
Min, Max	41,88	39,88
Age Group		
<65	214(41%)	235 (45%)
≥65	310 (59%)	290 (55%)

Source: CSR (ISE) page 52

6.1.3 Subject Disposition

Subject Disposition for both studies PA32540-301 and PA32540-302 have been discussed individually previously in this review in Section 5. In general the disposition of subjects in the combined analysis is described as the following. Combined there were 524 subjects in PA32540 and 525 subjects in ECASA 325mg which encompassed the ITT population. More subjects in the PA32540 group (80.9%) completed the study than those in the ECASA 325 mg treatment group (75.4%). Adverse events were the reason for discontinuation in 6.7% of subjects assigned to PA32540 and 11.2% of those subjects assigned to ECASA 325 mg.

Table 24 Subject Disposition: All randomized Subjects from Studies 301 and 302

	PA32540 N=524	ECASA 325 mg N=525
Intent to Treat Population (ITT)	524 (100%)	525 (100%)
Modified Intent to Treat Population (mITT)	521 (99%)	522 (99%)
Safety Population[1]	521 (99%)	524 (99%)
Per Protocol Population	506 (97%)	509 (97%)
Completed Study	424 (81%)	396 (75%)
Premature Discontinuations	100 (19%)	129 (25%)
Reasons for Discontinuations		
Adverse Events	35 (7%)	59 (11%)
Withdrew Consent	26 (5%)	24 (5%)
Lost to Follow-up	4 (0.8%)	7 (1.3%)
Study terminated by Sponsor	0	0
Other	35 (7%)	39 (7%)

Subjects 2301, 4322, 4579, and 4628 were randomized to PA32540 but received EC-ASA 325mg. Subjects 4507, 4582 and 4586 were randomized to EC-ASA 325mg but received PA32540. For all safety summaries, subjects are classified according to the treatment actually received.
Source CSR (ISE) Table E1 page 1 of 1.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint, the incidence of gastric ulcer through 6 months for Studies PA32540-301 and PA32540-302, are depicted in Tables 25 and 26 below.

Table 25: Analysis of Cumulative Proportion (n %) of Subjects Developing Gastric Ulcers through 1, 3, and 6 Months Study PA32540-301- ITT Population

Timepoint Ulcer Status	PA32540 N= 265	ECASA 325 mg N= 265	p-Value[1]
	n (%)	n (%)	
0-1 Month			
Gastric ulcer	3 (1.1%)	10 (3.5%)	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%)	18 (6.8%)	0.044
95% CI	(1.3%- 5.9%)	(4.1%- 10.5%)	
Gastric ulcer-free	257 (97%)	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 (25.35)	

Source: CSR PA32540-301 Table 11 Page 59.
1 P-value for ulcer occurrence from CMH test stratified by NSA D use (use=COX-2, other NSAID, or use=no) at time of randomization.
2 Maintained=continued in study.

Reviewer's comments: The incidence of gastric ulcers throughout 1, 3, and 6 months of treatment was lower with PA32540 than with ECASA 325 mg for all time periods. A notable difference between the therapies could be observed as early as the first month with durability of response persisting for PA32540 throughout the 6 month treatment period. The cumulative gastric ulcer incidence was 3.8% for subjects taking PA32540 and 8.7% for subjects who took ECASA 325mg.

Similarly the primary efficacy results for Study PA32540-302 show a lower incidence of gastric ulcer development over the 6 month treatment period in the PA32540 treatment group than the ECASA 325mg treatment group. The difference in ulcer development was observed in the first month of therapy with durability of response to PA32540 lasting throughout the six month treatment period. The cumulative gastric ulcer rate at 6 months was 2.7% for subjects taking PA32540 and 8.5% for subjects taking ECASA 325 mg. Results for the 3 intervals 1, 3, and 6 months are shown in Table 26.

Table 26: Analysis of the Cumulative Proportion (n, %) of Subjects Developing Gastric Ulcers through 1, 3, and 6 Months Study PA32540-302- ITT Population

Timepoint Ulcer Status	PA32540 N= 265	ECASA 325 mg N= 265	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[2]	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[2]	199 (76.8%)	176 (67.7%)	
Discontinued	53 (20.5%)	62 (23.8%)	

Source: CSR PA32540-302 Table 11 Page 58.
1 P-value for ulcer occurrence from CMH test stratified by NSA D use (use=COX-2, other NSAID, or use=no) at time of randomization.
2Mantel-Fleiss criteria was <5 when stratified by NSA D use with 3 strata, so only 2 strata (NSAID use=Yes/No) were used
3 Maintained=continued in study.

The cumulative incidence of gastric ulcers throughout the 1, 3, and 6 months study treatment intervals was consistently lower in the PA32540 treatment group than the ECASA 325mg treatment group in the combined (two-study) analysis. The cumulative gastric ulcer rate at 6 months in subjects taking PA32540 was 3.2% compared to 8.6% in subjects taking ECASA 325 mg. Because the combined analysis was not prespecified the p-values are provided for descriptive purposes only.

Table 27: Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers at 1, 3, and 6 months- ITT population in the Combined Analysis

Timepoint Ulcer Status	PA32540 N= 524	ECASA 325 mg N= 525	p-Value[1]
	n (%)	n (%)	
0-1 Month			
Gastric ulcer	4 (0.8%)	18 (3.4%)	0.003
95% CI	(0.2%- 1.9%)	(2.0%- 5.4%)	
0-3 Months			
Gastric ulcer	9 (1.7%)	35 (6.7%)	<0.001
95% CI	(0.8%- 3.2%)	(4.7%- 9.2%)	
0-6 Months			
Gastric ulcer	17(3.2%)	45 (8.6%)	<0.001
95% CI	(1.9%- 5.1%)	(6.3% - 11.3%)	

1 P-value for ulcer occurrence from CMH test stratified by NSA D use (use=COX-2, other NSAID, or use=no) at time of randomization.
Source: Table adapted from Table 28. Page 61 CSR (ISE)

Reviewer's comments: The addition of the omeprazole in this combination product appears to have provided gastroprotection for individuals at risk for developing gastric ulcers based on their daily use of aspirin. The overall cumulative incidence of gastric ulcers is remarkably low in both treatment arms but statistically significantly lower in the PA32540 group as compared to the ECASA 325 mg group at 3 and 6 months. These results appear clinically meaningful in light of the fact that the subjects had no gastric or duodenal ulcers at baseline and they were taking aspirin 325 mg at least 3 months prior to enrollment in the study.

6.1.5 Analysis of Secondary Endpoints(s)

A hierarchical series of four secondary and tolerability endpoints were examined to support the efficacy of PA32540 in reducing aspirin-associated damage to the GI tract by measuring duodenal ulcers, other asymptomatic findings to the gastrointestinal tract, and by symptomatology that could be associated with aspirin.

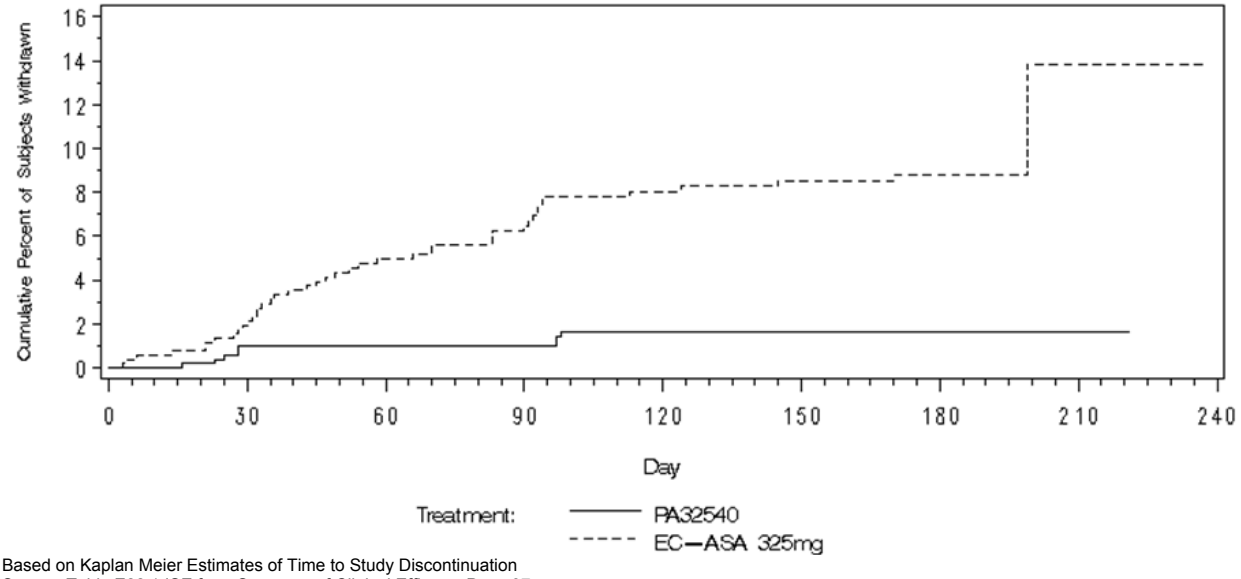
In both studies PA32540-301 and 302, the cumulative observed incidence of gastroduodenal ulcers throughout 6 months was significantly lower in the subjects who were treated with PA32540 compared to those subjects treated with ECSAS 325mg ($p=0.002$ and $p=<0.001$ in PA32540-301 and 302 respectively.) As observed for the primary efficacy endpoint, the difference in treatment effect between the study arms was observed at the 1 month interval and was sustained throughout the 6 months of therapy.

Treatment success
The occurrence of upper gastrointestinal (UGI) ulcerations or UGI AEs leading to discontinuation of chronic aspirin therapy for secondary prevention is clinically relevant because discontinuation of antiplatelet treatment increases the chance of recurrent ischemic events.
Therefore, the proportion of subjects continuing in the study throughout 6 months without the occurrence of gastric ulcers or pre-specified UGI AEs leading to discontinuation was termed Treatment Success.
In both studies PA32540-301 and 302, the proportion of subjects achieving treatment success was higher in those subjects who took PA32540 than in those subjects who took ECASA 325 mg.

Discontinuation Due to Pre-specified UGI AEs
More subjects in both studies and in the combined population who took ECASA 325 mg discontinued due to pre-specified upper gastrointestinal adverse events including duodenal ulcer (DU) compared to subjects who took 32540. Subjects with DU were required by protocol to be discontinued. Figure depicts the estimation of time to study

withdrawal based on the combined analysis for subjects who discontinued due to pre-specified upper GI adverse events.

Figure 5: Plot of Cumulative Incidence of Pre-specified Upper GI Adverse Events Leading to Study Discontinuation – ITT Population from Combined Analysis (Studies PA32540-301 and 302)



Based on Kaplan Meier Estimates of Time to Study Discontinuation
Source: Table E22.1 ISE from Summary of Clinical Efficacy. Page 37

Heartburn Resolution

Chronic aspirin use is associated with symptoms of heartburn and dyspepsia that may lead to erosive esophagitis, reflux esophagitis or gastroesophageal reflux disease (GERD), which may lead to study drug interruptions or discontinuation of aspirin treatment and put patients at risk for recurrent cardio- or cerebrovascular events. As a measure of tolerability of PA32540, heartburn was assessed at each visit.
Resolution of heartburn at each post-baseline visit was defined as having a severity rating of “None” on the heartburn questionnaire, regardless of whether the subject had heartburn at baseline or not. Only subjects with heartburn severity assessments at baseline and post-baseline were included in the analysis.

Table 28: Outcomes of Secondary Efficacy and Tolerability Endpoints-ITT Population Studies PA32540-301 and PA32540-302

	PA32540-301		PA32540-302	
	PA32540 N=265	ECASA 325 mg N=265	PA32540 N=259	ECASA-325 mg N= 260
Key Secondary Endpoints				
Incidence of Gastric and/or Duodenal Ulcers at 6 months	**4.2%**	**11.7%**	**2.7%**	**11.5%**
Treatment Success	**94%**	**83%**	**96%**	**84%**
Discontinuation of Treatment due to ASA-associated UGI AEs	**2.3%**	**8.3%**	**0.8%**	**8.1%**
Heartburn Resolution at 6 months	PA32540 N=214	ECASA 325 mg N=188	PA32540 N=215	ECASA 325mg N=190
	92.5%	**72%**	**93%**	**80%**

Source: Adapted from Table 11 SCE page 33.

Reviewer's comments: The choice of secondary endpoints seems appropriate. Ulceration can occur anywhere in the gastrointestinal tract. Chronic aspirin use may result in duodenal ulcers. However gastric ulcers and erosions occur more frequently with the use of chronic low dose aspirin. Because H. pylori infections are usually the primary source for duodenal ulcers, it is prudent that physicians screen for and treat H. pylori infection prior to administering this therapy. The discontinuation of chronic aspirin therapy due to UGI AEs, as well as heartburn, are important factors to be aware of because patient compliance would be compromised. Decreased compliance could potentially increase the risk for developing ischemic events in a patient population where the drug is administered to prevent secondary cardiovascular and cerebrovascular events from occurring.

6.1.7 Subpopulations

In both studies PA32540-301 and PA32540-302 the number of subjects in the ITT subgroups of NSAID users and ulcer history within 5 years of randomization were low. Therefore no meaningful comparison of ulcer risk reduction could be made.

Similarly, for both studies PA32540-301 and PA32540-302, the number of randomized subjects < 65 years and those ≥65 years of age was approximately the same in each treatment group. The overall incidence of gastric ulcers was consistently lower for both age cohorts in the PA32540 treatment group.

In the combined analysis of ITT subgroups the number of subjects on NSAIDs was low and no meaningful comparison of ulcer risk could be made in those subjects taking chronic NSAIDs or COX-2 medication.

The number of randomized subjects < 65 years of age and those ≥ 65 years old was approximately the same in each of the treatment groups. The overall incidence of gastric ulcers was significantly lower in those subjects ≥ 65 years old in the PA32540 treatment group than those assigned to EC-aspirin 325 mg treatment group, but not in those subject < 65 years of age. In addition, subjects 65 years of age or older taking PA32540 had a numerically lower incidence of gastric ulcers compared to those younger than 65. This was not the case for those taking EC-aspirin 325 mg.

Table 29: Analysis of Cumulative Proportion of Subjects Developing Gastric Ulcers Throughout 6 Months by Age Group- ITT Population in the Combined Analysis

Timepoint Ulcer Status	PA32540	ECASA 325 mg	p-Value[1]
Age < 65	**N= 214**	**N= 235**	
0-6 Month			
Gastric ulcer	10 (4.7%)	17 (7.2%)	NS
95% CI	(2.3%- 8.4%)	(4.3%- 11.3%)	
Age ≥ 65	**N=310**	**N= 290**	
0-6 Months			
Gastric ulcer	7(2.3%)	28 (9.7%)	<0.001
95% CI	(0.9%- 4.6%)	(6.5% - 13.7%)	

Additionally, subjects who were 65 to 74 years of age and those ≥ 75 years of age had significantly lower rates of gastric ulcer if assigned to PA32540 (2.5% and 1.4%, respectively) than if they were assigned to ECASA 325 mg (9.7% and 9.5%, respectively).

The number of subjects in the combined analysis with a history of gastric ulcer or duodenal ulcer within 5 years of randomization was low with 25 subjects on PA32540 and 32 subjects on ECASA 325 mg. Due to the small numbers involved, no meaningful comparison of ulcer risk were made.

Those subjects in the combined analysis treated with PA32540 had a significantly lower incidence of gastric ulcers than those subjects treated with EC-aspirin 325 mg treatment in both males and females. By 6 months of treatment, rates of gastric ulcers were 3.5% and 8.0% in males, and 2.7% and 9.9% in females for those subjects treated with PA32540 and those subjects treated with EC-aspirin 325 mg, respectively. There was no apparent difference in the incidence of gastric ulcers between males and females in either treatment group.

Since the combined study populations were predominantly white, no meaningful comparisons of ulcer risk reduction can be made among races. Similarly, since the study populations were predominantly of non-Hispanic ethnicity, no meaningful comparisons of ulcer risk reduction can be made among in subjects of Hispanic ethnicity.

Reviewer's comments: The combined number of subjects in the 65-74 years age group developing gastric ulcer throughout the 6 month treatment period in both studies was very small; 7 in the PA32540 group and 28 in the ECASA 325 mg group In the cohort of subjects greater than 75 years of age only 1 subject in the PA32540 treatment group compared to 6 subjects taking ECASA 325 mg developed gastric ulcers. Although age >65 years, a history of previous GI event, chronic debilitating disorders, high dose NSAID therapy, and concomitant use of anticoagulants, corticosteroids, or other NSAIDs including low dose aspirin are risk factors for developing gastric ulcers, PA32540 appears to be somewhat protective in individuals with advanced age requiring long term low dose aspirin therapy. These results may prove helpful in guiding physicians whose practice may be primarily geriatric with patients requiring daily aspirin use for secondary prophylaxis.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A fixed dose of PA32540 containing 325 of enteric coated aspirin and 40 mg of omeprazole was used during the phase 3 clinical trials. Please see the clinical pharmacology review for more detailed information pertinent to this topic.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In the ITT population, fewer subjects who took PA32540 in the combined population from studies PA32540-301 and PA32540-302 had gastric ulcers (GU) than subjects who took ECASA 325 mg at 1-month (0.8% to 3.4%, respectively), 3 months (1.7% to 6.7%, respectively) and at 6 months (3.2% to 8.6%, respectively).

There was no evidence of loss of effect of PA32540 in the reduction of aspirin-associated UGI adverse events. Adverse events which were pre-specified upper GI disorders leading to withdrawal from the study occurred primarily in the first 6 months of therapy with PA32540.

6.1.10 Additional Efficacy Issues/Analyses

Clinical Information requests were made October 4, 2013 and October 11, 2013. In summary, we asked the Sponsor to tabulate the proportion of subjects who were taking NSAIDs or COX2 inhibitors at baseline and of these subjects who met the primary endpoint. The sponsor submitted the number represented by these subjects is small for both studies i.e. less than 10% for those on NSAIDs and 1-2 % for subjects taking COX2 Inhibitors. The overall occurrence of gastric ulcers was very low. See Tables 7 and 17 in Section 5.

The sponsor also provided information regarding subjects developing ulcers stratified by previous GU/DU history and age. These results have been discussed previously in Section 5 and Section 6. Lastly, alcohol use was not recorded at baseline or during the study. Therefore the analysis of adverse reactions based on alcohol usage could not be determined. Notably, subjects with a history of alcoholism within a year prior to enrollment were excluded from study participation.

The sponsor provided information regarding subjects with no post baseline endoscopy. The number of subjects without the post baseline endoscopy was small and similar between treatment groups for both studies. For both studies the most common reasons for the lack of post baseline endoscopy included withdrawal of consent (usually due to the need for repeated endoscopies) or adverse events.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Studies PA32540-301 and PA32540-302 were designed to confirm the efficacy and safety of PA32540. These studies compared PA32540 to EC-aspirin 325 mg in subjects with cardiovascular disease who were: 1) age 18 to 54 with history of a documented uncomplicated gastric or duodenal ulcer within the past 5 years or 2) age ≥ 55 years regardless of prior history of ulcer, as age alone is acceptable as a risk factor to develop aspirin-associated upper GI damage. The primary objective of these studies was to demonstrate that PA32540 caused fewer gastric ulcers in subjects at risk for developing aspirin-associated gastric ulcers compared to ECASA 325 mg, as determined by serial UGI endoscopy throughout 6 months. Secondary objectives included demonstration of fewer gastric and/or duodenal ulcers in subjects taking PA32540, the proportion of subjects with “Treatment Success” defined as those subjects without gastric ulcers and without upper gastrointestinal (UGI) adverse events leading to discontinuation, the proportion of subjects discontinuing the study due to UGI adverse events, the proportion of subjects with heartburn resolution defined as the answer “None” on the heartburn assessment question and the overall safety of PA32540 as compared to ECASA 325 mg.

The long-term safety of PA32540 was demonstrated in PA32540-303, an open-label one-year study of PA32540 in subjects with either a recent history of documented

gastric or duodenal ulcer or who were over 55 years of age and expected to require daily aspirin therapy for at least 12 months.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were monitored throughout all of the studies and recorded in the electronic data collection system from the day of administration of the first dose of study drug through the final follow-up visit within each study.

Adverse events were sought by non-directive questioning at each visit after the subject had an opportunity to spontaneously mention any problems. Adverse events were also detected through physical examination, laboratory tests or other assessments. Medical conditions/diseases present before starting study drug were considered adverse events only if they worsened after starting study drug.

Therapeutic Failure as an Adverse Event
Therapeutic failure was defined as the development of a gastric ulcer or other upper gastrointestinal adverse events that led to discontinuation. The occurrence of gastric ulcers in any of the scheduled or unscheduled endoscopies was the primary efficacy endpoint in studies PA32540-301 and PA32540-302 and therefore, gastric ulcers were not captured as adverse events

Duodenal ulcers were not considered primary endpoints and were recorded as TEAEs. Other upper gastrointestinal adverse events were pre-specified in the Statistical Analysis Plans for studies PA32540-301 and 302.

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

Pooling of the populations across studies was for the comparison of the treatments of interest in the largest number of similarly exposed subjects to assess the safety profile of PA32540 over time. The populations included in the pooled data analyses are the following:

Primary Safety Population (PSP) - Included all treated subjects in the identical phase 3, adequate and well-controlled, double blind, 6-month studies. These studies enrolled identical populations treated with PA32540 or EC-aspirin 325 mg daily for 6 months and generated the UGI endoscopy data demonstrating a lower incidence of gastric ulcers with PA32540. All subjects in these 2 studies were to have protocol-required endoscopies at baseline, and Months 1, 3 and 6. The primary endpoint of gastric ulcer was assessed as a Treatment Emergent Adverse Event (TEAE) in the analysis of the PSP included in this Integrated Summary of Safety (ISS).The PSP includes the following studies: PA32540-301 and PA32540-302.

Long Term Safety Population (LSP) - Included all treated subjects in the phase 3, open label, 12-month study. This population is not technically pooled but simply included all subjects who took at least one dose of PA32540. This study did not include scheduled endoscopic examinations and did not have a control group. The LSP is derived only from the following study: PA32540-303.

Twelve Month Population (TMP) - Included all subjects from the Long Term Safety Study that completed at least 348 days of treatment with PA32540. The TMP is derived only from the following study: PA32540-303.

Six Month Population (SMP) - Included subjects who completed 6 months of therapy from the adequate and well-controlled phase 3, double-blind, placebo controlled studies which included endoscopy and subjects who completed at least 6 months of therapy in the Long Term Safety Study. Spontaneously reported adverse events other than those associated with endoscopic examination were pooled. The SMP includes the following studies: PA32540-301, PA32540-302 and PA32540-303. Table 30 provides an overview of the populations planned for the integrated safety analyses, and includes those subjects who had at least one dose of study drug.

Table 30: Exposure by Population, PA32540 and ECASA 325 mg

	Subjects	
	PA32540	ECASA 325 mg
Population		
Primary Safety Population (PSP)	521	524
Long –term Safety Population (LSP)	379	NA
Twelve Month Population (TMP)	290	NA
Six Month Population (SMP)	735	366

Source: Adapted from Table 2 ISS page 35. NA= Not applicable

7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate. Safety variables included adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs, and physical examination parameters. Patients who were given at least one dose of the study medication were included in the safety analysis population.

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

The vast majority of subjects (about 99%) in both treatment groups had ≥ 70% compliance overall from Baseline to Month 1, Month 3, and end of study in both studies. The median and mean doses per subject in the PSP were approximately 3 fewer doses than the median and mean number of days from first dose to last dose for each corresponding population. In each treatment group, for both studies, the mean and median doses per month were approximately 30. See Table 31 below.

Table 31: Extent of Exposure in the Primary Safety Population (PSP)

	PA32540		EC-aspirin 325 mg	
Number of Days from First to Last Dose	**PA32540-301 N=264**	**PA32540-302 N=257**	**PA32540-301 N=265**	**PA32540-302 N=259**
Mean (SD)	157.1 (51.8)	160.9 (47.8)	145.7 (59.3)	149.8 (56.6)
Median	178	178	175	177
Range	1 – 206	2 - 220	2.0 – 226	2 - 217
Duration of Treatment				
1-36 days	22 (8.3 %)	17 (6.6%)	35 (13.2%)	29 (11.2%)
37-108 days	24 (9.1%)	20 (7.8%)	32 (12.1%)	30 (11.6%)
>108 days	218 (82.6%)	220 (85.6%)	198 (74.7%)	200 (77.2%)
Number of Doses per Subject				
Mean (SD)	154.4 (51.4)	157.6 (48.3)	142.9 (58.7)	148.0 (56.6)
Median	175	175	173	175
Range	1 – 213	2 - 216	2 –212	2 - 216
Average Doses per Month				
Mean (SD)	29.6 (2.6)	29.3 (2.2)	29.5 (1.6)	29.7 (2.4)
Median	29.8	29.8	29.7	29.8
Range	13.3 – 52.5	15 - 40.8	20.5 – 36.2	21.5 - 60.0

Source: Table 14.1.8, PA32540-301 and Table 14.1.8, PA32540-302

7.2.2 Explorations for Dose Response

PA32540 tablets contain 325 mg of EC-aspirin and 40 mg of IR-omeprazole. The doses of aspirin and omeprazole in PA32540 are within the dose range approved by the FDA for the intended use of each of these products. EC-aspirin 325 mg was used as the comparator.

The phase 1 clinical pharmacology program for PA Tablets compared 20 mg and 40 mg of IR-omeprazole for the prevention of the UGI damage induced by EC-aspirin to support selection of the lowest effective dose of IR-omeprazole for inclusion in the PA formulation. The selection of 40 mg IR-omeprazole as the lowest effective dose is based on the sponsor's following 4 key points:

1. 40 mg IR-omeprazole provides 24-hour pH control comparable to the pH control achieved with currently marketed EC-omeprazole 20 mg.

2. Pharmacokinetic-pharmacodynamic analysis indicates that 20 mg IR-omeprazole would be sub-optimal for gastric mucosal protection relative to marketed EC products.

3. 40 mg IR-omeprazole produces approximately half the plasma omeprazole exposure of 40 mg EC-omeprazole and slightly higher exposure than that reported for 20 mg EC-omeprazole.

4. In phase 1 studies, 40 mg IR-omeprazole provides significant gastroduodenal mucosal protection that is superior to 20 mg IR-omeprazole.

For more information see the Clinical Pharmacology Review by Dr. Dilara Jappar.

7.2.3 Special Animal and/or In Vitro Testing

No new non-clinical data were submitted in support of this NDA.

7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments in the three submitted studies. See Table 2 Section 5.3 for detailed information on study visits and procedures.

7.2.5 Metabolic, Clearance, and Interaction Workup

For more information see the Clinical Pharmacology review by Dr. Dilara Jappar.

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

The studies were adequately designed to allow for safety analyses. The submitted studies also adequately monitored for adverse events known to occur with chronic aspirin use. The studies did not reveal any new safety signals.

7.3 Major Safety Results

7.3.1 Deaths

There were 6 deaths reported in any of the studies that comprise this application.

Three subjects who took PA32540 died during the study: Subject 302-499/3015 was an 87-yearold Hispanic Female who died of a non-related cerebrovascular accident on day 149 of the study, subject 302-572/4254 was a 66 y/o white male who had a non-related cardiac arrest after being struck by an automobile, and subject 303-612/5232 was a 60 y/o white male with a non-related cerebrovascular accident with infarction.

Two subjects who took EC-aspirin 325 mg died during the study: Subject 301-887/2639 sustained a non-related cardiac arrest after bouts of angina, and subject 302-876/4580 died of non-related renal cancer.

Additionally, the sponsor was made aware of one post-study death from Study PA32540-303 that occurred 75 days after the subject took her last dose of study drug. After 200 days of study drug Subject 303-655/5243 stopped the study drug due to an SAE of pancreatic cancer. The Investigator considered this SAE severe and unrelated to the study drug.

7.3.2 Nonfatal Serious Adverse Events

Twenty-five (25) Serious Adverse Events (SAEs) were reported by 16 (6.1%) subjects in PA32540-301 who took PA32540 and 32 SAEs in 24 (9.1%) subjects who took ECASA 325 mg. There were no substantive differences between the SOCs. The SOC of Gastrointestinal Disorders had the highest rate of reporting of SAEs; 1.9% and 2.3% of subjects who took PA32540 and ECASA 325 mg, respectively, reported SAEs.

In Study PA32540-302 twenty five (25) Serious Adverse Events were reported by 23 subjects who took PA32540 and 21 SAEs in 17 (6.6%) of subjects who took ECASA 325mg. A higher rate of reporting SAEs occurred in the SOC of Cardiac Disorders by subjects who took PA32540 (4.3%) and ECASA 325 mg (2.3%).

The differences in reporting rates in this SOC come from a number of preferred terms in which there were reports of one or two events including atrial fibrillation and myocardial infarction.

Table 32 compares the incidence of SAEs in the safety population for Studies PA32540-301 and 302 and the combined analysis i.e. the primary safety population.

Table 32: Incidence of Treatment Emergent Adverse Events-Primary Safety Population PA32540-301 and PA32540-302

System Organ Class / Preferred Term[1]	PA32540			EC-aspirin 325 mg		
	PA32540-301 n(%) N = 264	PA32540-302 n(%) N = 257	PSP n(%) N = 521	PA32540-301 n(%) N = 265	PA32540-302 n(%) N = 259	PSP n(%) N = 524
Number of SAEs	25	25	50	32	21	53
Subjects with any SAE	16 (6.1)	23 (8.9)	39 (7.5)	24 (9.1)	17 (6.6)	41 (7.8)
Gastrointestinal Disorders	5 (1.9)	2 (0.8)	7 (1.3)	6 (2.3)	2 (0.8)	8 (1.5)
Abdominal pain	1 (0.4)	0	1 (0.2)	0	1 (0.4)	1 (0.2)
Abdominal pain upper	1 (0.4)	0	1 (0.2)	0	0	0
Gastric ulcer haemorrhage	1 (0.4)	0	1 (0.2)	0	0	0
Intestinal obstruction	1 (0.4)	0	1 (0.2)	0	0	0
Pancreatic cyst	1 (0.4)	0	1 (0.2)	0	0	0
Pancreatitis	1 (0.4)	0	1 (0.2)	0	0	0
Diverticulitis	0	1 (0.4)	1 (0.2)	1 (0.4)	0	1 (0.2)
Duodenal ulcer haemorrhage	0	0	0	1 (0.4)	0	1 (0.2)
Gastrooesophageal reflux disease	0	0	0	1 (0.4)	0	1 (0.2)
Intestinal haemorrhage	0	0	0	1 (0.4)	0	1 (0.2)
Pancreatitis acute	0	0	0	1 (0.4)	0	1 (0.2)
Small intestinal obstruction	0	0	0	1 (0.4)	0	1 (0.2)
Large Intestinal haemorrhage	0	1 (0.4)	1 (0.2)	0	0	0
Oesophagitis obstruction	0	0	0	0	1 (0.4)	1 (0.2)
Cardiac Disorders	4 (1.5)	11 (4.3)	15 (2.9)	5 (1.9)	6 (2.3)	11 (2.1)
Angina pectoris	1 (0.4)	2 (0.8)	3 (0.6)	1 (0.4)	2 (0.8)	3 (0.6)
Atrial fibrillation	1 (0.4)	2 (0.8)	3 (0.6)	1 (0.4)	0	1 (0.2)
Atrial flutter	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.4)	0	1 (0.2)
Coronary artery disease	1 (0.4)	1 (0.4)	2 (0.4)	0	1 (0.4)	1 (0.2)

System Organ Class / Preferred Term[1]	PA32540			EC-aspirin 325 mg		
	PA32540-301 n(%) N = 264	PA32540-302 n(%) N = 257	PSP n(%) N = 521	PA32540-301 n(%) N = 265	PA32540-302 n(%) N = 259	PSP n(%) N = 524
Acute myocardial infarction	0	2 (0.8)	2 (0.4)	2 (0.8)	1 (0.4)	3 (0.6)
Arteriosclerosis coronary artery	0	1 (0.4)	1 (0.2)	0	0	0
Coronary artery occlusion	0	0	0	1 (0.4)	0	1 (0.2)
Sudden cardiac death	0	0	0	1 (0.4)	0	1 (0.2)
Myocardial infarction	0	2 (0.8)	2 (0.4)	0	0	0
Cardiac failure congestive	0	1 (0.4)	1 (0.2)	0	2 (0.8)	2 (0.4)
General Disorders and Administration Site Conditions	4 (1.5)	1 (0.4)	5 (1.0)	2 (0.8)	4 (1.5)	6 (1.1)
Infusion site extravasations	0	0	0	1 (0.4)	0	1 (0.2)
Accidental death	0	1 (0.4)	1 (0.2)	0	0	0
Chest pain	0	0	0	1 (0.4)	3 (1.2)	4 (0.8)
Non-cardiac chest pain	4 (1.5)	0	4 (0.8)	0	1 (0.4)	1 (0.2)
Infections and Infestations	3 (1.1)	3 (1.2)	6 (1.2)	3 (1.1)	1 (0.4)	4 (0.8)
Osteomyelitis	1 (0.4)	0	1 (0.2)	0	0	0
Septic shock	1 (0.4)	0	1 (0.2)	0	0	0
Wound infection	1 (0.4)	0	1 (0.2)	0	0	0
Chest wall abscess	0	0	0	1 (0.4)	0	1 (0.2)
Pneumonia	0	2 (0.8)	2 (0.4)	1 (0.4)	0	1 (0.2)
Sepsis syndrome	0	0	0	1 (0.4)	0	1 (0.2)
Periorbital cellulitis	0	1 (0.4)	1 (0.2)	0	0	0
Urinary tract infection	0	0	0	1 (0.4)	0	1 (0.2)
Cellulitis	0	0	0	0	1 (0.4)	1 (0.2)
Neoplasms, Benign, Malignant and Unspecified	2 (0.8)	1 (0.4)	3 (0.6)	1 (0.4)	2 (0.8)	3 (0.6)

System Organ Class / Preferred Term[1]	PA32540			EC-aspirin 325 mg		
	PA32540-301 n(%) N = 264	PA32540-302 n(%) N = 257	PSP n(%) N = 521	PA32540-301 n(%) N = 265	PA32540-302 n(%) N = 259	PSP n(%) N = 524
Colon cancer	1 (0.4)	0	1 (0.2)	0	1 (0.4)	1 (0.2)
Prostate cancer	1 (0.4)	0	1 (0.2)	0	0	0
Non-small cell lung cancer	0	0	0	1 (0.4)	0	1 (0.2)
Renal cancer	0	0	0	0	1 (0.4)	1 (0.2)
Squamous cell carcinoma of skin	0	1 (0.4)	1 (0.2)	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders	2 (0.8)	0	2 (0.4)	1 (0.4)	2 (0.8)	3 (0.6)
Chronic obstructive pulmonary disease	0	0	0	0	2 (0.8)	2 (0.4)
Haemoptysis	1 (0.4)	0	1 (0.2)	0	0	0
Sleep apnoea syndrome	1 (0.4)	0	1 (0.2)	0	0	0
Respiratory failure	0	0	0	1 (0.4)	0	1 (0.2)
Hepatobiliary Disorders	1 (0.4)	0	1 (0.2)	1 (0.4)	1 (0.4)	2 (0.4)
Cholecystitis	1 (0.4)	0	1 (0.2)	0	1 (0.4)	1 (0.2)
Cholelithiasis	0	0	0	1 (0.4)	0	1 (0.2)
Injury, Poisoning, and Procedural Complications	1 (0.4)	0	1 (0.2)	2 (0.8)	0	2 (0.4)
Humerus fracture	1 (0.4)	0	1 (0.2)	0	0	0
Ankle fracture	0	0	0	1 (0.4)	0	1 (0.2)
Femur fracture	0	0	0	1 (0.4)	0	1 (0.2)
Joint dislocation	0	0	0	1 (0.4)	0	1 (0.2)
Renal and Urinary Disorders	1 (0.4)	0	1 (0.2)	1 (0.4)	0	1 (0.2)
Azotaemia	1 (0.4)	0	1 (0.2)	0	0	0
Renal impairment	0	0	0	1 (0.4)	0	1 (0.2)

System Organ Class / Preferred Term[1]	PA32540			EC-aspirin 325 mg		
	PA32540-301 n(%) N = 264	PA32540-302 n(%) N = 257	PSP n(%) N = 521	PA32540-301 n(%) N = 265	PA32540-302 n(%) N = 259	PSP n(%) N = 524
Vascular Disorders	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.8)	0	2 (0.4)
Deep vein thrombosis	1 (0.4)	0	1 (0.2)	1 (0.4)	0	1 (0.2)
Aortic aneurysm	0	0	0	1 (0.4)	0	1 (0.2)
Carotid artery stenosis	0	1 (0.4)	1 (0.2)	0	0	0
Musculoskeletal and Connective Tissue Disorders	0	0	0	1 (0.4)	0	1 (0.2)
Myofascial pain syndrome	0	0	0	1 (0.4)	0	1 (0.2)
Nervous System Disorders	0	4 (1.6)	4 (0.8)	2 (0.8)	2 (0.8)	4 (0.8)
Transient ischaemic attack	0	2 (0.8)	2 (0.4)	2 (0.8)	0	2 (0.4)
Cerebrovascular accident	0	1 (0.4)	1 (0.2)	0	0	0
Reversible ischaemic neurological deficit	0	1 (0.4)	1 (0.2)	0	1 (0.4)	1 (0.2)
Syncope	0	0	0	0	1 (0.4)	1 (0.2)
Ear and Labyrinth Disorders	0	1 (0.4)	1 (0.2)	0	0	0
Vertigo	0	1 (0.4)	1 (0.2)	0	0	0
Metabolism and Nutrition Disorders	0	0	0	1 (0.4)	0	1 (0.2)
Hyperglycaemia	0	0	0	1 (0.4)	0	1 (0.2)

[1] Note: Events are summarized in decreasing order based on the occurrence rate in the PA32540 group in the PA32540-301 Study.
Source: Table 14.3.2.1, PA32540-301, Table 14.3.2.1, PA32540-302, and S2.33

7.3.2.1 Serious Adverse Events Related to Study Drug

Serious Adverse Events (SAEs) were reported equally between the treatment groups in the Primary Safety Population (7.5% of subjects taking PA32540 and 7.8% of subjects taking ECASA 325 mg). More events were reported from the SOC of Cardiac Disorders than other SOC's and were in general balanced 2.9% vs 2.1 respectively. All other SOCs were reported within 1% of each other with no apparent imbalances.

Three subjects who took PA32540 reported SAEs that were judged to be related to the study drug by the PI.

1) Subject 301-512/2201 was a 69-year-old white female with hemoptysis at day 16 of treatment that resolved, but the subject was also discontinued from the study
2) Subject 301-793/2382 was a 64-year-old white male with a gastric ulcer hemorrhage at day 50 of treatment that resolved, but the subject was also discontinued from the study
3) Subject 302-860/4598 was a 67-year-old white male who had a cecal hemorrhage at day 80 of treatment that resolved, but the subject was also discontinued from the study.

Three subjects who took ECASA 325 mg reported SAEs that were also judged to be related to the study drug by the PI.

1) Subject 301-530/2221 was a 77-year-old white male who had a duodenal ulcer hemorrhage at day 36 of treatment that resolve, but the subject was also discontinued from the study
2) Subject 301-545/2315 was a 64-year-old white male with intestinal hemorrhage at day 79 of treatment that resolved, but the subject was also discontinued
3) Subject 301-816/2374 was a 75-year-old white male who had worsening GERD at day 110 of treatment that resolved, but the subject was also discontinued from the study.

Table 33 compares the incidence of SAEs reported that were judged to be related to the study drug.

Table 33: Incidence of Serious Adverse Events related to Study Drug in Studies PA32540-301 and PA32540-302

System Organ Class / Preferred Term[1]	PA32540		EC-aspirin 325 mg	
	PA32540-301 n(%) (N=264)	PA32540-302 n(%) (N=257)	PA32540-301 n(%) (N=265)	PA32540-302 n(%) (N=259)
Number of SAEs	2	1	3	0
Subjects with any SAE	2 (0.8)	1 (0.4)	3 (1.1)	0
Gastrointestinal Disorders	1 (0.4)	1 (0.4)	3 (1.1)	0
Gastric ulcer haemorrhage	1 (0.4)	0	0	0
Duodenal ulcer haemorrhage	0	0	1 (0.4)	0
Gastrooesophageal reflux disease	0	0	1 (0.4)	0
Intestinal haemorrhage	0	0	1 (0.4)	0
Large Intestinal haemorrhage	0	1 (0.4)	0	0
Respiratory, Thoracic, and Mediastinal Disorders	1 (0.4)	0	0	0
Haemoptysis	1 (0.4)	0	0	0

[1]Note: Events are summarized in decreasing order based on the occurrence rate in the PA32540 group in the PA32540-301 Study

Source: Table was electronically reproduced from Table 66 ISS page 156.

7.3.3 Dropouts and/or Discontinuations

Fifty-two (52) subjects (10.0%) in the combined analysis who took PA32540 discontinued participation in either of the studies compared to 104 (19.8%) subjects discontinued who took ECASA 325 mg. This difference is primarily due to increased reporting of preferred terms in the SOC of Gastrointestinal Disorders in subjects who took ECASA 325 mg and included increases in discontinuations for gastric ulcer,

dyspepsia, and duodenal ulcer (gastric ulcers were not included in the separate analyses in PA32540-301 and PA32540-302).

More subjects in the PSP who took ECASA 325 mg discontinued due to pre-specified upper GI adverse events (16.8%) than those subjects who took PA32540 (4.8%). This was primarily due to discontinuation from gastric ulcer, dyspepsia, and duodenal ulcer Five (5) subjects who took PA32540 discontinued due to cardiovascular events compared to none who took ECASA 325 mg.

Table 34 displays discontinuations from the combined analysis from the SOC of gastrointestinal disorders.

Table 34: Incidence of Treatment Emergent Adverse Events of the SOC of Gastrointestinal Disorders Leading to Study Drug Discontinuation in the Primary Safety Population (PSP)

System Organ Class / Preferred Term[1]	PA32540 n(%) (N = 521)	EC-aspirin 325 mg n(%) (N = 524)
Number of AEs Leading to Discontinuation	52	104
Subjects with any AE Leading to Discontinuation	52 (10.0)	104 (19.8)
Gastrointestinal Disorders	31 (6.0)	91 (17.4)
Gastric ulcer	17 (3.3)	45 (8.6)
Abdominal pain upper	2 (0.4)	1 (0.2)
Diarrhoea	2 (0.4)	0
Dyspepsia	2 (0.4)	16 (3.1)
Abdominal pain	1 (0.2)	0
Constipation	1 (0.2)	0
Diverticulitis	1 (0.2)	0
Duodenal ulcer	1 (0.2)	10 (1.9)
Gastritis	1 (0.2)	0
Gastritis erosive	1 (0.2)	0
Large intestinal haemorrhage	1 (0.2)	0
Pancreatitis	1 (0.2)	0
Duodenal ulcer haemorrhage	0	1 (0.2)
Duodenitis	0	1 (0.2)
Dysphagia	0	1 (0.2)
Erosive oesophagitis	0	2 (0.4)
Gastritis haemorrhage	0	1 (0.2)
Gastrointestinal erosion	0	1 (0.2)
Gastrooesophageal reflux disease	0	3 (0.6)
Intestinal haemorrhage	0	1 (0.2)
Oesophageal ulcer	0	3 (0.6)
Oesophagitis	0	4 (0.8)
Pancreatitis acute	0	1 (0.2)

[1] Note: Events are summarized in decreasing order based on the occurrence rate in the PA32540 group.
Source: Electronically reproduced from table 70 ISS page 163

7.3.4 Significant Adverse Events

ICH E3 defines "other significant adverse events " as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of a test drug, dose reduction, or significant additional concomitant therapy other than those reported as serious adverse events. See Section 7.3.5

7.3.5 Submission Specific Primary Safety Concerns

Hemoglobin Decreases of >2g/dL from Baseline in the Primary Safety Population
Thirty five subjects in the PSP developed a > 2g/dl drop in hemoglobin from baseline over the course of the 6 month study. Of those 35, 6 of the 19 (31.6%) subjects who took PA32540 and sustained the drop were also on clopidogrel, compared to 4 of 16 (25%) of subjects who took ECASA 325 mg. Additionally, of the 35 subjects who experienced a >2g/dL drop in hemoglobin, 3subjects taking PA32540 and 1 subject taking ECASA were also on chronic NSAID therapy. Subjects who experienced this drop in hemoglobin in either treatment group had repeat levels of Hgb that did not meet the >2g/dL change and they were allowed to continue in the study. Notably several subjects in both treatment groups experienced AEs such as UGI bleeding or treatment for new onset neoplasia which might account for the drop in hemoglobin.

Changes in Hepatic Function in the Primary Safety Population
Mean values in alkaline phosphatase in the PSP increased 2.2 U/L in subjects who took PA32540 through 6 months and declined 2.3 U/L in those who took EC-aspirin 325 mg. The maximum change at any time point was 190 and 141 U/L, respectively. Mean changes for ALT at the Final visit were 0.4 and -0.8 U/L, respectively with maximum increases at any time of 182 and 142 U/L, respectively. Mean AST levels increased by 1.0 U/L and decreased by 0.3 U/L, and maximum increases were 188 and 100 U/L, respectively. Mean bilirubin levels were unchanged at the Final visit in both groups, and maximum increases were 0.8 mg/dL and 0.8 mg/dL, respectively.

Table 35 displays the hepatic related changes by fold increase from ULN at any time in the PSP. The changes were balanced between treatment groups. No subject in either treatment group had a combination of increased ALT or AST of >3x ULN and a bilirubin increase of >2 xULN.

Table 35: Clinically Relevant Hepatic-Related Changes in the Primary Safety Population (PSP)

Assessment	PA32540 (N=521) n (%)	ECASA 325 mg (N=524) n (%)
ALT		
≥3xULN	*3(0.6)*	*1 (0.2)*
≥5xULN	*0*	*0*
≥10xULN	*0*	*0*
≥20xULN	*0*	*0*
ALT		
≥3xULN	*3(0.6)*	*2 (0.4)*
≥5xULN	*1(0.2)*	*0*
≥10xULN	*0*	*0*
≥20xULN	*0*	*0*
Alkaline Phosphatase		
≥ 1.5x ULN	*3 (0.6)*	*1 (0.2)*
≥ 3x ULN	*0*	*0*
Bilirubin		
≥ 1.5x ULN	*1 (0.2)*	*2 (0.4)*
≥ 2x ULN	*0*	*1(0.2)*

Source: Table 83 ISS page 208

Reviewer Comment: There were no subjects in the PSP who met "Hy's Law" criteria (elevated ALT greater than 3 times the upper limit of normal (ULN) with concurrent increase in bilirubin greater than two times the upper limit of normal and alkaline phosphatase less than 2 times the upper limit of normal).

Changes in Renal Function in the Primary Safety Population (PSP)
Renal function in subjects was evaluated by changes and maximum shift analysis of creatinine, calculated creatinine clearance using the Cockcroft-Gault equation and BUN.

Chemistry shifts from Low or Normal to High in BUN, and serum creatinine and High or Normal to Low in calculated creatinine clearance are shown in Table 36. By shifts from normal ranges, more subjects treated with PA32540 shifted creatinine from Low or Normal to High than did those treated with ECASA 325 mg in the PSP. However, similar percentages of both treatment groups shifted BUN from Low or Normal to High, or creatinine clearance from High or Normal to Low. There are no substantive differences in shifts consistent with renal insufficiency between the treatment groups in the combined analysis.

When expanded ranges are applied, there are no substantive differences between the groups i.e. the rates of shifts in any marker of renal function occurs in about 3% of either treatment group.

Reviewer's comments: Expanded ranges were developed by POZEN medical personnel prior to the database lock of the Phase 3 studies. They are categorized by Male /Female; all ages; and range of values. See Table S1.11 in the ISS page 841.

Table 36: Incidence of Shifts Denoting Worsening Renal Function in the Primary Safety Population

Parameter	PA32540 % shifted		EC-aspirin 325mg % shifted	
	Normal Range	Expanded Range	Normal Range	Expanded Range
BUN	14.8	1.4	14.1	0.8
Creatinine	11.1	2.7	6.6	3.3
Creatinine Clearance	1.2	0	1.8	0

Source: Electronically reproduced and copied from ISS Table 88 page 213.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The safety population for the combined analysis (PSP) consisted of 521 subjects who took PA32540 and 524 subjects who took ECASA 325mg. Of those, 374 subjects (71.8%) sustained 989 TEAEs (1.9 events per subject, or 2.6 events per subject reporting any event) and 446 (85.1%) sustained 1467 TEAEs, respectively (2.8 events per subject, or 3.3 events per subject reporting any event).

The predominant SOC for reporting TEAEs was Gastrointestinal Disorders. Fifty-four point three percent (54.3%) of subjects who took PA32540 reported TEAEs from this SOC compared to 76.0% of subjects who took ECASA 325 mg. These differences were primarily accounted for by increases in reporting from the ECASA 325 mg treatment group compared to PA32540 treatment group for the preferred terms of dyspepsia (30.2% and 11.3%, respectively), erosive gastritis (26.3% and 11.5%, respectively), duodenitis (13.4% and 5.6%, respectively), esophagitis (12.0% and 3.3%, respectively), erosive duodenitis (7.1% and 1.3%, respectively), duodenal ulcer (3.6% and 0.2%, respectively), and erosive esophagitis (6.3% and 0.4%, respectively).

Additionally, gastric ulcers were reported in 8.6% and 3.3% of treatment groups, respectively. No TEAEs were reported by substantively more subjects who took PA32540 than EC-aspirin 325 mg in the primary safety population. All other preferred terms in this SOC were generally balanced or less than 3% reported

Table 37: Incidence of All Treatment Emergent Adverse Events by System Organ Class-Primary Safety Population from Studies 301 and 302

System Organ Class/ Preferred Term	PA32540 (N=521)	EC-ASA 325mg (N=524)
Number of Events	989	1467
Subjects with any Adverse Event	374 (71.8%)	446 (85.1%)
Gastrointestinal disorders	283 (54.3%)	398 (76.0%)
Gastritis	91 (17.5%)	84 (16.0%)
Gastritis erosive	60 (11.5%)	138 (26.3%)
Dyspepsia	59 (11.3%)	158 (30.2%)
Hiatus hernia	46 (8.8%)	56 (10.7%)
Duodenitis	29 (5.6%)	70 (13.4%)
Gastric ulcer	17 (3.3%)	45 (8.6%)
Nausea	17 (3.3%)	12 (2.3%)
Oesophagitis	17 (3.3%)	63 (12.0%)
Diarrhoea	15 (2.9%)	12 (2.3%)
Gastric polyps	11 (2.1%)	5 (1.0%)
Oesophageal disorder	11 (2.1%)	5 (1.0%)
Acquired oesophageal web	10 (1.9%)	11 (2.1%)
Abdominal pain upper	7 (1.3%)	3 (0.6%)
Erosive duodenitis	7 (1.3%)	37 (7.1%)
Gastrooesophageal reflux disease	7 (1.3%)	20 (3.8%)
Abdominal pain lower	6 (1.2%)	7 (1.3%)
Reflux oesophagitis	6 (1.2%)	17 (3.2%)
Abdominal pain	5 (1.0%)	2 (0.4%)
Gastrointestinal disorder	5 (1.0%)	6 (1.1%)
Constipation	4 (0.8%)	10 (1.9%)

Source: Electronically reproduced and copied. ISS Table S2.4. Page 1232.

System Organ Class/ Preferred Term	PA32540 (N=521)	EC-ASA 325mg (N=524)
Gastrointestinal disorders (Cont.)	283 (54.3%)	398 (76.0%)
Diverticulitis	4 (0.8%)	2 (0.4%)
Vomiting	4 (0.8%)	6 (1.1%)
Abdominal discomfort	3 (0.6%)	1 (0.2%)
Abdominal distension	3 (0.6%)	2 (0.4%)
Barrett's oesophagus	3 (0.6%)	8 (1.5%)
Flatulence	3 (0.6%)	2 (0.4%)
Gastritis atrophic	3 (0.6%)	0
Bezoar	2 (0.4%)	0
Diverticulum	2 (0.4%)	4 (0.8%)
Diverticulum intestinal	2 (0.4%)	1 (0.2%)
Diverticulum oesophageal	2 (0.4%)	0
Erosive oesophagitis	2 (0.4%)	33 (6.3%)
Gastroduodenitis	2 (0.4%)	1 (0.2%)
Gastrooesophageal sphincter insufficiency	2 (0.4%)	3 (0.6%)
Impaired gastric emptying	2 (0.4%)	0
Oesophageal ulcer	2 (0.4%)	5 (1.0%)
Regurgitation	2 (0.4%)	0
Abdominal tenderness	1 (0.2%)	2 (0.4%)
Abnormal faeces	1 (0.2%)	0
Dental caries	1 (0.2%)	1 (0.2%)
Diabetic gastroparesis	1 (0.2%)	0
Duodenal neoplasm	1 (0.2%)	0
Duodenal ulcer	1 (0.2%)	19 (3.6%)
Dysphagia	1 (0.2%)	4 (0.8%)

Source: Electronically reproduced and copied. ISS Table S2.4. Page 1233

System Organ Class/ Preferred Term	PA32540 (N=521)	EC-ASA 325mg (N=524)
Gastrointestinal disorders (Cont.)	283 (54.3%)	398 (76.0%)
Eosinophilic oesophagitis	1 (0.2%)	0
Frequent bowel movements	1 (0.2%)	0
Gastric haemorrhage	1 (0.2%)	4 (0.8%)
Gastric ulcer haemorrhage	1 (0.2%)	0
Gastrointestinal angiodysplasia	1 (0.2%)	0
Gastrointestinal mucosal disorder	1 (0.2%)	2 (0.4%)
Gastrointestinal sounds abnormal	1 (0.2%)	0
Gastrointestinal stenosis	1 (0.2%)	0
Haematochezia	1 (0.2%)	0
Intestinal obstruction	1 (0.2%)	0
Large intestinal haemorrhage	1 (0.2%)	0
Oesophageal spasm	1 (0.2%)	0
Pancreatic cyst	1 (0.2%)	0
Pancreatitis	1 (0.2%)	0
Salivary hypersecretion	1 (0.2%)	0
Toothache	1 (0.2%)	0
Umbilical hernia	1 (0.2%)	0
Varices oesophageal	1 (0.2%)	0
Abdominal hernia	0	1 (0.2%)
Colitis	0	1 (0.2%)
Dry mouth	0	2 (0.4%)
Duodenal ulcer haemorrhage	0	1 (0.2%)

Source: Electronically reproduced and copied. ISS Table S2.4. Page 1234

System Organ Class/ Preferred Term	PA32540 (N=521)	EC-ASA 325mg (N=524)
Gastrointestinal disorders (Cont.)	283 (54.3%)	398 (76.0%)
Eructation	0	2 (0.4%)
Faeces discoloured	0	1 (0.2%)
Gastric mucosal hypertrophy	0	2 (0.4%)
Gastric mucosal lesion	0	4 (0.8%)
Gastritis haemorrhagic	0	1 (0.2%)
Gastrointestinal erosion	0	1 (0.2%)
Gastrointestinal inflammation	0	6 (1.1%)
Gastrooesophageal heterotopia	0	2 (0.4%)
Glossitis	0	1 (0.2%)
Haemorrhoids	0	1 (0.2%)
Intestinal haemorrhage	0	1 (0.2%)
Melaena	0	1 (0.2%)
Oesophageal discomfort	0	1 (0.2%)
Oesophageal obstruction	0	1 (0.2%)
Oesophageal stenosis	0	1 (0.2%)
Oral disorder	0	1 (0.2%)
Pancreatitis acute	0	1 (0.2%)
Presbyoesophagus	0	1 (0.2%)
Rectal haemorrhage	0	2 (0.4%)
Small intestinal obstruction	0	1 (0.2%)

Source: Electronically reproduced and copied. ISS Table S2.4. Page 1235

Reviewer's comment: The entire listing of TEAEs by SOC and PT would have been too lengthy to present here. I have shown the GI SOC because the events of interest, gastric ulcers and any GI bleeding are represented in this class grouping. Notably the numbers of terms that are related to GI bleeding are quite small in both groups represented in the PSP.

More subjects in the combined analysis who took EC-aspirin 325 mg (72.5%) than those subjects who took PA32540 (44.1%) reported TEAEs that were in the SOC of Gastrointestinal Disorders and were pre-specified as upper GI (UI) adverse events. This is presented in Table 38 below. Subjects reported the preferred terms of gastritis, nausea and the combined terms consistent with abdominal pain in similar frequencies in both treatment groups while dyspepsia, gastritis erosive, duodenitis, gastric ulcer, esophagitis, erosive esophagitis, erosive duodenitis, GERD, reflux esophagitis, and duodenal ulcer were reported more frequently in subjects who took ECASA 325 mg than those subjects who took PA32540. No other preferred term was reported with more than 1% of either population.

Table 38: Pre-specified UGI Adverse Events with Proportion of Subjects (≥ 2% in Either Treatment Group) in the Primary Safety Population

Preferred Term	PA32540 N=521	ECASA 325 mg N=524
Number of UGI Events	382	822
Subjects with any UGI Adverse Events	230 (44)	380 (72)
Gastritis	91 (17)	84 (16)
Gastritis Erosive	60 (12)	138 (26)
Dyspepsia	59 (11)	158 (30)
Duodenitis	29 (6)	10 (13)
Gastric Ulcer	17 (3)	45 (9)
Nausea	17 (3)	12 (2)
Esophagitis	17 (3)	63 (12)
Esophageal disorder	11 (2)	5 (1)
Erosive duodenitis	7 (1)	37 (7)
GERD	7 (1)	20 (4)
Reflux esophagitis	6 (1)	17 (3)
Erosive esophagitis	2 (0.4)	33 (6)
Duodenal ulcer	1 (0.2)	19 (4)

Source: Adapted from table 30 ISS page 79.

Reviewer's comment: The TEAEs recorded in the PSP were consistent with the currently approved labeling for the component products. Overall, there were fewer TEAEs with PA32540 compared to ECASA 325 mg. In the SOC of GI disorders there were fewer TEAEs in subjects taking PA32540 compared to ECASA 325 mg. There were no unexpected TEAE findings in PA32540 seen in the PSP that were inconsistent with the labeling of the components.

TEAEs in the SOC of Cardiac disorders were similar between PA32540 and ECASA 325mg. Major Cardiovascular Adverse Events (MACE) were not common in the PSP population. An analysis of MACE was performed in the PSP. Analysis of these events are reported as unadjudicated (using preferred terms consistent with cardiovascular death, nonfatal myocardial infarction, and non-fatal stroke) and adjudicated (based on an independent Cardiovascular Review Committee[CRC] review of TEAEs consistent with cardiovascular events) More MACE was observed in subjects on clopidogrel during the study treatment in subjects taking PA32540 than ECASA 325mg. Seven subjects on PA32540 experienced adjudicated MACE at any time compared to six subjects on ECASA.

While this subgroup of subjects on clopidogrel is too small to support further analysis, the Sponsor states that the proposed labeling for PA tablets will include a warning against the concomitant use of clopidogrel with the PA tablets. This is consistent with Prilosec labeling.

The TEAEs in other SOCs seen in the PSP were comparable in frequency and severity. There were no substantial differences between demographics and subgroups, ages, or prior health history.

7.4.2 Laboratory Findings

Clinical laboratory trends, individually clinically significant abnormalities, and changes over time were reviewed for clinical chemistry, hematology, and urinalysis parameters. No clinically important findings were seen that have not been described previously in this review.

7.4.3 Vital Signs

Vital sign trends were reviewed. No clinically important findings were seen

7.4.4 Electrocardiograms (ECGs)

Omeprazole and ECASA are approved products with no known effects on ECG findings. ECG data was recorded at screening and not repeated.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed.

7.4.6 Immunogenicity

No new data regarding the immunogenic potential of PA32540 (Yosprala) was included in this submission.

7.5 Other Safety Explorations

No other safety explorations were performed. No new non-clinical safety studies were conducted in support of this application.

7.5.1 Dose Dependency for Adverse Events

No dose ranging studies were done in patients in this 505 (b) 2 application. Specific information about the relationship of dose of each of the components and adverse events is compiled from the approved product label of each of the components. It is noted that the anticipated prescribed dose of omeprazole (40 mg/day) and aspirin (325 mg/day) are within the recommended dose range of each of the approved products. See section 7.2.2

7.5.2 Time Dependency for Adverse Events

No explorations for time dependency of adverse events were conducted.

7.5.3 Drug-Demographic Interactions

There were no specific differences in the safety of the use of PA32540 compared to ECASA 325 mg noted in this application in those subjects more than 65 or 75 years of age by race or ethnicity (although the numbers of non-white or Hispanic/Latino subjects were few and difficult to compare). For each of the system organ classes, the sponsor analyzed treatment emergent adverse events by gender, race and ethnicity. Overall, there were no substantial differences in the rates of treatment emergent adverse events between any of the treatment groups based on race, ethnicity, or gender.

7.5.4 Drug-Disease Interactions

No particular explorations for drug-disease interactions were conducted. There was no significant effect of prior history of UGI disorders on the effect of PA32540.There were no differences in reports of TEAEs by prior history of diabetes.

The population studied that ultimately comprised the PSP had prior history of cardiovascular disease, thus the rates of cardiovascular and neurovascular events were high, and consistent with that general population. On a time-event basis, there was no difference in the reporting of TEAEs or SAEs of these events from those subjects who took PA32540

Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time. A small minority of subjects who took PA32540 as well as those who took ECASA 325 mg demonstrated mild increases in BUN and serum creatinine.

7.5.5 Drug-Drug Interactions

Potential drug interactions involving aspirin and omeprazole are well characterized and are reported in the respective approved product labeling. Because the use of aspirin and omeprazole together in PA Tablets has not demonstrated any pharmacokinetic interaction and is not expected to lead to novel or unknown drug interactions, no additional studies were performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application. Results from preclinical carcinogenicity studies have been previously reviewed and are reflected in the current Prilosec® product label.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. PA32540 (Yosprala) is categorized as Pregnancy Category C prior to 30 weeks gestation and Category D starting at 30 weeks gestation.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety of PA32540 (Yosprala) has not been established in children.
PA32540 should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no clinical data on overdosage with PA32540 (Yosprala) Tablets.
The drug abuse potential for both omeprazole and aspirin is small.

Per current labeling for omeprazole reports have been received of over-dosage in humans where the doses ranged up to 2400mg. Manifestations were variable but included confusion drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, and dry mouth.

Aspirin toxicity may result from acute ingestion or chronic intoxication. Severe toxic effects are associated with levels above 400 mg/mL. The early signs of salicylic overdose, including tinnitus occur at plasma concentrations approaching 200 mg/mL.

No effects of pharmacological withdrawal from PA32540 were seen in any subject who withdrew or stopped treatment in the development program.

7.7 Additional Submissions / Safety Issues

Not applicable

8 Postmarket Experience

PA32540 (Yosprala) Tablets are not currently approved or marketed in any country and therefore no post-marketing data exists on the use of these tablets. However both of the individual components of Yosprala are approved in the United States and are available as over the counter products. Aspirin is the most commonly prescribed antiplatelet agent for the long-term prevention of cardiovascular and cerebrovascular events. In the United States 81 mg and 325 mg are the most commonly prescribed doses. The most common toxicities associated with long term aspirin use at both doses include gastric ulcers and upper GI bleeding.

Long term PPI therapy may be associated with an increase in certain adverse events such as bone fractures. Another risk that may be associated with long term PPI exposure is *C. difficile* infections. These events are likely to be important co-morbid conditions in elderly patients on long term aspirin therapy for secondary prevention of cardiovascular or cerebrovascular events.

Despite, the side effects associated with either product separately, the combination of aspirin and omeprazole appears to provide gastroprotection in the patients who may benefit from daily use of aspirin therapy to prevent secondary cardiovascular and cerebrovascular events.

9 Labeling Recommendations

At the time of finalization of this review, labeling negotiations with the sponsor were pending.

(b) (4)

(b) (4) Refer to the statistical review for additional insight.

Refer to the Division of Cardiology and Renal Products consult review to determine if the proposed aspirin indications for this product are accurate and appropriate.

10 Advisory Committee Meeting

No advisory committee meeting convened for this application.

11 Appendices

11.1 Literature Review/References

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/s/

ZANA H MARKS
03/21/2014

ROBERT FIORENTINO
03/21/2014

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA/BLA #	205103
Applicant Name	Pozen, Inc.
Date of Submission	March 25, 2013
PDUFA Goal Date	April 25, 2013 (three month extension)
Proprietary Name / Established (USAN) Name	Yosprala/(aspirin, omeprazole)
Dosage Forms / Strength	Tablet, Delayed release aspirin 81 mg or 325 mg/Immediate release omeprazole 40 mg
Proposed Indication(s)	(b) (4)
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Zana Marks, MD, MPH/Robert Fiorentino, MD, MPH
Statistical Review	Milton C. Fan, PhD/Freda Cooner, PhD
Pharmacology Toxicology Review	Tamal Chakraborti, PhD/Sushanta Chakder, PhD
CMC Review	Zhengfang Ge, PhD/Moo-Jhong Rhee, PhD Jessica G. Cole, PhD/Bryan Riley, PhD (microbiology)
CMC/Biopharmaceutics	Banu Zolnick, PhD/ Sandra Suarez Sharp, PhD/Richard Lostritto, PhD
Clinical Pharmacology Review	Dilara Jappar, PhD/Sue-Chih Lee, PhD

OSI	Clinical Trials: Khairy Malek/Susan Leibenhaut, MD/Kassa Ayalew, MD, MPH Bioequivalence: Xingfang Li, MD, RAC/Michael Skelly, PhD/Sam Haidar, RPh, PhD/William Taylor, PhD
CDTL Review	Robert Fiorentino, MD
OSE/DMEPA	Denise Baugh, PharmD, BCPS/Lisa Khosla, PharmD, MHA/Lubna Merchant, MS, PharmD/Carol Holquist, RPh
OPDP	Meeta Patel, PharmD
PMHS	Donna Snyder, MD/Hari Cheryl Sachs, MD/Jeanine Best, MSN, RN, PNP/Lynne Yao, MD
DCRP OCP/DCP1	Preston M. Dunnmon, MD/XXX Sudharshan Hariharan, PhD/Rajanikanth Madabushi, PhD
DMPP	Karen Dowdy, RN, BSN/LaShawn Griffiths, MSHS-HS, BSN, RN/Sharon Mills, BSN,RN,CCRP
SEALD	Jeanne Delasko/ Eric Brodsky, MD

OND=Office of New Drugs
DCP= Division of Clinical Pharmacology
DCRP=Division of Cardiovascular and Renal Drug Products
DMPP=Division of Medical Policy Programs
OCP=Office of Clinical Pharmacology
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
PMHS=Pediatric and Maternal Health Staff

Division Director Summary Review

1. Introduction

In this 505(b)(2) NDA, the applicant proposes a fixed dose combination product consisting of aspirin and omeprazole, in two aspirin dose presentations: aspirin 81 mg and 325 mg. The omeprazole dose in both combinations is 40 mg. The applicant has proposed that the product labeling will contain all the Monograph aspirin secondary cardiovascular prevention indications (21 CFR 343.80) covered by these two aspirin doses, including (b) (4)

They propose labeling will state that the omeprazole component of the combination reduces the risk of developing ulcers from the aspirin component. The Clinical Reviewer has noted in her review that a consensus document from the American College of Cardiology Foundation, the American College of Gastroenterology and the American Heart Association recommend proton pump inhibitors be co-prescribed with antiplatelet therapy such as aspirin to reduce increased risk of GI complications.

Two proton pump inhibitors have been approved with an indication for reducing the risk of NSAID associated ulcers. Omeprazole, which is the PPI component of the product proposed in this NDA, does not carry that indication (although it does have an indication for short term treatment of gastric and duodenal ulcers, for which the dose is 40 mg and 20 mg, respectively). However, esomeprazole (the S-isomer component of omeprazole) does. The following table summarizes the doses and indications of the two approved single agent PPI's with the indication. In addition, it contains the information for the only currently approved fixed combination of a PPI with NSAID, Vimovo, which contains esomeprazole and naproxen. Although Vimovo is available in a fixed combination with two different naproxen doses, the ulcer risk reduction studies were conducted with only the higher naproxen dose.

Table 1: Summary of Proton Pump Inhibitor Products Approved for Reducing Risk of Developing Ulcers Associated with NSAIDs.

Drug	Dose	Indication	Trial Design
Single Agent PPI			
Esomeprazole	20 mg or 40 mg	"Reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing	Age range: 29-89 yo; median age 66. 71% female. Age and/or hx of gastric or duod. ulcer in past 5 years. No significant reduction in

Drug	Dose	Indication	Trial Design
		gastric ulcers. Patients are considered to be at risk due to their age (≥60) and/or document history of gastric ulcers. Controlled studies do not extend beyond 6 months."	duodenal ulcers "due to low incidence" Results: ulcer free at 20 mg was 95% vs. 83% in one study and 88% in another study on placebo.
Lansoprazole.	15 mg	"Reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID. Controlled studies did not extend beyond 12 weeks."	Age range: 23-89 yo; median age 60. 65% female. Hx of gastric or duod. ulcer in past 5 years. Results: ulcer free at 15 mg was 80% vs. 51% on placebo
Fixed Combination Product			
Vimovo	Naproxen/esomeprazole 375 mg/20 mg; and 500 mg/20 mg	"VIMOVO is a combination product that contains naproxen and esomeprazole. It is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. Controlled studies do not extend beyond 6 months"	Age: >17 yo; majority 50-69 yo (83%); 25% were also on low dose ASA. 67% female. Expected to require daily NSAID therapy for at least 6 months, and, if less than 50 yo, with a documented history of gastric or duodenal ulcer within the past 5 years. Two trials studied only the higher dose of Naproxen (500 mg). Results: ulcer free a (20 mg) was 93% and 96% vs. 77% on Naproxen only

The reviewers found this NDA approvable, with the exception of the deficiencies identified at a manufacturing site inspection. These deficiencies resulted in a Withhold recommendation from the Office of Compliance. A Complete Response letter will be issued on the basis of this recommendation. In addition, at the time of receipt of the Withhold recommendation, there were outstanding labeling negotiations. Negotiations ended upon receipt of this recommendation. For this reason, labeling was included as a deficiency in the Complete Response letter.

2. Background

This is a 505(b)(2) application for a fixed combination product in two dose presentations, which differ only in the amount of aspirin contained in the tablet. The applicant referenced

Ecotrin (an enteric coated aspirin product available in 325 mg and 81 mg tablets) and Prilosec (a delayed release omeprazole magnesium product).

As stated in the CMC review, "The tablets for both strengths consist of an aspirin core that is coated with (b) (4) film coats, (b) (4) as shown below:"

(b) (4)

(b) (4) The currently marketed omeprazole product, Prilosec, is a delayed release product. The omeprazole in the product proposed (b) (4) in this product presentation is an "immediate" release omeprazole product. This is similar to the design of the Vimovo product, in which the PPI is an outer coat to the naproxen component, and is similarly an "immediate" release esomeprazole, in contrast to marketed Nexium. This product design results in pharmacokinetic (PK) differences between the omeprazole in the proposed product and the referenced Prilosec product.

Although the applicant submitted two identical randomized, controlled trials to support that the addition of omeprazole to aspirin reduces the risk of developing ulcers caused by aspirin (omeprazole + aspirin vs. aspirin + placebo), only the 325 mg aspirin combination with omeprazole was studied in these efficacy trials. Neither trial evaluated the aspirin 81mg combination also proposed for marketing. The applicant submitted a Special Protocol Assessment for review. The Division issued a non-agreement letter on July 29, 2008. However, the Division did agree to studying the ASA 325 mg dose (as a component of the fixed combination and as the comparator) in phase 3 development. The applicant's development plan focused on the 325 mg ASA dose level, and this fact was subject of deliberative review discussions across the review disciplines and review divisions. These discussions ultimately included OND and Center leadership. As noted by the CDTL in his review, the optimal dose of aspirin (ASA) for secondary prevention of cardiovascular and cerebrovascular events has been subject to some controversy. The Division of Cardiovascular and Renal Products (DCRP) consultants challenged the appropriateness of approving a combination containing 325 mg of aspirin, in light of growing evidence to support that doses of <100 mg per day are adequate for secondary prevention [the 2006 American College of Cardiology /American Heart Association (ACC/AHA) guidelines recommends 75 - 162 mg for

secondary prevention[1]; the American College of Chest Physicians (ACCP) recommends 75 to 100 mg[2].]. However, the aspirin professional labeling monograph (under 21 CFR 343.80) provides for higher doses for the same indication, up to and including 325 mg.

The lack of efficacy trials conducted with the 81 mg ASA combination product raised review challenges in determining whether there was adequate evidence to support both the need for a proton pump inhibitor combination with this lower dose of aspirin (i.e., evidence that ASA 81 mg was associated with a risk for developing ulcers) and that the omeprazole in the lower aspirin dose combination would be effective in reducing any risk of ulcer associated with the lower dose. Assuming that there was a risk of ulcers with lower dose aspirin, and that it was reasonable to expect that the same dose of omeprazole would be effective in reducing the risk if it reduced the risk of ulcers associated with higher doses of aspirin, the reviewers identified an absence of key information in the NDA necessary to support approval of the lower dose combination under those circumstances, i.e., the initial submission of this NDA did not include a study that established the bioequivalence of the omeprazole component of the lower aspirin dose fixed combination product to that of the higher aspirin dose fixed combination. During the course of the review, the absence of this relative bioavailability information for the omeprazole components of the two proposed presentations of the fixed dose combinations was identified as a critical deficiency that would preclude approval, given the absence of an efficacy trial that established reduction of risk of ulcers with the 81mg aspirin + 40 mg omeprazole combination. The applicant was informed of this critical deficiency during the course of the review, and they subsequently submitted the results of a study to address this issue, during the review cycle. The review clock was extended three months, accordingly.

3. CMC

I have summarized the major CMC review findings in this section. In general, the reviewers found the CMC portion of this NDA approvable; however, one of the inspections, which was not scheduled to occur until the last week in the review cycle, resulted in issuance of a 483. Compliance entered a Withhold recommendation in EES, based on deficiencies identified at that site (b) (4) The deficiencies included the following, which were conveyed to the Division by email:

(b) (4)

[redacted]

[1] AHA, ACC, National Heart, Lung, and Blood Institute, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute. J Am Coll Cardiol 2006; 47:2130.

[2] Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e637S.

(b) (4)

The following language was recommended for inclusion in the Complete Response letter:
"**FACILITY INSPECTIONS**
During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."

In the remainder of this section, I will summarize the other CMC review findings.

Stability testing supports an expiry of 36 months for the product containing 325 mg of aspirin. For the 81 mg aspirin product, a 24 month expiration could be supported for tablets packaged in 30 (b) (4) count HDPE bottle (b) (4) Although a recent DMF review of the aspirin drug substance found the DMF to be inadequate due to insufficiently validated HPLC method, the CMC reviewer found the drug substance information submitted in this application to be adequate because the drug substance is tested upon receipt by the manufacturer of the drug product with an HPLC method, different from the DMF methodology, which the reviewer found to be adequately validated.

With regard to labeling, the CMC reviewers did not agree with the applicant's proposal to express the established name with "delayed/immediate" qualifiers associated with each of the drug components. Based on the Vimovo precedent, they recommended that there be a "delayed release" qualifier outside the established name parentheses, associated only with the "tablets" , i.e., YOSPRALA (aspirin and omeprazole) delayed release tablets.

Microbiology
The applicant proposed to waive microbial limits release testing for the drug product. The reviewers sent a request for information to support this proposal. The applicant's response included an update to the post approval stability protocol and commitment to include microbial limits testing (b) (4) The Microbiology reviewer found the response acceptable and recommended approval from the standpoint of product quality microbiology.

Biopharmaceutics
The Biopharmaceutics reviewers found the applicant's dissolution methods acceptable for both the aspirin and omeprazole components of the product. They reached an agreement with the applicant on "interim" dissolution acceptance criteria (b) (4) Although the reviewers had some concerns about the acceptance criteria for the aspirin component of the product, they were willing to approve the product with the plan for future interim reassessment in light of discussions with the DCRP Clinical Pharmacology and Clinical consultants, who provided information that the dose-response curve for aspirin is flat in dosages greater than 50 mg. In addition the

Biopharmaceutics reviewers noted that aspirin "is considered a highly soluble and highly permeable substance" based on a publication cited (J Pharm Sci. 2012 Aug; 101(8):2653-67). The Biopharmaceutics reviewers identified the following two PMC's (b) (4)

(b) (4)

However, as stated above, due to the Withhold Recommendation based on manufacturing site inspection issues, this NDA will not be approved at this time.

A formulation change (b) (4) that occurred between the batches used in the bioequivalence studies and the phase 3 trials was considered a minor change by CMC reviewers. The Biopharmaceutics reviewers assessed the dissolution testing and determined that the data supported similar performance for the omeprazole component, (b) (4) Reanalysis with multivariate analysis demonstrated that the dissolution profiles were similar between the to-be-marketed formulation and the Phase 3 and BE batches. The Biopharmaceutics reviewers concluded that the change (b) (4) was acceptable.

Additional review findings included that both combination tablet strengths were associated with *in vitro* dose dumping in the presence of 40% alcohol.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the Pharmacology/Toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. The applicant did not conduct new nonclinical studies with the product proposed in this 505(b)(2) NDA. The NDA contained summaries of relevant nonclinical information from the published literature.

The Pharmacology/Toxicology reviewer evaluated the excipients in the proposed product and concluded that (b) (4) With regard to impurities/degradants associated with each of the components of the product (aspirin and omeprazole), the reviewers determined that the applicant's proposed acceptance

criteria/specifications were acceptable. The CMC reviewer noted in his review that although the applicant's proposed acceptance criteria [redacted] of not more than (NMT) [redacted]% is [redacted] the ICH Q3B qualification limit, the USP monograph of aspirin delayed release tablets is NMT [redacted]% [redacted] The Pharmacology/Toxicology reviewer states in his review that "As per the ICH Q3B(R2) guidance, "degradation products that are also significant metabolites are generally considered qualified. In addition, [redacted] limit defined in the USP monographs for aspirin coated tablets is [redacted]%. Therefore, the proposed specification of NMT [redacted]% [redacted] in the drug product does not appear to raise any safety concern from nonclinical perspective and is acceptable."

5. Clinical Pharmacology

I concur with the Clinical Pharmacology reviewers' conclusions. There are no outstanding clinical pharmacology issues that preclude approval. The applicant submitted data from two bioequivalence studies to successfully establish a bridge between the aspirin (ASA) component at the two proposed doses in the combination (81 mg and 325 mg) to the referenced product Ecotrin. The initial submission also included a relative bioavailability study that evaluated the omeprazole component of the fixed combination for ASA 325mg/omeprazole 40 mg to Prilosec 40 mg. However, as outlined in Section 2 Background of my review, the reviewers identified deficiencies in the adequacy of the data to bridge the 40 mg omeprazole component in the proposed lower ASA dose combination (81 mg/40 mg) product to the omeprazole component of the 325 mg/40 mg product, (the product studied in the two efficacy trials) [redacted] and at the request of the reviewers (teleconference dated December 6, 2013), the applicant submitted the results of a relative bioavailability study that evaluated the omeprazole component of the two fixed combination products proposed in this NDA.

Omeprazole. As discussed below in Section 5 Efficacy, two identical clinical trials conducted with the ASA 325 mg/omeprazole 40 mg combination product established the efficacy of the omeprazole component of the combination in reducing the risk of gastric ulcers induced by ASA 325 mg. The relative bioavailability of the omeprazole component of the combination product containing aspirin 325 mg/omeprazole 40 mg compared to Prilosec 40 mg was investigated in a study conducted to support the 505(b)(2) reliance on Prilosec. The AUC of the immediate release omeprazole in the fixed combination was found to be approximately 51-58% of that of Prilosec 40 mg in a single dose study (PA32540-113) and a multidose study (PA32540-112). After multiple dosing (7 days in Study PA32540-112), the omeprazole exposure increased for both the immediate release omeprazole component of the applicant's combination product and for Prilosec, and the omeprazole exposure of the fixed combination remained lower than the exposure associated with Prilosec. The data from these two studies are presented in the tables below, reproduced from the Clinical Pharmacology review.

Table 2: Statistical Analysis Results of Omeprazole PK Parameters following single dose administration in Study PA32540-113 (Fixed combination vs. EC-ASA + omeprazole 40 mg)

	Ratios of Geometric Least-Squares Means for Omeprazole (90% CIs)	
Omeprazole PK Parameter	PA32540*/ EC-ASA + EC-Omeprazole 40 mg	PA32540*/ EC-Omeprazole 40 mg
AUC_{0-inf}	0.548 (0.477 – 0.629)	0.564 (0.491 – 0.648)
AUC_{0-t}	0.548 (0.477 – 0.629)	0.563 (0.490 – 0.647)
C_{max}	0.877 (0.703 – 1.095)	0.930 (0.745 – 1.160)

***PA32540=proposed fixed combination ASA 325 mg/Omeprazole 40mg**

Table 3: Statistical Analysis of Omeprazole PK Parameters between Treatments following single dose (Day 1) and multiple doses (Day 5 and Day 7) administration in Study PA32540-112

Omeprazole	***PA32540 vs. EC-ASA 325 mg + EC omeprazole 40 mg** Geometric LSM Ratio (90% Confidence Interval)		
PK Parameter	Day 1	Day 5	Day 7
AUC_{0-24} (hr*ng/mL)	0.511 (0.422-0.620)	0.505 (0.403-0.634)	0.565 (0.454-0.703)
AUC0-12 (hr*ng/mL)	0.550 (0.439-0.688)	0.508 (0.405-0.637)	0.578 (0.462-0.722)
C_{max} (ng/mL)	0.642 (0.473-0.870)	0.689 (0.564-0.842)	0.741 (0.592-0.928)

***PA32540=proposed fixed combination ASA 325 mg/Omeprazole 40mg**

The Day 7 pharmacodynamic effects on intragastric pH were compared between Prilosec 40 mg (plus Ecotrin 325 mg) vs. the proposed ASA 325 mg/omeprazole 40 mg product, and the percentage time with pH>4 was higher with Prilosec than the proposed combination product (58% vs. 51%, p=0.004), which is consistent with the approximate 50% lower systemic exposure associated with omeprazole in the immediate release combination product. This study (PA32540-112) was a randomized, 2-way cross over study that evaluated dosing over 7 treatment day for each of the two combinations. Of some interest, in cross study comparisons of PD effects, the results observed for the applicant's combination product (ASA 325mg/omeprazole 40 mg) appear similar to those previously reported for enteric coated omeprazole 20 mg (half the dose). These data are summarized in the table below, which is reproduced from the Clinical Pharmacology review.

Table 4: Data Summary of POZEN and Published Data on 24-hour Gastric pH Control in Healthy Subjects

Mean Percent Time with pH> 4 Over 24 Hours for Various Forms of Omeprazole/Esomeprazole				
10 mg EC-Omeprazole	20 mg EC-Omeprazole	40 mg IR-Omeprazole	40 mg EC-Omeprazole	20 mg EC-Esomeprazole
18.3%[2] 33%[4]	49%[2]	51%[1]	63%[2] 58%[1]	56%[2] 57%[3]

[1] PA32540-112 Table 14.2.1.1 (following 7 consecutive daily doses).
[2] Kirchheiner 2009.
[3] Miner 2010.
[4] Burget 1990.

The relative bioavailability study data comparing the relative bioavailability of the omeprazole components of the two ASA dose levels of the fixed combination (ASA 325mg/omeprazole 40 mg and ASA 81 mg/omeprazole 40 mg) was submitted late in the review cycle. The study was a multiple-dose (7 day treatment period), 2-way crossover PK study in 30 healthy subjects that evaluated the 81mg/40 mg and 325mg/40 mg products. This study demonstrated a slightly higher omeprazole AUC in the lower ASA dose (81 mg) fixed combination than in the 325mg/40mg combination. However, the Cmax of the two fixed combination presentations were very similar. These results suggest that similar omeprazole efficacy can be expected with the 81mg/40 mg fixed combination. The results of the multiple dose bioavailability study are summarized in the tables below, reproduced from the Clinical Pharmacology review.

Table 5: Omeprazole PK Parameters for Each Fixed Combination on Day 7

Treatment	Statistics	C_{max} (ng/mL)	t_{max}* (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-24} (hr*ng/mL)	$t_{½}$ (hr)
A PA8140*	Mean %CV	1488 71	0.83 0.33-1.25	3059 101	3063 101	1.26 43
B PA32540**	Mean %CV	1385 73	0.50 0.33-1.25	2284 91	2288 91	1.16 28

***PA8140=proposed fixed combination ASA 81mg/Omeprazole 40mg**
****PA32540=proposed fixed combination ASA 325 mg/Omeprazole 40mg**

Table 6: Summary of Statistical Analysis Results of Omeprazole PK Parameters between Each Fixed Combination on Day 7

PK Parameter	Treatment A vs. Treatment B (PA8140* vs PA32540**) GLSM Ratio (90% Confidence Interval)
AUC_{0-24} (hr*ng/mL)	1.27 (1.04 – 1.54)
AUC_{0-t} (hr*ng/mL)	1.27 (1.04 – 1.54)
C_{max} (ng/mL)	1.04 (0.855 – 1.27)

***PA8140=proposed fixed combination ASA 81mg/Omeprazole 40mg**
****PA32540=proposed fixed combination ASA 325 mg/Omeprazole 40mg**

Aspirin. Acetylsalicylic acid was evaluated as the primary analyte in the bioequivalence studies because the cardioprotective activity is attributed to it. Salicylic acid was evaluated as a secondary analyte. The 81 mg aspirin/omeprazole combination tablet was found to be

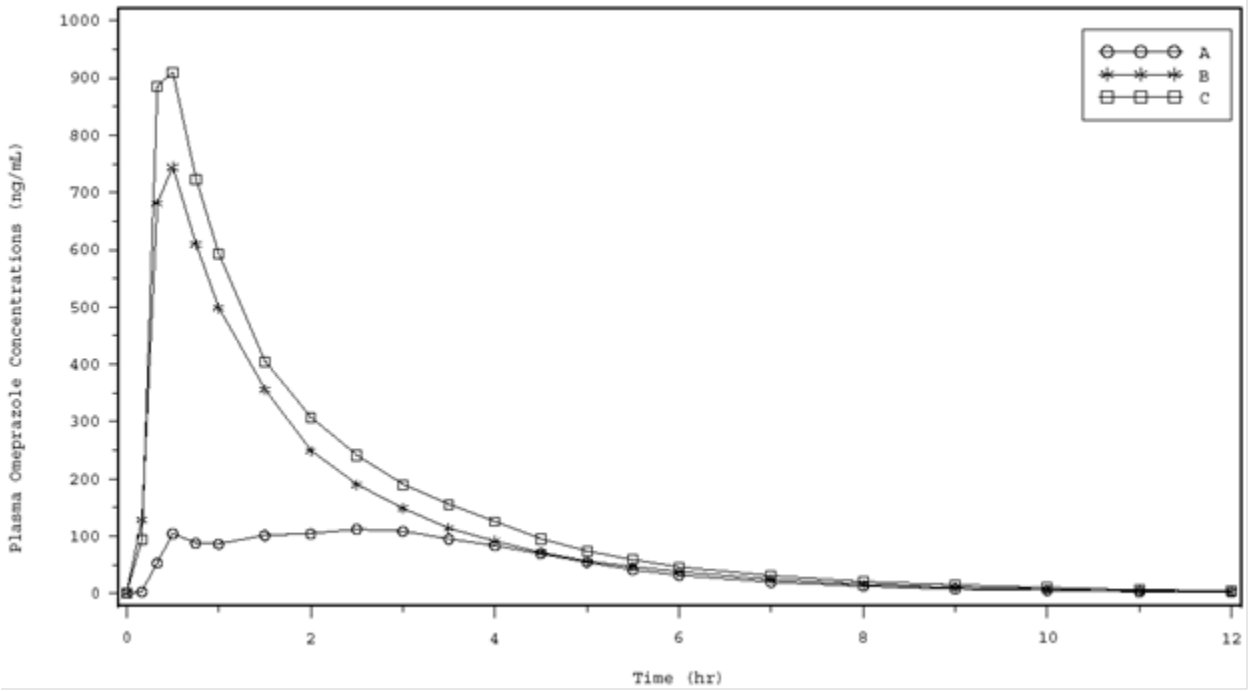
bioequivalent to the Ecotrin 81 mg tablet, based on acetylsalicylic acid exposure. However, the aspirin 325 mg/omeprazole 40 mg dose level tablet was not bioequivalent to Ecotrin 325 mg. Acetylsalicylic acid bioavailability for the higher ASA dose combination was 10-15% lower than Ecotrin 325 mg.

The review team consulted the Division of Cardiovascular and Renal Products (DCRP) and Clinical Pharmacologists from the DCP1 team that reviews cardiovascular drugs regarding the clinical meaningfulness of the slight reduction of acetylsalicylic acid exposure associated with the proposed combination325 mg/40 mg product. The consultants stated that because the meaningful impact on platelet aggregation occurs at a much lower acetylsalicylic acid exposure, the slight reduction could not be expected to have any impact on the efficacy of the aspirin component.

The Clinical Pharmacology reviewer noted that the within-subject standard deviation of acetylsalicylic acid PK parameters for Ecotrin 81 mg were greater than 0.294, which confirmed that the EC-aspirin PK parameters qualified for the reference-scaled average BE procedure utilized by the applicant to establish bioequivalence between their lower dose aspirin 81 mg/omeprazole combination product and Ecotrin 81 mg. This was also true for the aspirin 325 mg products (Ecotrin 325 mg and the applicant's aspirin 325 mg/omeprazole combination).

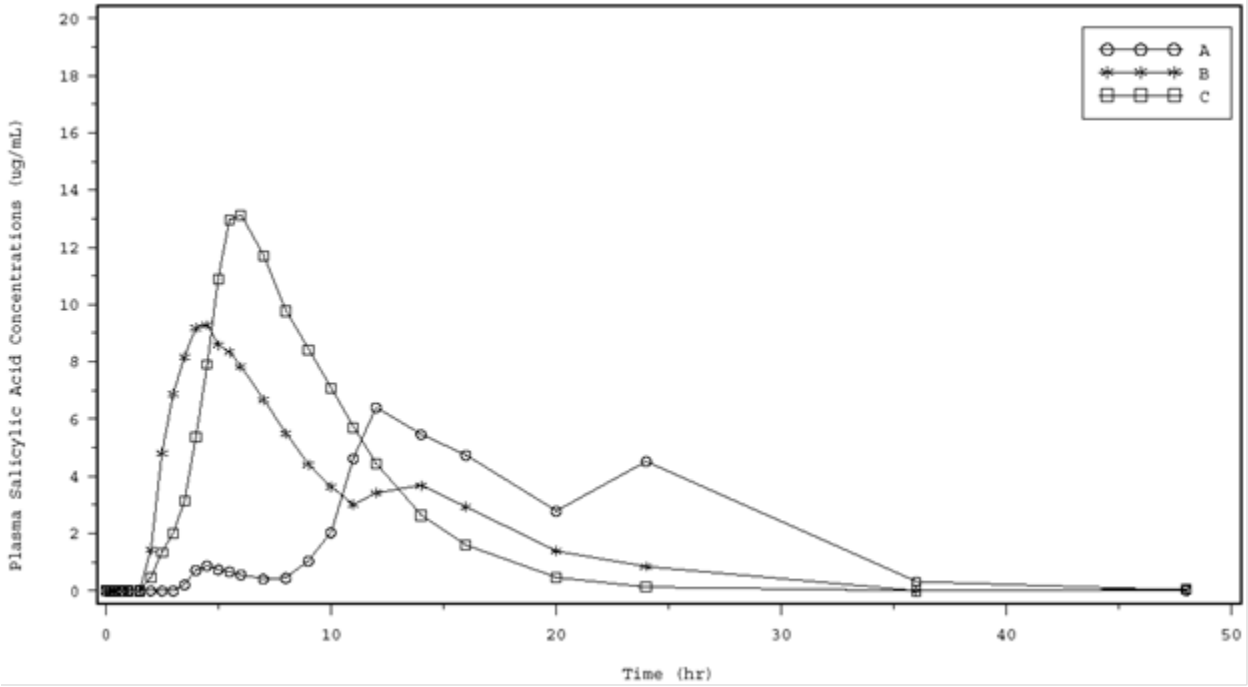
Food effect. The product was administered 60 minutes prior to breakfast in the two phase 3 efficacy trials. A food effect study comparing exposures associated with administration either 60 minutes or 5 minutes before a high fat breakfast (relative to fasting) found that the omeprazole exposure was markedly reduced when administered shortly before a meal relative to administration 60 minutes before a meal. These data are summarized in the graph below (reproduced from the Clinical Pharmacology review).

Figure 1: Mean Plasma Omeprazole Concentration vs. Time Curves after Yosprala Administration (ASA 325 mg/omeprazole 40 mg). A = 5 minutes prior to meal, B= 60 minutes prior to meal, C= fasting



Salicylic acid exposure was minimally impacted by dosing shortly prior to a meal; however, the tmax was markedly prolonged. These data are summarized in the graph below (reproduced from the Clinical Pharmacology review).

Figure 2: Mean Plasma Salicylic Acid Concentration vs. Time Curves after Yosprala Administration (ASA 325 mg/omeprazole 40 mg). A = 5 minutes prior to meal, B= 60 minutes prior to meal, C= fasting



The following table, reproduced from the Clinical Pharmacology review, summarizes the data for acetylsalicylic acid relative to levels obtained fasting. Acetylsalicylic acid data were missing due to unmeasurable concentrations in multiple subjects. This impacted reliability of summary statistics for acetylsalicylic acid.

Table 7: Statistical Analysis of Acetylsalicylic Acid Pharmacokinetic Parameters

	Ratios of Geometric Least-Squares Means (90% Confidence Interval)	
Acetylsalicylic Acid PK Parameter	**With High-Fat Meal/ Fasting Conditions**	**60 Min Prior to High-Fat Meal/ Fasting Conditions**
AUC_{0-inf}	n/a	0.831 (0.652 – 1.060)
AUC_{0-t}	n/a	0.874 (0.696 – 1.097)
C_{max}	n/a	0.830 (0.465 – 1.480)

n/a = not applicable; pharmacokinetic parameters could not be estimated in ≥50% of the subjects when PA32540 was administered immediately after a high-fat meal; thus, no comparisons between the high-fat meal and fasting conditions were made.

The Clinical Pharmacology reviewers point out in their review the dedicated drug interaction studies the applicant submitted to describe an interaction between aspirin and omeprazole were inadequate to exclude an interaction, because aspirin's active metabolite, acetylsalicylic acid, was not evaluated. However, they concluded that no further studies were needed as no drug-drug interaction is expected between the two drugs based on their metabolism and elimination pathways. In addition, the results of the relative bioavailability/bioequivalence studies, Study 8140-102 and Study 32540-115, provide evidence that there is no meaningful interaction between the omeprazole and aspirin when administered together as part of a fixed combination.

Clopidogrel. A platelet aggregation study was submitted that evaluated the interaction between the omeprazole component of the combination and clopidogrel. The consultants from DCP1 (Clinical Pharmacology) and DCRP (Clinical) both concluded that an interaction could not be excluded, whether administered concomitantly or separated by 10 hours.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant conducted two identical multicenter, randomized, double-blind, controlled trials that evaluated the efficacy of the omeprazole component of the proposed combination product in reducing the risk of ulcers caused by 325 mg aspirin. I will refer to these trials as Study 301 and Study 302. They were conducted in the United States. The two treatment arms were the proposed combination product containing 325 mg aspirin (ASA325mg/ omeprazole 40 mg) and enteric coated (EC) ASA 325 mg. Subjects were instructed to take study medication 1 hour prior to the first meal of the day. (See Section 5 Clinical Pharmacology discussion of food effects on PK.) The trials were 6 months in duration and the primary endpoint evaluated proportion of subjects who developed gastric ulcers at any time over 6 months of treatment, based on endoscopies performed at screening, one month, 3 months and 6 months. (Ulcers were defined as a mucosal break of at least 3 mm in diameter with depth.) An ulcer endpoint has been the primary efficacy parameter in PPI products previously approved for reduction of risk of developing ulcers associated with NSAID use. Sample size (250 per arm) was based on an assumption that 13% of subjects treated with EC ASA 325 mg would develop a gastric ulcer over the 6 month period compared to 5% in subjects treated with the combination product containing omeprazole 40 mg (ASA 325mg /omeprazole 40 mg), with 86% power and a two-sided significance level of 5%.

To be eligible for participation in the trials, subjects who were taking ASA 325 mg for secondary prevention of cardiovascular or cerebrovascular events (for at least 3 months prior to study entry, and expected to continue it for at least 6 months more) had to be considered at risk for developing aspirin-associated ulcers, based on age 55 years or older in both trials, or history of documented gastric or duodenal ulcer within the five years prior to study entry. Patients had to be expected to use daily aspirin 325 mg for at least 6 months. See the Clinical Review for the specific ASA secondary prevention indications that were utilized in the trials. Subjects were not excluded if they were taking chronic NSAIDs; however, randomization was stratified for 1) chronic non-specific NSAID use; 2) chronic COX-2 inhibitor user and 3) non-use of either NSAID or Cox-2 inhibitors. Patients found to be positive for H. pylori and/or who had an active ulcer $\geq$ 3mm diameter (and with depth) identified during screening were excluded from the trial.

Secondary endpoints included proportion of subjects with gastric and/or duodenal ulcers, treatment success (proportion without gastric ulcer and without upper gastrointestinal adverse

events leading to discontinuation), proportion discontinuing study due to upper GI adverse events, proportion of subjects with "*resolution"* of heartburn (based on answering "none" on a post-baseline heartburn assessment question in which the subject was asked to assess the 7 prior days at months 1, 3 and 6) and safety. The CDTL review notes that the latter "*resolution*" analysis was based on proportion of subjects who reported they were without heartburn at Months 1, 3 and 6, *regardless of whether they actually had heartburn at baseline*.

The primary efficacy analysis was conducted in the intent to treat population using a Cochran-Mantel-Haenszel (CMH) test stratified by NSAID use at randomization [Yes(COX-2 or other)/No]. The analysis was not adjusted for center differences. The secondary endpoints were tested in a prespecified sequential order, using a hierarchical fixed-sequence testing approach to adjust for multiplicity. Once a p-value exceeded 0.05, endpoints further down in the sequence were not considered statistically significant if nominal differences were observed.

The patient disposition in the two trials, Study 301 and Study 302, is summarized in the two tables below, which are reproduced from the Statistical Review. As shown, each trial randomized approximately 260-265 per trial arm, and ≥75% of patients in each arm of both trials completed 6 months of treatment and had a 6 month endoscopy or had an ulcer documented prior to 6 months. Numerically, a slightly higher number of patients completed the trial in the combination ASA325mg/omeprazole 40 mg (referred to in the tables that follow as PA32540) arm of both trials. The most common reason for withdrawing from the trials prior to completion was adverse event. In both trials the proportion of subjects who withdrew due to adverse event was numerically higher in the EC-ASA control arm.

Table 8 Subject Disposition - Study 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.

Table 9 Subject Disposition – Study 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.

Regarding entry criteria specifically related to increasing risk for developing an ulcer (age and/or history of prior ulcer, concomitant NSAID use), the median age was 66 years in both trials. Only 1% of patients were <55 years of age in Study 301, whereas in Study 302, nearly 4% of patients were <55 years. Approximately 13% in both trials were ≥75 years of age. Approximately 5% in both arms of Study 301 had a history of either a gastric or duodenal ulcer in the 5 years prior to study entry. In Study 302, there was a numerically slightly higher proportion of patients in the EC-ASA arm who had a history of ulcer in the prior 5 years, 7%, compared to 5% in the fixed combination 325/40 arm. Gastric ulcers were the predominant site of prior ulcer in both trials. In Study 302, there was a numerically higher proportion of patients in the combination 325/40 arm whose prior ulcer was a duodenal ulcer (3.5% vs. 1.5% in the EC-ASA arm). The proportion was also numerically higher than in both arms of Study 301 (1.1-1.5%). Less than 10% of subjects in Study 301 (8-9%) and Study 302 (9-9.6%) were taking chronic NSAIDs at randomization.

Subjects in both trials were predominantly male (approximately 70% in both Study 301 and Study 302) and white (approximately 90% in Study 301 and >85% in Study 302). The most common underlying diagnosis that led to use of aspirin as secondary prevention in these trials was history of cardiac disorder (82-89% in Study 301 and 84-90% in Study 302). History of stroke was numerically higher in Study 301 among the EC-ASA arm – 17% vs. 11% in the fixed combination 325/40 arm. Approximately 27%-32% of subjects had a history of coronary artery bypass graft and 27%-37% had a history of stent placement. Approximately 20% of patients in Study 301 and Study 302 were taking clopidogrel at the time of randomization.

The efficacy results from the two trials are presented in the two tables below, which are reproduced from the Statistical Review. The primary analysis was comparison of cumulative

incidence of gastric ulcers over the 6 months. The tables present the cumulative incidence at each of the endoscopic assessment points in the trials, i.e., 1 month, 3 months and 6 months. Please note that the analyses at Months 1 and 3 are not adjusted for multiplicity and must be viewed with caution. The primary efficacy analysis is presented in the row **"0-6 Months; Gastric Ulcer".** A statistically significantly lower proportion of subjects developed gastric ulcers over 6 months in the fixed combination (ASA 325mg/omeprazole 40 mg)arm, i.e., the omeprazole 40 mg in the combination product reduced the risk of developing ulcers in patients exposed to enteric coated aspirin. The primary efficacy results were consistent across trials. (In the tables below, PA32540 refers to the fixed combination product.)

Table 10 Study 301: Cumulative Proportion (n, %) of Subjects with Gastric Ulcers through Months 1, 3, and 6 (ITT Population)

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.

Table 11 Study 302: Cumulative Proportion (n, %) of Subjects with Gastric Ulcers through Months 1, 3, and 6 (ITT Population)

Time period	PA32540 N = 259 n (%)	EC-Aspirin 325 mg N = 260 n (%)	P-value[1]
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.

In planning the study, the applicant estimated that 13% of subjects in the EC-ASA arm would develop a gastric ulcer. The actual observed rate in the trials was slightly lower: Study 301= 8.7% [95% CI: 5.6%-12.7%] and Study 302 = 8.5% [95% CI: 5.4%-12.5%]. A numerically higher number of subjects in the fixed combination 325/40 arm of Study 301 developed an ulcer than in the 325/40 arm of Study 302. The 325/40 arm ulcers in Study 301 were identified early in the trial, i.e., in the first 3 months. In Study 302, the subjects in the 325/40 arm that developed ulcers did so in the last 3 months of the trial (between the month 3 endoscopy and month 6 endoscopy). In the EC-ASA comparator arms of the two trials, there was a steady increase in incidence of gastric ulcers over time, beginning at the Month 1 endoscopy.

As noted in the Statistical Review and in the Secondary Statistical Review by Dr. Freda Cooner, ulcer events were only counted in these trials if an ulcer was observed at endoscopy. If a patient discontinued from the trials without endoscopy, the patient was considered to be ulcer free in the pre-specified primary analysis. Dr. Cooner stated in her review, "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 that 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." Both the primary and secondary statistical reviewers concluded that the pre-specified primary analysis of the primary endpoint demonstrated statistically significant benefit associated with the omeprazole combination (325/40). See the CDTL reviewer's summary of the Primary and Secondary Statistical Reviewers' interpretation of the results of the exploratory "worst case" analysis in which subjects with missing data on the EC-ASA 325 mg arm were considered responders, while subjects on the fixed combination with missing data were considered non-responders. I concur with the Secondary Statistical Reviewer's comment that these sensitivity analyses are exploratory in nature, and her conclusion that the two phase 3 trials results established statistically significant benefit associated with the combination product.

The first ranked secondary endpoint analysis was cumulative incidence of gastric and/or duodenal ulcers at 6 months. In both trials, a statistically significant reduction was noted in the combination 325/40 arm, when the analysis combined both sites of ulcers. The pre-specified secondary analysis of combined gastric and/or duodenal ulcers is found in row **"0-6 months Gastric/Duodenal ulcer"** in the tables below, which are reproduced from the Statistical review. Please note that the analyses at Months 1 and 3 are not adjusted for multiplicity and must be viewed with caution. When the number of events in the tables below is compared to the number of events in the gastric ulcer tables above, a numerically higher rate of duodenal ulcers in the EC-ASA arms relative to the combination 325/40 arms suggests that omeprazole also has an impact on reducing the risk of duodenal ulcers. The duodenal ulcers were identified early (Month 1 assessment) in both trials. (In the tables below, PA32540 refers to the fixed combination product.)

Table 12 Study 301: Cumulative Proportion (n, %) of Subjects with Gastric and/or Duodenal Ulcers at Months 1, 3, and 6 (ITT Population)

	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

Table 13 Study 302: Cumulative Proportion (n, %) of Subjects with Gastric and/or Duodenal Ulcers at Months 1, 3, and 6 (ITT Population)

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.

(b) (4)

The applicant proposed (b) (4)

(b) (4)

This issue remained unresolved at the time of the Complete Response action for this NDA.

Table14: Outcomes of Secondary Efficacy and Tolerability Endpoints-ITT Population Studies PA32540-301 and PA32540-302

	PA32540-301		PA32540-302	
	PA32540* N=265	ECASA 325 mg N=265	PA32540* N=259	ECASA-325 mg N= 260
Key Secondary Endpoints				
Incidence of Gastric and/or Duodenal Ulcers at 6 months	**4.2%**	**11.7%**	**2.7%**	**11.5%**
Treatment Success	**94%**	**83%**	**96%**	**84%**
Discontinuation of Treatment due to ASA-associated UGI AEs	**2.3%**	**8.3%**	**0.8%**	**8.1%**
Heartburn Resolution at 6 months	PA32540 N=214	ECASA 325 mg N=188	PA32540 N=215	ECASA 325mg N=190
	92.5%	**72%**	**93%**	**80%**

Source: Adapted from Table 11 SCE page 33

***PA32540 = fixed combination of ASA 325 mg and Omeprazole 40 mg.**

Subgroup analyses based on gender, age and race provided interesting exploratory results. In Study 301, the impact of omeprazole in the fixed combination 325/40 on cumulative incidence of ulcers appeared greater in females than in males. Despite the dramatically smaller female sample size, the upper bound of the confidence interval of the difference between the 325/40 and EC ASA 325 arms excluded 0. The difference between treatment arms in the male subset was numerically smaller than in the female subgroup and the confidence interval for the difference crossed 0. However, this finding was not replicated in gender subgroup analyses of Study 302, which had a similar female sample size. Similarly, in Study 301, age analysis utilizing a cut point of 65 years suggested the treatment effect of 325/40 appeared greatest in patients ≥65 years (despite similar sample sizes between the two subgroups). Again, in this subgroup, the difference was numerically greater than in the younger subgroup, and the confidence interval excluded 0. In the younger subgroup, the confidence interval crossed 0. Unlike the previous gender analysis, this finding was replicated in the age subgroup analysis of Study 302.

Table 15: Study 301: Subgroup Analyses of Cumulative Proportion of Subjects with Gastric Ulcers through 6 Month (ITT Population) *PA32540 = fixed combination

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%)

Table 16 Study 302: Subgroup Analyses of Cumulative Proportion of Subjects with Gastric Ulcers through 6 Month (ITT Population)

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%)

***PA32540 = fixed combination of ASA 325 mg and Omeprazole 40 mg.**

The subgroups with either a history of ulcer at study entry or using NSAIDs at study entry were too small to yield interpretable results. The Statistical reviewer requested an exploratory analysis of cumulative ulcers over 6 months (including both gastric and duodenal ulcers), redefining ulcer based on size of at least 5 mm (instead of the protocol specified 3 mm). These analyses were consistent with the prespecified primary analysis.

Efficacy issues related to ASA dose. Two dose levels of ASA are proposed for the fixed combination with omeprazole 40 mg: ASA 325 mg and ASA 81 mg. No efficacy trials were conducted utilizing ASA 81 mg. There were two key review issues related to the aspirin dose:

1) DCRP consultants expressed concern about approval of an ASA 325mg dose combination because lower ASA doses are effective for secondary prevention of cardiovascular events and because ASA is associated with a risk of bleeding, for which they noted there is evidence of a dose/response relationship.

2) In the absence of a clinical trial that evaluated omeprazole in combination with ASA 81 mg, the reviewers needed to establish that ASA 81 mg increases the risk of development of ulcers to justify the fixed combination. It was reasonable to assume that if omeprazole decreases the risk of ulcers when combined with the higher dose of ASA, then omeprazole would reduce the risk of gastric ulcers associate with lower ASA doses (*presuming lower doses increase the risk of ulcers*). However, a bridge for the bioavailability of the omeprazole between the two dose level combinations had to be established. The applicant successfully established that latter bridge through submission of the results of a bioequivalence study (see Section 5 Clinical Pharmacology).

These two major issues are discussed below.

ASA doses for secondary prevention. With regard to the ASA 325mg dose level, the professional labeling for aspirin in the Monograph (21CFR343.80) includes the following secondary prevention of cardiovascular event indications, with associated aspirin doses:

- Reduction of the combined risk of death and non-fatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli (50-**325 mg** once a day, continued indefinitely),

- Reduction of risk of vascular mortality in patients with a suspected acute MI (160-162.5 mg once a day for 30 days),

- Reduction of combined risk of death and non-fatal MI in patients with previous MI or unstable angina pectoris (75-**325 mg** once a day, continued indefinitely), and

- Reduction of combined risk of MI and sudden death in patients with chronic stable angina pectoris (75-**325 mg** once a day, continued indefinitely).

- Revascularization procedures: For CABG, **325 mg** daily is started post- procedure and continued for 1 year. For PTCA, 325 mg is administered pre-surgery, and the maintenance dose post-surgery is 160-**325 mg** daily, continued indefinitely. For carotid endarterectomy, the **dose ranges from 80 mg once daily to 650 mg twice** daily, continued indefinitely.

The lower end of the recommended dose range in stroke/transient brain ischemia, previous MI or unstable and stable angina, and post carotid endarterectomy includes the 81 mg dose level proposed by the applicant as the lower ASA dose fixed combination product. The 325 mg dose level is included in all of the above indications except acute MI, for which the dose is 160 to 162.5 mg.

The DCRP clinical consultant summarized key publications (including, the CURE[3] and ACCENT-OASIS-7[4] trials) and current cardiovascular clinical practice guidelines to support DCRP's position that there is no clear advantage of ASA doses as high as 325 mg for secondary prevention, and that there are more bleeding events with increasing doses of ASA. They also pointed out that use of the applicant's product in the acute MI setting would not be appropriate because of the release properties desired in that setting.

These ASA dose issues were discussed with the applicant. The applicant concurred with specifying in product labeling that the product was not appropriate for use at the time of presentation with an acute event. However, with regard to limiting marketing to an 81 mg combination, they countered that there are still clinicians in the US who recommend the 325 mg dose, pointing to the enrollment of patients in the two phase 3 trials submitted in support of this application, which only enrolled at sites in the United States. (Enrollment occurred between November 2009 to January 2012, compared to the 2011 date of the American College of Cardiology/American Heart Association Guidelines.) Ultimately, the DCRP consultants' position, which contrasts with the Monograph, was presented to OND and CDER leadership. OND/CDER leadership could not support DCRP's recommendation to limit the approval to the lower aspirin dose (81 mg) combination, in light of the Monograph's inclusion of the 325 mg dose level in the recommended dose ranges for secondary prevention.

Ulcer Risk for ASA 81 mg justifying combination with omeprazole. To answer the question of whether a proton pump inhibitor is a necessary component of a fixed combination with the lower 81 mg dose of aspirin, i.e., that there was an increased risk of gastric ulcers with low dose (81mg) aspirin, the Clinical Reviewers conducted a literature review. They also considered the PK/PD studies conducted by the applicant, in which Lanza scores were evaluated after ingestion of aspirin and after treatment with a combination of aspirin 81 mg and omeprazole. Study PA325-102) included an EC aspirin 81 mg dose and the endoscopic data collected included presence of "stomach ulcer" and "duodenal ulcer". In the latter study, after only 14 days of dosing, 2/39 of healthy volunteer subjects treated with EC aspirin 81 mg had a stomach or duodenal ulcer (1 of each).

Publications in the literature refer to "low dose aspirin" as a range that includes the 325 mg daily dose as the upper end of the range of "low dose". Multiple publications cite the risk of upper and lower gastrointestinal ulcers and gastrointestinal bleeding associated with "low dose aspirin". Consistent with prior approvals of PPIs for NSAID-induced ulcer risk reduction, the primary endpoint of the two randomized, controlled trials submitted to support approval of the 325 mg ASA/40 mg omeprazole combination was gastric ulcer, not gastrointestinal bleeding. For this reason, the primary focus of the review was identification of evidence that "lower dose range" low-dose ASA is associated with increased risk of developing upper GI ulceration.

Aspirin irreversibly inactivates COX-1 in platelets, which inhibits platelet thromboxane A2 synthesis. COX-1 is also present in gastrointestinal mucosa and, through COX-1 inhibition, aspirin also reduces prostaglandin levels in the mucosa, increasing the risk of gastrointestinal injury. Cryer and Feldman (Gastroenterology 1999;117:17-25) reported the results of a double

[3] Circulation. 2003;108:1682-1687.
[4] NEJM. 2010;363:930-942.

blinded study conducted to identify an ASA dose that inhibits platelet TXA2 synthesis, while having little effect of gastrointestinal mucosa prostaglandin synthesis. Twenty-nine healthy volunteers with a mean age of 46 years (range = 24-81 years) underwent baseline endoscopy to obtain tissue for mucosal PGE2 and PGF2a levels. Biopsies were obtained from the gastric body, antrum, duodenal bulb, postbulbar duodenum. In addition, some patients underwent rectal mucosa biopsies. Subjects were randomized to a daily ASA dose of 10 mg (n=8), 81 mg (n=11) or 325 mg (n=10). Follow-up upper endoscopies with biopsies were performed after 1.5 and 3 months of daily aspirin. The subjects who underwent flexible sigmoidoscopy had a single subsequent rectal mucosa biopsy at 3 months.

The investigators found that the ASA 10 mg dose resulted in a 34-44% reduction of PG levels in the gastric mucosa from baseline, and that the reduction at this lowest dose was similar to that achieved with the higher ASA doses. (The 1.5 month and 3 month levels were averaged.) The impact on PG levels in duodenal mucosa differed, in that the lowest dose (10 mg) did not have an impact on PG levels, while the 81 mg and 325 mg ASA doses were similar in causing an approximate reduction to 45% of baseline PG levels. The results for the rectal mucosal impact of ASA revealed no change from baseline for the 10 mg dose, a reduction to approximately 80% of baseline for the 81 mg dose, and a reduction to approximately 60% of baseline for the 325 mg dose.

None of the subjects had ulcers at baseline. Three subjects had gastric ulcers on follow-up endoscopy. One treated with 10 mg ASA had a 5 mm gastric ulcer at 1.5 months. The other 2 were taking 325 mg aspirin, and both had these ulcers detected at the 3 month examination. No duodenal ulcers were observed.

These data suggest, based on ASA's observed impact on mucosal PG levels, that the 81 mg ASA dose would have a similar impact on gastric mucosa and duodenal mucosa as the ASA 325 mg combination. (The apparent dose response impact on PG levels in the rectal mucosa is not relevant as the PPI component of the fixed combination as a PPI wouldn't be expected to protect the colonic mucosa.) The sample size of this study reported by Cryer and Feldman was too small to yield interpretable results regarding an ASA dose response for producing actual gastric and/or duodenal ulcers.

In order to establish whether there is an ASA dose response relationship for risk of upper GI ulcers, and whether there is a risk of upper GI ulcers associated with the changes in mucosal PG levels that Cryer, et al, described for ASA 81 mg (the lowest ASA proposed in this NDA), the reviewers conducted a literature search to identify trials/studies that specifically examined the ends of the spectrum of "low dose aspirin", which generally includes 325 mg at the upper end. This search yielded little information from randomized, controlled trials to address this question. Although there was general agreement that even ASA doses at the lower end of the "low dose aspirin" dose range result in gastrointestinal bleeding, including upper GI bleeding, there are very few randomized, controlled trials that address whether ASA doses in the lower range of "low dose" causes ulceration, and the two key, frequently cited trials came to different conclusions regarding ulcer risk. I'll discuss those here, and will follow with the results of key publications of meta-analyses and epidemiological studies that are frequently cited as sources to address the question of dose effect for ulcers.

Gastroduodenal Ulceration

The Women's Health Study (Ridker, et al. NEJM. March 31, 2005. Vol 352 No 13 Pages 1293-11304) evaluated the effect of 100 mg of ASA administered every other day on major cardiovascular events. This was a very large randomized, controlled trial. Gastrointestinal adverse events were collected via questionnaire (no scheduled interval endoscopies). The women in this trial (19,934 on the aspirin arm and 19,942 on placebo) were generally not considered high risk for gastrointestinal adverse outcomes from aspirin. Mean age of the women in this trial was 54.6 years. Sixty percent were <55 years of age. Thirteen percent were smokers. The mean follow up was 10 years. There was a statistically significantly higher report of "peptic ulcer" in the aspirin arm (2.7%) compared to placebo (2.1%), with a relative risk of 1.32 (95% CI: 1.16-1.50), $p<0.001$. There was also a significantly higher rate of any gastrointestinal bleeding and GI bleeding requiring transfusion on the aspirin arm (4.6% and 0.6%, respectively, on the aspirin arm compared to 3.8% and 0.5 % on placebo). The relative risk for any GI bleeding was 1.22 (1.10-1.34) and the relative risk for bleed requiring transfusion was 1.40 (1.07-1.83). This trial demonstrated an increased risk of clinically significant ulcer (not found on scheduled routine EGD) with 100 mg ASA, a dose of ASA substantively lower than 325 mg, and close to the 81 mg ASA dose proposed in this NDA. A limitation of the study findings is that the data were self-reported, and since there were no scheduled EGDs, it is possible that there was lack of ascertainment of even symptomatic ulcers.

Laine, et al, reported the results of a smaller trial that randomized patients ≥ 55 years of age with osteoarthritis to 4 arms: placebo, aspirin 81 mg, rofecoxib 25 mg + ASA 81 mg and ibuprofen 800 mg TID (L. Laine, et al. Gastroenterology 2004;127:395-402). Subjects underwent a baseline endoscopy and repeat endoscopies at 6 and 12 weeks. There were approximately 380 subjects in each of the 4 arms. Sample size was based on an expected cumulative incidence of ulcers over 12 weeks of 10% in the ASA-only and the rofecoxib + ASA arms vs. 2.5% in the placebo arm. The study was designed with 98% power to detect a difference between aspirin and placebo based on those assumptions. Gastroduodenal ulceration was defined as a mucosal break ≥3mm in length. The primary endpoint was cumulative proportion of patients who developed gastric and/or duodenal ulcers by 12 weeks, and the primary analysis was a comparison of the rofecoxib + ASA arm vs. ibuprofen.
The authors concluded that aspirin 81 mg did not significantly increase ulcer incidence over placebo, based on a secondary analysis comparing the results in those two arms. The life table incidence (95% CI) of ulcer (at least 3 mm in length) by 12 weeks in the placebo arm was 5.8% (3.4%-8.3%); in the ASA 81 mg arm it was 7.3% (4.6%-9.9%). Although the incidence in the ASA was numerically higher, the difference was not statistically significant. The placebo incidence was higher than predicted and the ASA incidence was lower than predicted. An exploratory analysis compared the change in number of erosions from baseline at 12 weeks, and in this analysis, the increase in number in the ASA arm compared to placebo was nominally statistically significant.

No significant treatment-by-subgroup interaction was identified for specific risk factors for ulcer, including age ≥ 65 years, prior history of upper GI clinical event (symptomatic ulcer, upper gi perforation, bleeding episode), H. pylori status, presence of baseline erosions or

history of NSAID use. However, for patients aged ≥ 65 and for patients with history of prior GI event, there did appear to be a numerically higher risk of developing ulcers in the ASA 81 mg arm than in placebo. The data presented below for these two exploratory sub-analyses are reproduced from Table 5 of the publication. Of note, the placebo incidence remains stable between subgroups, whereas there is a shift to numerically higher incidence in the subgroups generally considered to be at higher risk for ulcer, including in the ASA-only arm. There is an apparent marked shift to numerically higher incidence (relative to placebo) in the ASA-only arm in the prior GI event subgroup, with an incidence similar to that reported for the other NSAID arms; however, the very small denominator in this higher risk subgroup across all arms must be considered.

Table 17: Exploratory subgroup Analyses of 12 Week incidences of Gastroduodenal Ulcers, reproduced from Table 5 of L. Laine et. Al. Gastroenterology 2004;127:395-402.

	Placebo	ASA	Rofecoxib/ASA	Ibuprofen
Age<65	14/248 =5.6%	18/275=6.6%	32/267=12%	39/262=14.9%
Age ≥65	7/133 = 5.3%	9/112=8.0%	26/110=23.6%	23/112=20.5%
No prior GI event	19/349=5.4%	19/357=5.3%	49/342=14.3%	54/341=15.8%
Prior GI event	2/32=6.3%	8/30=26.7%	9/35=25.7%	8/33=24.2%

The authors stated that the lack of significant increase of ulcers at 12 weeks in the ASA-only arm relative to placebo in the face of "the well-documented increase in GI bleeding with low-dose aspirin" supports a conclusion that endoscopic ulcers "may not predict clinical GI bleeding in patients taking low-dose aspirin."

In considering the apparent conflicting conclusions between the Women's Health Study and the latter trial reported by Laine, I do not believe the differences are attributable to the difference in ASA dose, i.e. 100 mg vs. 81 mg. The Women's Health Study was much larger and longer in duration. Although it did not conduct systematic repeat EGD's, as in the trial that studied 81 mg, the ulcers detected were presumably found on an EGD performed for clinical symptoms, indicating that the ulcers were clinically relevant. As noted above, the assumptions that were used to power the trial reported by Laine, et al, were not what was actually observed in the trial (higher placebo rate and a lower ASA rate). In a subsequent review (published in 2006: Alimentary Pharmacology and Therapeutics. 24, 897-908), Laine evaluated the available randomized, controlled data on ulcers and gastrointestinal bleeding with low-dose aspirin. He noted that the aforementioned trial was the only placebo controlled data for ASA 81 mg. He also noted that given the low incidence of ulcers observed in this trial, it would take very large endoscopic trials to detect an increase in ulcers. He further stated that the higher erosion rate with aspirin relative to placebo indicates that ASA 81 mg does cause mucosal damage and that the antiplatelet effect of aspirin increases the likelihood that any ulcers that develop will be complicated by bleeding.

An epidemiological study that examined dose of ASA and gastric/duodenal ulcer risk was identified. Garcia Rodriguez and Hernandez-Diaz (American Journal of Epidemiology. 2004;159:23-31) reported a population-based cohort study from the United Kingdom, with a nested case control analysis using the General Practice Research Database (population-based day in UK from general practitioners). Study population included ages 40-79 years. The two study cohorts were patients exposed to at least one prescription of ASA and/or non-aspirin NSAIDs (N= 258,840) and a cohort who were not (N=463,296). A 50% random sample was obtained from the latter cohort to include in the analysis. The outcome of interest was uncomplicated peptic ulcer (bleeding or perforation). From a total of 1967 patients in the two cohorts, 1197 were identified that met the ulcer definition. Ten thousand controls were then randomly sampled from the nested study cohort from which the ulcer cases had been identified. The authors noted that among the study subjects, there was little use of ASA doses >300 mg per day. The risk of ulcers associated with aspirin use was increased similarly between lower dose range "low dose" ASA and higher dose range "low dose" ASA. The following table summarizes the data, presented by aspirin dose, in Table 1 of the publication:

Table 18: Relative risk of peptic ulcer by dose of aspirin, GPRD, UK, 1995-1999 (Garcia Rodriguez and Hernandez-Diaz. American Journal of Epidemiology. 2004;159:23-31).

Aspirin Dose	Cases (N)	Controls (N)	Adjusted Relative Risk	95%CI
Nonuse	935	8608		
75 mg	112	529	2.9	2.2, 3.7
150 mg	44	234	2.6	1.8, 3.9
300 mg	34	144	3.0	1.9, 4.6
>300 mg	4	10	3.8	1.0, 14.4

* adjusted for age, sex, calendar year, cohort, history of gi symptoms, smoking and steroid use, gastroprotective drug, non-aspirin NSAID use and acetaminophen use

Taken together, I have concluded that these lines of evidence support that the ASA 81 mg component of the proposed lower ASA dose fixed combination is associated with an increased risk of gastrointestinal mucosal injury, including ulceration.

Gastrointestinal Bleeding

Since there was concern expressed by the DCRP reviewer regarding lowest effective dose of ASA and the increased risk of bleeding with increasing ASA dose, I have included an overview of publications that have examined an ASA dose response for gastrointestinal bleeding across the dose range of low dose aspirin. Conclusions varied across the publications.

In his 2006 review, cited above, Laine pointed to the meta-analysis by Derry and Loke (BMJ. Volume 321. 11 November 2000: pages 1183-1187) as evidence that lower dose aspirin (doses 50mg -162.5 mg daily) is associated with a similar increase in relative risk of GI bleeding compared to placebo (OR=1.59; 95% CI: 1.40-1.81) as higher doses of aspirin (162.5 mg-1500mg/day). The rate of GI hemorrhage (hematemesis and melena) in the pooled lower dose aspirin population in the meta-analysis (8 trials, 49,927 subjects) was 2.3% vs. 1.45% in the placebo subjects. Five of 16 of the RCT's that were in the higher dose ASA trial group included doses in the 300-325 mg range. Meta-regression test "for a linear relation between ASA dose and risk of gastrointestinal hemorrhage resulted in a pooled Odds Ratio of 1.015 (0.984 to 1.047) per 100 mg dose reduction, with an estimated relative reduction in the incidence of gastrointestinal hemorrhage of 1.5% per 100 mg reduction of dose". However, this was not statistically significant (p=0.3).

Another and more recent meta-analysis reported by McQuaid and Laine (American Journal of Medicine. 2006; 119, 624-638) identified 9 trials that compared aspirin to placebo, where the aspirin dose did not exceed 325 mg/day. Subset analyses by aspirin dose category, also using 162.5 mg as the cut-point, found overlapping 95% confidence intervals for relative risk of "major GI bleeding" (GI bleed requiring transfusion) between lower and higher dose categories of "low dose" ASA. The relative risk for the lower dose ASA group was 2.22 (95% CI:1.61-3.06), and the relative risk in the higher dose subgroup was 2.35 (95%CI: 0.98-5.66). The sample size in the lower dose subgroup was much larger than the higher dose: 14,842 vs. 2843. Overall, relative to placebo, for patients treated with ASA $\leq$ 325 mg, the authors reported that the absolute rate increase over placebo was 0.12% per year, with a number need to harm at 1 year of 833 (95% CI: 526-1429).

Furthermore, Laine identified two randomized trials that included head to head comparisons of ASA 81 mg and ASA 325 mg. One was a carotid endarterectomy trial (Taylor et al. Lancet. 1999;353:2179-2184) of 3 months duration that randomized 1417 subjects (to 4 different ASA doses ranging from 81 mg to 1300 mg) with median age of 69 years, and the other was colonic adenoma prevention trial (Baron, et al. NEJM. 2003; 348:891-899), for which 33 months of follow up data had been reported and the mean age was 57 years. Neither included endoscopic evaluation for upper GI ulcers. GI bleeding (melena and hematemesis in the endarterectomy trial; and GI bleed resulting in hospitalization or surgical intervention in the adenoma trial) rates were reported and were similar between the 81 mg and 325 mg ASA doses. The rate in the shorter duration endarterectomy trial was 1.1% in each arm. In the colon study, although there was a numerically higher rate of GI bleeding in the ASA 325 mg arm (0.5% vs. 1.1%), the difference was not statistically significant. The sample size in this trial was relatively small, approximately 370 per arm. The rate in the placebo arm was 0.8%.

Two large trials were cited by the DCRP consultants to support the dose response relationship for aspirin and bleeding. One was a report by the CURRENT-OASIS investigators (NEJM 2010;363:930-942). This randomized, 2-by-2 factorial design trial, which examined both clopidogrel and aspirin, included randomization between to ASA dose levels: 300 mg to 325 mg or 75-100 mg. The trial enrolled 25,086 patients with acute coronary syndrome referred for invasive procedure. The authors reported that there was no significant difference between aspirin dose levels for major bleeding in this trial; however, they reported a "nominally

significant" increase in minor bleeding among patients on the higher dose (hazard ration, 1.13; 95% CI, 1.00 to 1.27; p=0.04). There was no strategy for adjusting for multiple comparisons reported. There was a "small increase" in major gastrointestinal bleeding with the higher ASA dose range: 0.4% vs. 0.2% (p value also reported: p=0.04).

The second study was an exploratory analysis (non-randomized for ASA) of the effects of aspirin dose (both benefit and risk) in the data from a large randomized, controlled trial designed to examine the impact of addition of clopidogrel to aspirin in patients with acute coronary syndromes without ST-Segment elevation (The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial). Patients on aspirin were randomized between placebo and clopidogrel. Patients in the trial (n=12,562) were taking a range of aspirin doses (75 mg to 325 mg) and were not randomized based on aspirin dose. In the publication (Peters, et al. Circulation. 2003;108:1682-1687) the investigators explored outcomes in 3 aspirin dose subgroups: ≤ 100mg (n=5320), 101 through 199 mg (n=3109) and ≥ 200 mg (n=4110). The authors noted that the highest dose bracket was most commonly used in North and South America.

The investigators reported that there was a significant increase in risks of major bleeding complications with increasing aspirin dose, observed in both the clopidogrel arm patients and in the placebo arm patients. In the placebo group, across the increasing dose 3 ASA dose brackets, the proportions were 1.9%, 2.8% and 3.7%. Major bleeding was defined as significantly disabling, intraocular bleeding leading to significant vision loss or requiring transfusion of 2 or 3 units of red blood cells. The authors reported that among the bleeding sites with significant increase in major bleeding were gastrointestinal sources. The data for this analysis were not presented in the publication. No significant trend was noted for minor bleeding.

A case-control study, published in 1995 (Weil, et al. BMJ. Volume 310. 1 April 1995: 827-830) identified cases of hematemesis and melena arising from gastroduodenal ulcers admitted to 5 United Kingdom hospitals between 1987-1991. The investigators identified 1121 cases, 1126 hospital controls and 989 community controls. Thirteen percent of the cases were taking daily aspirin, compared to 9% of the hospital controls and 8% of community controls. Aspirin doses ranged 75 mg to >300 mg. The most commonly used dose among the cases and controls was 300 mg: 62/144 cases taking ASA were taking 300 mg, compared to 27 who were taking 150 mg and 27 who were taking 75 mg. The authors concluded "no particular dose of aspirin between 75 mg and 300 mg daily currently used in cardiovascular prophylaxis is free of risk of causing bleeding from gastric or duodenal ulcers."

An observational study reported by Serrano, et al (Aliment Pharmacol Ther 2002; 16:1945-1953) did not conclude that there is a similar risk for gastrointestinal bleeding for lower dose vs. higher doses of aspirin. However, this study is relatively small, i.e., compared to the meta-analyses discussed earlier. The investigators evaluated the risk of upper GI bleed in 903 patients in Spain who were discharged on low-dose aspirin from a hospital's cardiology unit. The ASA doses included 75 mg, 100 mg, 125 mg, 150 mg, 200, 250 mg, and 300 mg. The most commonly prescribed dose (in 46% of patients) was 200 mg/day. Less than 4% were taking doses ≤100 mg /day. Of the 903 patients followed over a mean of 45 months, 4.5%

developed an upper gastrointestinal bleed that led to hospitalization. In 53%, gastric or duodenal ulcers were the source of bleeding for those events. The source in the remaining 19 patients (46%) was "acute gastro duodenal mucosal lesion". The authors reported that a multivariate analysis found that aspirin dose (per every 100 mg/day increase) and history of prior upper GI bleeding increased the risk of an event in this study population.

Based on the two randomized, controlled trials that established the efficacy of the omeprazole component of the proposed fixed combination product containing low dose aspirin at the upper end of the dose range, 325 mg, and the literature reviewed above, which indicates that there is in fact risk of developing upper gastrointestinal ulcers associated with lower aspirin doses, including the proposed lower dose, 81 mg, I concur with the reviewers' recommendation to approve both combination dose levels. The higher dose level will be approved, in alignment with the recommendations from CDER and OND leadership, and in concordance with the aspirin Monograph. The omeprazole dose in the fixed combination that was found to be effective for reducing the risk of ulcers associated with aspirin 325 mg, can be expected to be effective for the lower aspirin dose, 81 mg, which literature indicates is associated with a risk for causing upper gastrointestinal ulceration. The Clinical Pharmacology reviewers have reviewed the pharmacokinetic bridging data between the two proposed fixed combination products, and have determined that the omeprazole exposure between the two aspirin dose level fixed combination dose levels are comparable, which supports that the omeprazole efficacy associated with the lower aspirin dose fixed combination product can be expected to be comparable to that of the higher aspirin dose fixed combination product.

I agree with the review team's conclusion that effectiveness of the two proposed ASA dose level fixed combination has been established. I agree with the reviewers' plan to state in the Dosage and Administration section of the product label that prescribers should consider practice guidelines and the potential for increased risk of bleeding with increasing doses of aspirin when selecting the dose for patients. The indication will include a description of patients at particular risk for developing ulcers for whom the combination product would be appropriate (reflecting the population studied in the trials), including patients of advanced age and patients with a history of upper gastrointestinal ulcer. There will be a Limitation of Use statement in the Indication Section of the product label stating the Yosprala has not been shown to reduce the risk of upper gastrointestinal hemorrhage. The two upper gastrointestinal hemorrhages that were SAEs in the two trials will be included in Section 14 Clinical Studies, given the presence of the Limitation of Use for upper gastrointestinal hemorrhage (consistent with guidance provided to the Division during the course of the labeling review from Office of Medical Policy staff).

8. Safety

As of 2005, all prescription NSAIDs have been required to include a Boxed Warning and Medication Guide as parts of the product label due to the risk of cardiovascular and gastrointestinal adverse events. Aspirin, an NSAID, is in a class of drugs called salicylates that have a known risk of gastrointestinal adverse events associated with chronic or long term

use, even at low doses. Therefore, a Medication Guide is necessary to communicate these risks; however, a REMS is not necessary.

The currently approved PPI labels contain class labeling in Warnings and Precautions including, but not limited to, atrophic gastritis, increased risk of Clostridium difficile associated diarrhea, bone fracture, and hypomagnesaemia. (See Clinical review for more details.) In addition, the Prilosec (omeprazole) label includes a warning regarding concomitant use with clopidogrel and concomitant use with St. John's Wort or rifampin. Those Warnings will be included in the proposed product label.

Both arms of the two phase 3 trials submitted in support of this application included aspirin. The arms differed only in the addition of omeprazole to one of the arms. Dosing was six months in duration. A total of 521 subjects were exposed to the proposed fixed combination of ASA 325 mg/omeprazole 40 mg (325/40) in these two trials. In addition, the applicant conducted an open label single arm trial (n=379) to evaluate safety over a period of 12 months. Patients in the safety study took the combination product containing ASA 325 mg.

Deaths. There were 6 deaths in the safety dataset. Four subjects treated with the combination product (325/40) died, 3 with cardiovascular events: two in Study 302 and two in the 12 month open label study. Two of the 3 events were cerebrovascular accidents (one in Study 302 and one in the safety study, both non-hemorrhagic). One was a cardiac arrest that occurred in a subject when struck by an automobile (Study 302). The death of the fourth subject (in the safety study), which was secondary to pancreatic cancer, occurred 200 days after stopping study drug.

There were deaths of two subjects treated with EC-aspirin 325 mg – one in Study 301 and one in Study 302. One (Study 301) was due to cardiac arrest after angina and the other was secondary to renal cancer.

Nonfatal Serious Adverse Events. In the controlled trial Study 301, there was a numerically higher rate of SAEs in the enteric coated aspirin arm (EC-ASA) subjects than in the fixed combination (325/40) subjects (9.1% vs. 6.1%). Gastrointestinal disorders were the most common type of SAE in Study 301. In Study 302, a numerically higher proportion of SAEs was observed in the fixed combination arm: 23/257 (9.0%) in the fixed combination arm vs. 17/259 (6.6%) in the enteric coated aspirin arm. Cardiac disorders were the most common type of SAE in Study 302.

The following tables, reproduced from the Clinical Review, summarize the types and distribution of the GI and cardiac SAEs reported for Study 301 and Study 302. As noted in the CDTL review, an independent Gastrointestinal Clinical Event Committee (blinded) adjudicated potential clinically significant major adverse gastrointestinal events. The only upper gastrointestinal hemorrhages that were classified as SAEs in the two trials occurred in one patient taking the fixed combination product (gastric ulcer bleed) and in one patient on the enteric aspirin arm (duodenal ulcer bleed). There was also a lower gastrointestinal hemorrhage classified as an SAE in each of both arms, as well as an intestinal obstruction SAE in both

arms. (In the tables below, PA32540 refers to the fixed combination ASA 325 mg/omeprazole 40 mg.)

Table 19: Incidence of Treatment Emergent Non-fatal Serious Adverse Events-Primary Safety Population Study 301 and Study 302

System Organ Class / Preferred Term[1]	PA32540			EC-aspirin 325 mg		
	PA32540-301 n(%) N = 264	PA32540-302 n(%) N = 257	PSP n(%) N = 521	PA32540-301 n(%) N = 265	PA32540-302 n(%) N = 259	PSP n(%) N = 524
Number of SAEs	25	25	50	32	21	53
Subjects with any SAE	16 (6.1)	23 (8.9)	39 (7.5)	24 (9.1)	17 (6.6)	41 (7.8)
Gastrointestinal Disorders	5 (1.9)	2 (0.8)	7 (1.3)	6 (2.3)	2 (0.8)	8 (1.5)
Abdominal pain	1 (0.4)	0	1 (0.2)	0	1 (0.4)	1 (0.2)
Abdominal pain upper	1 (0.4)	0	1 (0.2)	0	0	0
Gastric ulcer haemorrhage	1 (0.4)	0	1 (0.2)	0	0	0
Intestinal obstruction	1 (0.4)	0	1 (0.2)	0	0	0
Pancreatic cyst	1 (0.4)	0	1 (0.2)	0	0	0
Pancreatitis	1 (0.4)	0	1 (0.2)	0	0	0
Diverticulitis	0	1 (0.4)	1 (0.2)	1 (0.4)	0	1 (0.2)
Duodenal ulcer haemorrhage	0	0	0	1 (0.4)	0	1 (0.2)
Gastrooesophageal reflux disease	0	0	0	1 (0.4)	0	1 (0.2)
Intestinal haemorrhage	0	0	0	1 (0.4)	0	1 (0.2)
Pancreatitis acute	0	0	0	1 (0.4)	0	1 (0.2)
Small intestinal obstruction	0	0	0	1 (0.4)	0	1 (0.2)
Large Intestinal haemorrhage	0	1 (0.4)	1 (0.2)	0	0	0
Oesophagitis obstruction	0	0	0	0	1 (0.4)	1 (0.2)
Cardiac Disorders	4 (1.5)	11 (4.3)	15 (2.9)	5 (1.9)	6 (2.3)	11 (2.1)
Angina pectoris	1 (0.4)	2 (0.8)	3 (0.6)	1 (0.4)	2 (0.8)	3 (0.6)
Atrial fibrillation	1 (0.4)	2 (0.8)	3 (0.6)	1 (0.4)	0	1 (0.2)
Atrial flutter	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.4)	0	1 (0.2)
Coronary artery disease	1 (0.4)	1 (0.4)	2 (0.4)	0	1 (0.4)	1 (0.2)

System Organ Class / Preferred Term[1]	PA32540			EC-aspirin 325 mg		
	PA32540-301 n(%) N = 264	PA32540-302 n(%) N = 257	PSP n(%) N = 521	PA32540-301 n(%) N = 265	PA32540-302 n(%) N = 259	PSP n(%) N = 524
Acute myocardial infarction	0	2 (0.8)	2 (0.4)	2 (0.8)	1 (0.4)	3 (0.6)
Arteriosclerosis coronary artery	0	1 (0.4)	1 (0.2)	0	0	0
Coronary artery occlusion	0	0	0	1 (0.4)	0	1 (0.2)
Sudden cardiac death	0	0	0	1 (0.4)	0	1 (0.2)
Myocardial infarction	0	2 (0.8)	2 (0.4)	0	0	0
Cardiac failure congestive	0	1 (0.4)	1 (0.2)	0	2 (0.8)	2 (0.4)
General Disorders and Administration Site Conditions	4 (1.5)	1 (0.4)	5 (1.0)	2 (0.8)	4 (1.5)	6 (1.1)
Infusion site extravasations	0	0	0	1 (0.4)	0	1 (0.2)
Accidental death	0	1 (0.4)	1 (0.2)	0	0	0
Chest pain	0	0	0	1 (0.4)	3 (1.2)	4 (0.8)
Non-cardiac chest pain	4 (1.5)	0	4 (0.8)	0	1 (0.4)	1 (0.2)
Infections and Infestations	3 (1.1)	3 (1.2)	6 (1.2)	3 (1.1)	1 (0.4)	4 (0.8)
Osteomyelitis	1 (0.4)	0	1 (0.2)	0	0	0
Septic shock	1 (0.4)	0	1 (0.2)	0	0	0
Wound infection	1 (0.4)	0	1 (0.2)	0	0	0
Chest wall abscess	0	0	0	1 (0.4)	0	1 (0.2)
Pneumonia	0	2 (0.8)	2 (0.4)	1 (0.4)	0	1 (0.2)
Sepsis syndrome	0	0	0	1 (0.4)	0	1 (0.2)
Periorbital cellulitis	0	1 (0.4)	1 (0.2)	0	0	0
Urinary tract infection	0	0	0	1 (0.4)	0	1 (0.2)
Cellulitis	0	0	0	0	1 (0.4)	1 (0.2)
Neoplasms, Benign, Malignant and Unspecified	2 (0.8)	1 (0.4)	3 (0.6)	1 (0.4)	2 (0.8)	3 (0.6)

The CDTL tabulated adverse events that were consistent with gastrointestinal bleeds, not limited to upper GI bleeds. In Study 301, 1% of subjects on the 325/40 combination arm had a GI bleed vs. 3% on the EC-ASA arm. In Study 302, 0.4% had GI hemorrhagic AEs on the 325/40 arm, compared to <0.3% in the EC-ASA arm. I concur with the CDTL that these AE data show the risk of GI bleeding is not eliminated by omeprazole.

The tables above also include cardiac SAEs. An independent Cardiovascular Review Committee (blinded) adjudicated the major cardiovascular events reported in these trials. When the adverse event data from Study 301 and Study 302 were combined, there were 9 events (1.7%) adjudicated as MACE in the subjects randomized to the combination product (325/40 mg) vs. 14 adjudicated events in 13 subjects (2.5%) randomized to EC-ASA. There were 16 (4.2%) adjudicated MACE events in the uncontrolled open label safety trial (Study 303). The following tables (reproduced from the CDTL review) summarize the adjudicated MACE events. The adjudication committee included TIA, angina, heart failure, and planned CABG as MACE events. In general, the FDA has been moving away from classification of these types of events as MACE. If those are eliminated, the numbers of MACE events from the combined population of Study 301 and Study 302 are 5/521 (1.0%) in the combination arm and 9/524 (1.7%) in the EC-ASA arm. Elimination of the events designated ACS, decreases the count in the EC-ASA arm to 4/524 (1%). Similarly, when a stricter definition of MACE is

utilized, the number of events in the open label study decreases. (In the tables below, PA32540 refers to the fixed combination ASA 325 mg/omeprazole 40 mg.)

Table 20. Adjudicated Major Cardiovascular Adverse Events in Primary Safety Population

MACE Category	Adverse Event Preferred Term
PA32540	
CAD	Non-Cardiac Chest Pain
Non fatal MI	Myocardial Infarction
Non fatal MI	Myocardial Infarction
Non fatal MI	Acute Myocardial Infarction
Non fatal MI	Acute Myocardial Infarction
Non fatal MI	Acute Myocardial Infarction
Planned Coronary Artery Bypass Graft	Arteriosclerosis Coronary Artery
TIA	Reversible Ischaemic Neurological Deficit
Heart Failure	Cardiac Failure Congestive
EC-aspirin 325 mg	
Non fatal MI	Acute Myocardial Infarction
Non fatal MI	Acute Myocardial Infarction
Non fatal MI	Acute Myocardial Infarction
ACS	Coronary Artery Occlusion
ACS	Angina Pectoris
ACS	Angina Pectoris
TIA	Transient Ishchaemic Attack
TIA	Transient Ishchaemic Attack
CV Death	Sudden Cardiac Death
ACS	Coronary Artery Disease
ACS	Angina Pectoris
TIA	Transient Ishchaemic Attack
TIA	Reversible Ischaemic Neurological Deficit
Heart Failure	Cardiac Failure Congestive

Reproduced from CDTL review (Table 13)

Table 21. Adjudicated MACE in Subjects Who Entered PA32540-303

MACE	Adverse Event Preferred Term
CV death-stroke	Cerebral Infarction
Non-fatal MI	Angina Pectoris
Non-fatal MI	Myocardial Infarction
Non-fatal MI	Coronary Artery Disease
Non-fatal MI	Myocardial Infarction
Non-fatal MI	Myocardial Infarction
ACS	Angina Unstable
ACS	Angina Pectoris
ACS	Cardiac Failure Congestive
Ischemic Stroke	Thalamic Infarction
Heart Failure	Angina Unstable
Unplanned PCI	Angina Unstable
Unplanned PCI	Myocardial Ischemia
Heart Failure	Cardiac Failure Congestive
Other CV Event	Carotid Artery Stenosis
Unplanned CABG	Coronary Artery Disease

Reproduced from CDTL review. Table 14.

The Prilosec (omeprazole) label contains a warning against concomitant use with clopidogrel. Some patients in this trial took concomitant clopidogrel. As summarized in the table below, among patients taking concomitant clopidogrel in the two trials, there was a numerically higher proportion of nonfatal myocardial infarction in subjects taking the fixed combination containing omeprazole compared to the subjects who were randomized to aspirin only. Analysis of the larger subgroup who were not taking concomitant clopidogrel revealed that the rate of any major CV AE (here, nonfatal MI and CV death) was numerically higher in the EC-ASA arm subjects relative to the fixed combination. The overall rate of events was lower in the subjects who were not taking concomitant clopidogrel than among those who were.

Table 22. Proportion of Subjects with Pre-Specified Major Cardiovascular Adverse Events by Concomitant Use of Clopidogrel in the Primary Safety Population from Studies PA32540-301 and PA32540-302

	Clopidogrel Use = Yes[1]				Clopidogrel Use = No	
	PA32540 n(%) (N=117)		EC-Aspirin 325 mg n(%) (N=115)		PA32540 n(%) (N=404)	EC-Aspirin 325 mg n(%) (N=409)
	Any Time	Within 7 Days	Any Time	Within 7 Days		
Subjects with Any Major CV AE	4 (3.4)	4 (3.4)	0	0	1 (0.2)	4 (1.0)
Non-Fatal Stroke	0	0	0	0	0	0
Non-Fatal Myocardial Infarction	4 (3.4)	4 (3.4)	0	0	1 (0.2)	3 (0.7)
CV Death	0	0	0	0	1 (0.2)	1 (0.2)

[1]'Any Time' columns include subjects on clopidogrel at any time during the treatment period. 'Within 7 Days' columns include only MACE Adverse Events that occurred following at least 7 consecutive days of clopidogrel use.

Approximately 19% (n=71)) of subjects in the safety trial (Study 303) also took concomitant clopidogrel. Two patients in Study 303 who had CV death, nonfatal MI or non-fatal stroke, were taking concomitant clopidogrel.

DCRP was asked in a consult whether the adjudicated and unadjudicated analyses of cardiovascular events suggest a new safety concern and whether they warranted inclusion in the product label. The DCRP clinical consultants considered the number of events and duration of exposure too short to draw reliable conclusions regarding cardiac safety; however, they noted that all the MACE events in patients in the trials who were taking clopidogrel occurred in subjects who were receiving the fixed combination containing omeprazole, which is now a well-known interaction (clopidogrel with omeprazole). I concur with the CDTL's recommendation to not include the MACE data in the product label, as no specific safety concerns were identified by the DCRP consultant, and as was stated by the consultant, the data are inadequate to draw conclusions. The labeling for the omeprazole component of this fixed combination will be consistent with the current warnings regarding the interaction in the currently approved omeprazole label.

The reviewers did not recommend that the applicant be required to conduct a postmarketing safety study or trial. I concur.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this 505(b)(2) application. There were no scientific issues identified that required input from an Advisory Committee. Neither components of this fixed combination product is a new molecular entity.

10. Pediatrics

The applicant submitted a request for a full waiver of pediatric studies on the grounds that necessary studies are impossible and highly impractical (very low prevalence of pediatric patients with myocardial infarction, stroke, chronic stable angina or transient ischemia of the brain who would also be at risk for aspirin associated ulcers) and on the grounds that the product would be unsafe for use in the pediatric population because of the association between aspirin and Reye's syndrome. The aspirin monograph (21 CFR 343.80) includes a contraindication for its use in pediatric patients with viral infections because of the risk of Reye's Syndrome. Since Yosprala® may be used chronically, pediatric patients may develop intercurrent viral illnesses while on the product and be at risk for Reye's Syndrome.

The PeRC agreed to the full waiver on the grounds that studies would be impossible or highly impractical "because the proposed indication in the pediatric population is rare, therefore the incidence of aspirin associated gastric ulcers would also expected to be rare."

Esomeprazole and omeprazole labels were recently subject to safety labeling changes in the Pregnancy, Nursing Mothers and Pediatric Use sections, based on nonclinical data indicating that use of esomeprazole in pregnancy may cause fetal harm with changes in bone morphology and physeal dysplasia in pre- and postnatal developmental toxicity studies in rats. Adverse effects were also seen on maternal bone in pregnant and lactating rats. The Yosprala label was revised accordingly.

11. Other Relevant Regulatory Issues

As stated in the Clinical Review, "For studies PA32540-301 and PA32540-302 the Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)."

OSI audited two sites from the two major randomized, controlled clinical trials that supported this application. One was a California site that participated in Study 301. Thirty-one patients were randomized at this site. The records from 15 were audited. The inspection revealed no violations of federal regulations and the data from the site were considered reliable. The other was a Kansas site that participated in Study 302 and randomized 22 subjects. The records of all 26 subjects were reviewed. No significant regulatory violations were observed and the data generated at this site were considered reliable.

OSI also audited the clinical analytical portions of the following two studies:

1) Study PA32540-115: "Single Dose Randomized Crossover Study to Assess the Intrasubject Variability of Acetylsalicylic Acid from Administration of an Enteric-Coat Aspirin Formulation (Ecotrin 325 mg) and to Evaluate the Relative Bioavailability of PA32540 with the Partial Reference-Replicated 3-Way Design and the Reference-Scaled Average Bioequivalence Approach"

2) Study PA8140-102: "Single-Dose, Randomized, 3-Way Crossover Study to Assess the Bioavailability of Acetylsalicylic Acid from Administration of Three Tablets

(Dosed Concurrently) of PA8140 Relative to Three Tablets of an Enteric Coat Aspirin Formulation (Ecotrin 81 mg) Using the Partial Reference-Replicated Design"

The audit of the clinical portion was conducted at PPD Phase I Clinic in Austin Texas. There were no significant findings at this site. The Bioanalytical site inspected was at (b) (4) (b) (4) There were no significant findings at this site as well. OSI issued a document stating that they recommended that data for clinical and analytical portions of these two studies "are acceptable for further agency review."

12. Labeling

At the time of receipt of the Withhold recommendation from Compliance, there were outstanding labeling negotiations for issues upon which the Division and the applicant had not reached agreement. For this reason, labeling was included as a deficiency in the Complete Response letter. The major unresolved issue related to presentation of one of the secondary endpoint analyses in labeling, which is discussed above in Section 7 of this review.

See the Section 7 Clinical/Statistical Efficacy discussion of labeling recommendations regarding the Limitation of Use addressing the fact that the omeprazole combination has not been shown to reduce the risk of gastrointestinal bleeding. The two upper gastrointestinal hemorrhages that were SAEs will be included in Section 14 Clinical Studies. In addition, there will be a statement in Dosage and Administration to take into consideration current practice guidelines and the potential for increased risk of bleeding with increased aspirin doses when selecting the Yosprala aspirin dose.

As stated in Section 8 Safety and in Section 10 Pediatrics, class labeling consistent with NSAID required class safety labeling and to safety class labeling for omeprazole were included in the Yosprala label.

The PMHS Maternal Health Team consultants recommended revising the applicant's proposed Pregnancy and Nursing Mothers Labeling to be consistent structure to the Proposed Pregnancy and Lactation Labeling rule published in May 2008. Their recommendations were incorporated.

OPDP and DMPP labeling reviews were considered and most of the recommendations were incorporated in labeling. The OPDP recommendation to remove the word "rarely" from the description of hypomagnesaemia warning was discussed with the Deputy Director of Safety in DGIEP, who noted that the wording of this warning was recommended by OSE as part of class safety labeling. For this reason, the word "rarely" was not deleted.

DMEPA reviewed multiple proposed proprietary names over time and found them unacceptable (b) (4) The reviewers ultimately found the

applicant's proposed name "Yosprala," acceptable. DMEPA also made a number of recommendations to increase the readability and prominence of important information on the label, in addition to recommendations to promote safe use and to mitigate confusion. Their recommendations were incorporated in labeling negotiations with the applicant.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete Response.

- Risk Benefit Assessment – Compliance entered a Withhold recommendation in EES, based on deficiencies identified at that site (b) (4) This NDA can't be approved until these deficiencies are addressed. In addition, there are labeling negotiations that were not resolved at the time that the Withhold recommendation was issued. Although the labeling could have been resolved prior to an approval action, given that the manufacturing issues could not be resolved in this review cycle, labeling negotiations ended and labeling will be included as a deficiency in the Complete Response letter.

  Both components of this fixed combination are approved drugs and the applicant presented substantial evidence that the omeprazole component of the fixed combination reduces the risk for gastric ulcers induced by enteric coated aspirin 325 mg. The applicant also established bioequivalence based on the active moiety of ASA, i.e., acetylsalicylic acid, for both combination presentations (ASA 325 mg/omeprazole 40 mg; ASA 81 mg/omeprazole 40 mg). Based on the monograph for aspirin professional labeling (21 CFR 343.80), the secondary cardiovascular prevention indications can be included in the Yosprala label.

  Although no adequate and well controlled trials that evaluated the efficacy of the ASA 81mg + IR omeprazole 40mg Yosprala tablet (PA8140) were submitted for review, I concur with the CDTL that there is adequate evidence to support the approval of the lower ASA dose combination, since there is no reason to believe that ASA 81 mg would have a greater risk for development of gastric ulcers, making it more difficult for the omeprazole to reduce the risk of ulcers, and given that there is evidence in the literature indicating that there is in fact a risk for developing upper gastrointestinal injury, including ulcers, with aspirin doses lower than 325 mg. Furthermore, PK data from a relative bioavailability study established that the bioavailability of the omeprazole component of the lower ASA dose fixed combination product (81/40) was not lower than that of the fixed combination tested in the two phase 3 trials (325/40).

  The DCRP concerns regarding marketing a combination that includes a 325 mg dose of aspirin when lower doses of aspirin have been found to be effective for secondary prevention were carefully considered, including the concerns about increasing risk for bleeding with increasing doses of aspirin. These issues were discussed with OND and CDER leadership, and in light of inclusion of the ASA 325 mg dose in 21 CFR343.80,

a decision to limit approval to the 81 mg ASA combination was not supported. Presumably, when practice of medicine aligns with clinical guidelines for secondary prevention, based on comparable efficacy and apparent improved safety for lower ASA doses, the lower dose combination product presentation will be selected for use by clinicians. The review team has worked to assure that Yosprala labeling will address DCRP concerns. The Dosage and Administration section will encourage prescribers to consider current practice guidelines and the potential for an increased risk of bleeding with increasing aspirin doses when selecting the Yosprala aspirin dose. A Limitation of Use in the indication will state that the omeprazole component has not been shown to reduce the risk of upper GI bleeding. In fact, upper gastrointestinal hemorrhage occurred in the trials submitted for review (an SAE in each treatment arm). An additional Limitation of Use statement will inform prescribers that Yosprala is not appropriate for use in an acute cardiovascular event setting due to the delayed release characteristics of the aspirin component.

Safety labeling associated with currently approved omeprazole and NSAID products will be included in the Yosprala product label. These have been discussed in my review and include new animal safety data and pregnancy warnings for Prilosec, as well as an interaction with clopidogrel.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – none necessary

- Recommendation for other Postmarketing Requirements and Commitments – There will be no postmarketing requirements. (b) (4) [redacted] See Section 3 CMC of this review, or the Approval letter.

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

/s/

DONNA J GRIEBEL
04/25/2014

Cross-Discipline Team Leader Review

Date	April 25, 2014
From	Robert P. Fiorentino, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA #	205103
Applicant	POZEN, Inc.
Date of Submission	March 25, 2013
PDUFA Goal Date	April 25, 2014 (includes a 3 month review extension)
Proprietary Name / Established (USAN) names	YOSPRALA, omeprazole, aspirin
Dosage forms / Strength	Enteric coated (EC) aspirin (325 mg, 81mg) and immediate release omeprazole (40mg) once a day
Proposed Indications	(b) (4)
Recommended:	Complete Response

Table of Contents

1. Introduction

This original 505(b)(2) NDA was submitted by POZEN Inc. on March 25, 2013. A 3 month review extension was taken on December 19, 2013 based in a major amendment received December 18, 2013. The extended user fee goal date is April 25, 2014.

Yosprala tablets are a multilayer orally administered tablet consisting of an enteric-coated (EC) aspirin core (81 mg or 325 mg), and an immediate release (IR) omeprazole 40 mg film coat. This allows for a sequential release, first of omeprazole followed by aspirin (b) (4) The tablets are intended for once daily use to provide the benefits of aspirin with the upper gastrointestinal (UGI) protection of omeprazole, a proton pump inhibitor (PPI).

The applicant proposes the following indications for Yosprala Tablets: (b) (4)

The applicant has submitted the result of two adequate and well-controlled clinical trials to support the efficacy of Yosprala in decreasing the incidence of gastric ulcers (as well as combined gastric and/or duodenal ulcers) in patients at risk of developing ulcers due to aspirin use. Clinical safety and efficacy were assessed in 1429 subjects with a history of established cardiovascular disease receiving daily 325 mg aspirin and at risk of developing aspirin associated gastric ulcers in the two controlled studies of 6-months duration (PA32540- 301and PA32540-302) as well as in a 12-month, open-label, safety study (PA32540-303).

Although the clinical trials were conducted using the ECASA 325mg + omeprazole 40mg combination tablet (PA32540), the sponsor has submitted additional PK data to supporting the effectiveness of the ECASA 81mg + omeprazole 40mg tablet (PA8140) in reducing ulcers in the same at risk population.

<u>Documents Reviewed</u>

Clinical
- Zana H. Marks, MD, MPH (review signed 3/21/2014, addendum signed 4/04/2014)

Biostatistics (Division of Biometrics III)
- Freda Cooner, Ph.D., Team Leader (separate review signed 03/28/2014)
- Milton C. Fan, Ph.D., Primary Statistics Reviewer (review signed 03/28/2014)

Nonclinical
- Tamal K. Chakraborti, Ph.D. (review signed 12/13/2013)

Clinical Pharmacology
- Dilara Jappar, Ph.D. (review signed 4/18/2014)

Biopharmaceutics
- Banu Sizanli Zolnik, Ph.D., (review signed 3/21/2014)

CMC (Office of New Drug Quality Assessment)
- Zhengfang Ge, Ph. D. (initial review signed 11/21/2013, Final Recommendation 4/24/2014)

Product Quality Microbiology (CDER/OPS/NDMS)
- Jessica G. Cole, PhD (review signed July 08, 2013)

Office of Scientific Investigations
- Clinical Inspections: Susan Leibenhaut, M.D. (dated 12/11/2013)
- Bioequivalence Inspections: Xingfang Li, M.D. and Michael F. Skelly, Ph.D. (review dated 11/14/2013)

Pediatric and Maternal Health Staff (PMHS)
- Donna Snyder, MD (reviewed signed 12/22/2013)
- PeRC Meeting Minutes (signed 10/07/2103, DARRTS reference ID: 3385395)

Division of Medication Error Prevention & Analysis
- Proprietary Name Review: Denise V. Baugh, PharmD, BCPS (6/21/2013) & Lisa Vo Khosla, PharmD, M.H.A. (09/12/2013)
- Labeling Review: Karen Dowdy, RN, BSN (signed 4/22/2014)

Office of Prescription Drug Promotion (OPDP)
- Meeta Patel, PharmD (signed 4/21/2014)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information (SRPI)
- Jeanne M. Delasko (signed 4/24/2014)

Division of Cardiovascular and Renal Drug Products (DCRP) and Office of Clinical Pharmacology, DCP1
- Preston M. Dunnmon, M.D., Sudharshan Hariharan, Ph.D., Rajanikanth Madabushi, Ph.D., (joint DCRP & DCP1 consult review signed 1/16/2014)

2. Background

Aspirin is used widely as an antithrombotic drug for prevention of cardiovascular and cerebrovascular events. The mechanism by which aspirin reduces the risk of cardiovascular (CV) events is through inhibition of platelet aggregation via irreversible acetylation of the cyclooxygenase-1 (COX-1) enzyme within platelets. Inhibition of COX-1 prevents conversion of arachidonic acid to thromboxane A2 (TxA2), which a potent agonist of platelet aggregation and therefore of thrombosis.

The optimal dose of aspirin for prevention of CV events is controversial, as current guidelines and evolving evidence suggest that doses <100mg/day are sufficient to provide adequate cardioprotection and that doses higher than this, including 325mg, provide no additional benefit. This is despite the fact that the professional labeling for aspirin (per the monograph under 21 CFR 343.80) provides for doses as high as 325mg daily. Table 1 presents the approved doses of aspirin within the Professional Labeling.

Table 1. Professional labeling for aspirin (21 CFR 343.80)

Indications	Recommended Daily Dose	Duration of Therapy
Vascular Indications:		
Ischemic Strokes and TIA	50-325 milligrams (mg) daily	Indefinitely
Suspected Acute MI	160-162.5 mg taken as soon as infarction is suspected; then once daily	For 30 days post infarction (after 30 days consider further treatment based on indication for previous MI)
Prevention of Recurrent MI	75-325 mg daily	Indefinitely
Unstable Angina Pectoris	75-325 mg daily	Indefinitely
Chronic Stable Angina Pectoris	75-325 mg daily	Indefinitely
Revascularization Procedures in Select Patients:		
CABG	325 mg daily starting 6 hrs. postprocedure	1 year
PTCA	325 mg 2 hours presurgery Maintenance therapy: 160-325 mg daily	Indefinitely
Carotid Endarterectomy	80 mg daily to 650 mg twice a day started presurgery	Indefinitely
Rheumatologic Disease Indications:		
Rheumatoid Arthritis	Initial dose 3 g daily. Target plasma salicylate levels 150-300 micrograms/milliliter (μg/mL)	As indicated
Juvenile Rheumatoid Arthritis	Initial dose 90-130 mg/kilograms/day. Target plasma salicylate levels 150-300 μg/mL	As indicated
Spondylcarthropathies	Up to 4 grams (g) daily	As indicated
Osteoarthritis	Up to 3 g daily	As indicated
Arthritis and Pleurisy of SLE	Initial dose 3 g daily. Target plasma salicylate levels 150-300 μg/mL	As indicated

The 2011 American College of Cardiology /American Heart Association (ACC/AHA) guidelines recommends daily doses of 75 to 162 mg for secondary prevention[1]. The 2012 American College of Chest Physicians (ACCP) recommends a daily dose of 75 to 100 mg[2].

Despite the benefit of lower doses of aspirin for cardioprotection, it is important to note that the risk of aspirin induced GI injury, particularly GI bleeding, appears to be elevated across a range of aspirin doses. One metanalysis found that that the relative risk of major GI bleeding with 'lower' low-dose aspirin (75–162.5 mg daily) was similar to the relative risk with 'higher' low-dose aspirin (>162.5–325 mg daily): 2.22 (95% CI: 1.61–3.06) vs. 2.35 (95% CI: 0.98–5.66).[3]

The Women's Health Study also observed a higher rate of self-reported peptic ulcers in women taking ASA 100mg every other day compared to placebo [5.6% vs. 4.7%, HR=1.2 (95%CI: 1.10, 1.31)].[4]

A study by Laine *et al*[5] showed that patients receiving ASA 81mg are still at risk of developing both gastric and/or duodenal ulcers and at risk of developing gastroduodenal erosions. The observed rate of gastroduodenal ulceration in from the Laine *et al* study is presented in Table 2.

[1] A Sidney C. Smith, Jr, Emelia J. Benjamin, Robert O. Bonow, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update: A Guideline From the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124:00-00.)

[2] Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e637S.

[3] McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med; 2006; 119: 624–638.

[4] Nancy R. Cook, ScD; I-Min Lee, ScD; Shumin M. Zhang, ScD, et al. Alternate-Day, Low-Dose Aspirin and Cancer Risk: Long-Term Observational Follow-up of a Randomized Trial. *Ann Intern Med.* 2013;159(2):77-85

Table 2. 12-Week Cumulative Incidences of Gastroduodenal Ulcers in Laine et al[5] in Placebo and ASA 81mg

	Placebo (N = 381)	Aspirin (N = 387)
Ulcer ≥3 mm		
Patients with ulcers	21	27
Life-table cumulative	5.8%	7.3%
Incidence (95% CI)	(3.4%–8.3%)	(4.6%–9.9%)
Ulcer ≥5 mm		
Patients with ulcers	15	18
Life-table cumulative	4.2%	4.9%
Incidence (95% CI)	(2.1%–6.3%)	(2.7%–7.1%)

Although the rate of gastroduodenal ulcers was numerically higher in the aspirin arm, the difference was substantially higher in the subgroup of patients who had a prior GI event (upper GI perforation, bleeding episode, or symptomatic ulcer).

Table 3. Selected Subgroup Analysis of 12-Week Incidences of Gastroduodenal Ulcers (Laine et al[5])

	Placebo	Aspirin 81mg
No prior GI event[a]	19/349 (5.4%)	19/357 (5.3%)
Prior GI event	2/32 (6.3%)	8/30 (26.7%)

[a] Upper GI perforation, bleeding episode, or symptomatic ulcer.

Although the denominators were small for subjects with prior GI events, the differences observed in this subgroup highlight that patients with a history of gastric ulcers are at increased risk due to NSAIDS, including low dose aspirin.This observation was also made in other treatment arms in this same subgroup (aspirin + rofecoxib and ibuprofen; not shown), an internal consistency that supports a higher risk of GD ulcers in patients with the defined prior GI events.

Data from Laine *et al* that stratifies the results presented in Table 2 by ulcer type, as well as changes from baseline of gastroduodenal erosions is presented in Table 4 & Table 5, respectively.

[5] LOREN LAINE, ERIC S. MALLER, CHANG YU, Ulcer Formation with Low-Dose Enteric-Coated Aspirin and the Effect of COX-2 Selective Inhibition: A Double-Blind Trial. GASTROENTEROLOGY 2004;127:395–402

Table 4. Rates of Gastric and Duodenal ulcers in Laine et al[5] in Placebo and ASA 81mg

	Placebo (N = 381)	Aspirin (N = 387)
Gastric ulcer		
Patients with ulcers	17	22
Life-table cumulative Incidence (95% CI)	4.7% (2.5%–6.9%)	5.9% (3.5%–8.4%)
Duodenal ulcer		
Patients with ulcers	4	7
Life-table cumulative Incidence (95% CI)	1.1% (0.0%–2.2%)	1.9% (0.5%–3.3%)

Table 5. Mean Changes[a] in Number of Gastroduodenal Erosions From Baseline to Week 12 in Laine et al[5] in Placebo and ASA 81mg

	Placebo (N = 381)	Aspirin (N = 387)
Baseline mean ± SD	0.54 ± 1.82	0.68 ± 2.02
12-wk mean ± SD	0.71 ± 2.42	1.44 ± 3.21
Least-squares mean change (95% CI)	0.17 (−0.14 to 0.48)	0.85[b] (0.55–1.16)

[a] Mean change adjusted for covariates including baseline erosions, GI history, treatment, and study site.
[b] p = 0.002 vs. placebo.

It should also be noted that the aspirin monograph contains a description of "GI side effects," and makes no distinctions of the risk of GI events across aspirin doses.

The risk of gastroduodenal injury due to aspirin therefore provides a rationale for combining a PPI with aspirin in a combination tablet. It should be noted that omeprazole (Prilosec) does not carry a gastric ulcer *prevention* claim, however it is indicated for short-term *treatment* of active benign gastric and duodenal ulcers in adults.

As described further in my review, there was extensive discussion regarding the most appropriate ASA dose to be approved for Yosprala among the DGIEP review team, consultants from the Division of Cardiovascular and Renal Drug Products (DCRP), ODEIII management and other senior representatives from the Office of New Drugs (OND). Because the applicant only provided clinical trial data to support efficacy of the ECASA325mg + omeprazole 40mg tablet, additional PK data were obtained (and literature reviewed) to support approval of the ECASA 81mg + omeprazole 40mg tablet, such that a Yosprala tablet containing ECASA 81mg could be made available and allow a treatment option in accordance with current clinical practice guidelines.

3. CMC / Device

General product quality considerations

Drug Substance: The CMC reviewer deemed the information on the drug substance submitted in the NDA to be adequate.

Drug Product: The tablets for both strengths consist of an aspirin core that is coated with (b) (4) film coat (b) (4) (see Figure 1).

Figure 1

Figure 1 Schematic of PA32540 and PA8140 Tablet (not to scale)

(b) (4)

PA32540 tablets were used in phase 1 and phase 3 studies. Except minor modifications, the formulation of PA32540 is the same for the phase 3 and the commercial product. (b) (4) PA8140 tablets were only used in phase 1 clinical studies. The formulation of PA8140 used in phase 1 study is different from the commercial formulation.

Impurities: (b) (4)

Stability: The stability batches of the drug products are identical to the proposed commercial drug products. For the PA32540 tablets, stability data obtained at the long term condition over 36 months and at accelerated condition over 6 months met the specification for the tablets stored in (b) (4) 30, 90 (b) (4) (b) (4) count high-density polyethylene (HDPE) bottles. CMC deemed the proposed expiration dating period of 36 months for the PA32540 tablet to be acceptable based on the real time stability data. However, based on the review of the stability data for the PA8140 tablet, only 24 months expiration dating period can be granted for the PA8140 tablets packaged in 30, 90 (b) (4) count HDPE bottles, (b) (4)

CMC requested revisions to the labeling during the review. The revised labeling/labels were deemed to be adequate from the CMC perspective.

Microbiology: The Microbial Limits specification for PA8140 and PA32540 was deemed acceptable from the Product Quality Microbiology perspective (review dated July 08, 2013). The applicant's response to 4 microbiology comments during the review was deemed adequate and the NDA was recommended for approval from the standpoint of product quality microbiology.

Facilities review / Inspection

On April 24th 2014, the Office of Compliance issued a ***"Withhold"*** recommendation for a (b) (4) (b) (4) manufacturing facility (where the aspirin component of the tablet is manufactured). However, the inspection did not close until (b) (4) At the time of finalization of this review Form 483 was not available and the applicant was not made aware of the CR deficiencies.

4. Nonclinical Pharmacology / Toxicology

The Applicant did not conduct new nonclinical study with PA Tablets. The Agency agreed in a July 9, 2007 Pre-IND meeting (minutes dated August 8, 2007) that the Applicant could file a 505(b)(2) application relying on the Agency's previous findings of safety and publicly available information on the toxicology of aspirin and omeprazole to support the 505(b)(2) application. The Applicant provided summaries of the relevant nonclinical information available for aspirin and omeprazole in the published literature.

The Nonclinical reviewer determined that the proposed acceptance criteria for the aspirin and omeprazole related impurities were acceptable and in accordance with ICH Q3B guidelines.

From a nonclinical perspective, this NDA was recommended for approval. Changes to the proposed label were recommended as per the recommendations of the Pediatric and Maternal Health Staff (PMHS) regarding results of juvenile animal toxicity studies (conducted under NDA 202342, esomeprazole strontium) that were incorporated into the omeprazole (Prilosec) label during the course of this NDA review.

5. Clinical Pharmacology / Biopharmaceutics

Clinical Pharmacology Review

The application was deemed acceptable from the clinical pharmacology perspective, "provided that a mutual agreement is reached on the labeling languages."

The sponsor conducted 6 PK studies, 1 PK/PD study, 5 PD (mucosal damage) studies, and 2 inhibition of platelet aggregations studies.

Because the clinical pharmacology review subdivides each review section into aspirin and omeprazole subsections, I've summarized her review findings similarly.

Aspirin

Two bioequivalence bridging studies have been conducted with proposed products (PA8140 and PA32540) with the respective strengths of the RLD, Ecotrin, to support for the efficacy of proposed products for the cardiovascular and cerebrovascular indications.

The bioequivalence of aspirin between the proposed products (PA32540 and PA8140) and the reference products (Ecotrin® 81 mg and 325 mg) were established based on bioequivalence of

acetylsalicylic acid as the primary analyte, as the cardio-protective activity of aspirin products is attributed to aspirin (acetylsalicylic acid) and not salicylic acid.

Mucosal Injury Study: Study PA325-102 was a phase 1, stratified, randomized, open-label, investigator-blinded, parallel group, single-center study in 80 healthy volunteers with 27 days of dosing to compare the gastroduodenal effects of a once daily dose of PA32520 tablet (delayed release aspirin 325 mg/ immediate release omeprazole 20 mg tablet) versus a once-daily dose of 81 mg EC aspirin (Bayer® EC aspirin 81 mg tablets) utilizing Lanza scores from endoscopy findings. Gastric pH was monitored at baseline, Day 14 and Day 28. The observed incidence of ulcers at Day 14 and Day 28 are presented in Table 6 and Table 7, respectively. Note that ulcers are observed in the EC 81mg arm, even within 14 days.

Table 6. Endoscopy Assessment, Presence of Ulcers at Day 14 Intent-to-Treat Population

	PA325 (N= 41)	EC Aspirin 81 mg (N= 39)	P-Value
Stomach or Duodenal Ulcer:			
No	40 (97.6%)	37 (94.9%)	
Yes	1 (2.4%)	2 (5.1%)	
Fishers Exact Test P-Value:			0.611
Stomach Ulcer:			
No	40 (97.6%)	38 (97.4%)	
Yes	1 (2.4%)	1 (2.6%)	
Fishers Exact Test P-Value:			1.000
Duodenal Ulcer:			
No	41 (100%)	38 (97.4%)	
Yes	0	1 (2.6%)	
Fishers Exact Test P-Value:			0.487

Source: Study PA325-102 Study Report, Table 14.2.4.1

Table 7. Endoscopy Assessment Presence of Ulcers at Day 28 Intent-to-Treat Population

	PA325 (N= 41)	EC Aspirin 81 mg (N= 39)	P-Value
Stomach or Duodenal Ulcer:			
No	39 (95.1%)	37 (94.9%)	
Yes	2 (4.9%)	2 (5.1%)	
Fishers Exact Test P-Value:			1.000
Stomach Ulcer:			
No	39 (95.1%)	38 (97.4%)	
Yes	2 (4.9%)	1 (2.6%)	
Fishers Exact Test P-Value:			1.000
Duodenal Ulcer:			
No	41 (100%)	38 (97.4%)	
Yes	0	1 (2.6%)	
Fishers Exact Test P-Value:			0.487

NOTE: Missing data at Day 28 have been imputed by carrying forward data from Day 14.

Source: Study PA325-102 Study Report, Table 14.2.4.2

Omeprazole

As summarized in the OCP review, plasma exposure, pH control and gastroduodenal mucosal protection data were the basis for selection of 40 mg IR-omeprazole as the lowest effective dose. The results of these studies are as follows:

1. Following 7 days of multiple dosing, 40 mg IR-omeprazole provides 24-hour pH control comparable to the pH control achieved with currently marketed EC-omeprazole 20 mg.
2. PK/PD analysis suggested that 20 mg IR-omeprazole would be sub-optimal for gastric mucosal protection relative to marketed EC products.
3. 40 mg IR-omeprazole produces approximately half the plasma omeprazole exposure of 40 mg EC-omeprazole following both single and multiple dosing. Following single and multiple dosing, the relative bioavailability (AUC) of omeprazole following IR formulation from PA32540 is about 51%-58% that of EC formulation from Prilosec® for the same dose amount of omeprazole (40 mg).
4. In phase 1 studies, 40 mg IR-omeprazole provides greater gastroduodenal mucosal protection compared 20 mg IR-omeprazole for aspirin 325 mg dose level. However, there was no dose ranging study conducted for 81 mg aspirin dose level.

Relative bioavailability of omeprazole from PA8140 compared to PA32540

Initially, the relative bioavailability of omeprazole following IR-omeprazole 40 mg from PA8140 administration compared to that of reference product Prilosec® 40 mg (EC formulation) or PA32540 was not evaluated in this NDA application. The applicant was asked to perform this study to demonstrate that the omeprazole 40mg IR in the PA8140 and PA32540 tablets had comparable bioavailability.

Study PA8140-103 was an open-label, randomized, single-center, multiple-dose, 2-way crossover PK study in 30 healthy subjects with 7-day treatment period to compare the relative bioavailability of omeprazole from PA8140 to that of PA32540.

The clinical pharmacology review made the following comments (section 2.4.4.) regarding study PA8140-103:

- Following 7 days of multiple dosing, omeprazole exposure (AUC) from PA8140 was slightly higher (27%) than that of PA32540, where the Cmax was very similar between PA8140 and PA32540.
- Multiple dose omeprazole PK of PA32540 following 7 days of dosing is consistent with the multiple dose omeprazole PK of PA32540 from study PA32540-112.
- PK and BE analysis were re-analyzed and results are consistent with sponsor's analysis

Combination Related Issues

DDI: As per the Clinical Pharmacology review, co-administration of aspirin and omeprazole does not affect each other's PK profiles regardless of omeprazole formulation (IR or EC) suggesting the absence of PK drug-drug interaction between aspirin and omeprazole components of PA32540.

Food Effects: Timing of food administration had significant effect on overall omeprazole exposure, but minimal effect on salicylic acid overall exposure

- When PA32540 was administered 60 minutes before breakfast, there was minimal effect of food on salicylic acid AUCs and C_{max}; a mild food effect was observed for omeprazole AUCs and C_{max} (about 15% reduction) relative to fasting conditions.
- When PA32540 was administered within 5 minutes after breakfast, there was a significant delay in the absorption of aspirin/salicylic acid (t_{max} was prolonged by about 10 hours), with minimal effect on salicylic acid AUCs and C_{max} (9% reduction in C_{max}); however, there was substantial reduction in omeprazole AUCs and C_{max} (about 67% and 84%, respectively) relative to fasting conditions.

Office of Clinical Pharmacology / DCP1 Review
Within the DCRP consult review (signed 01/16/2014) are incorporated review and comment by OCP/DCP1 regarding platelet aggregation studies evaluating an interaction with clopidogrel. Within the DGIEP consult request, they were asked to review two platelet aggregation studies, PA32540-110 and PA32540-111 and provide recommendations on whether or what information from these studies should be included in the label.

Clopidogrel is an inactive prodrug requiring metabolism by cytochrome P450 isozymes, importantly CYP2C19, to form its active metabolite. The active metabolite acts by irreversibly binding to the P2Y12 receptor of platelets thereby inhibiting platelet aggregation. Clopidogrel is often co-administered with PPIs. Some PPIs are inhibitors of CYP2C19. By inhibiting CYP2C19, PPIs may decrease the formation of the clopidogrel active metabolite, thereby attenuating the desired effect of inhibiting platelet aggregation.

Study PA32540-110 was a randomized, open-label, crossover study to evaluate the inhibitory effect of clopidogrel plus EC aspirin (325 mg) and clopidogrel plus PA32540 on platelet aggregation in healthy volunteers. Primary study objective was to compare inhibition of platelet aggregation induced by adenosine diphosphate (ADP) 20 μM between clopidogrel + EC aspirin 325 mg and clopidogrel + PA32540 treatment arms taken concomitantly and at least 10 hours apart.

DCP1 commented that platelet aggregation results following Day 1 in this study were not discussed in their review because the timing of study drugs may have resulted in incomplete CYP2C19 inhibition. They note that maximal inhibition effects following the first dose of clopidogrel can only be observed upon pre-treatment with omeprazole which is not how the study was designed. The reviewer also notes that the Division of Cardio-Renal Products has used 80-125% bioequivalence limits to the plasma exposure of clopidogrel active metabolite as the primary basis to address drug interactions between clopidogrel and PPIs (and not via platelet aggregation studies).

Study PA32540-111 was a randomized, open-label, crossover study to evaluate the inhibitory effect of clopidogrel, EC aspirin 81 mg and EC omeprazole 40 mg all dosed concomitantly and PA32540 and clopidogrel dosed separately on platelet aggregation in healthy volunteers.

The DCP1 reviewer noted again that drug interactions between clopidogrel and PPIs have been primarily addressed by pharmacokinetic results, i.e., exposure to the active metabolite of clopidogrel, with platelet inhibition data used as supportive evidence.

The DCP1 reviewer concluded that this study lacked an appropriate control arm since the comparison of importance is the platelet inhibitory effects of PA32540 + clopidogrel administered 10 h apart relative to EC aspirin + clopidogrel. However, based on the results from the previous study PA32540-110, the reviewer stated that, "we know that there is a decrease in mean IPA by approximately 10-14% when PA32540 is administered with clopidogrel separated by 10 h relative to clopidogrel + EC aspirin

325 mg. As the relationship between platelet inhibition and clinical outcomes is poorly understood, this interaction cannot be addressed in the absence of pharmacokinetic data."

Biopharmaceutics

From ONDQA-Biopharmaceutics perspective, the NDA was recommended for approval. The dissolution method was found acceptable; however the acceptance criteria for PA8140 and PA32540 Tablets are found acceptable "on an interim basis." ONDQA recommended at least 2 PMCs to further refine the acceptance criteria (see below).

The Biopharmaceutics made the following comments and observations in their review:

- (b) (4)
- The Applicant provided sufficient information to support the validity of the analytical methods for dissolution testing of the aspirin and omeprazole components of the proposed product.
- The Applicant compared omeprazole release from PA8140 and PA32540 strengths (b) (4)

(b) (4)

- Some of the dissolution acceptance criteria for both PA32540 and PA8140 tablets were deemed to be acceptable "on an interim basis only" (b) (4) Biopharmaceutics therefore had recommended the following PMCs (prior to determination of a Complete Response very late in the review cycle):

(b) (4)

(b) (4)

- The Biopharmaceutics reviewer commented that there are major compositional differences between the phase 1 (BE study for aspirin) and Primary Stability batch for PA 8140. Initial phase 1 studies were conducted to evaluate gastroduodenal mucosal damage of PA32540, however major formulation changes were implemented to this formulation (b) (4) and therefore the Applicant conducted another clinical study (PA325-106) with a formulation called Phase 1 formulation. Furthermore, the applicant changed the manufacturer of Phase 1 formulation and implemented minor changes to the Phase 1 formulation. The majority of the clinical development was conducted with the Phase 3 / BE formulation. There is a formulation change (b) (4) implemented for Phase 3 and BE batches, however this change was considered minor by the ONDQA-CMC review team.
- The applicant provided the f2 values comparing the dissolution profiles of aspirin and omeprazole for the Phase 3, BE and the To-Be-Marketed Formulation of PA 32540.
- As shown from the omeprazole release profiles and the f2 similarity factors, omeprazole release is similar between the phase 3 studies and the to-be-marketed formulations.

In addition, *in vitro* "dose dumping" of aspirin at 40% alcohol levels was observed for both PA8140 and PA32540. Clinically, this effect could reduce the delayed release of aspirin in Yosprala, presumably when undiluted distilled liquor is consumed. However, since aspirin does not require an "enteric coating" or delayed release to be made bioavailable and exert its antiplatelet effect, loss of the release properties is not expected to result in a clinically meaningful reduction of efficacy for the aspirin component. Further, the aspirin monograph doesn't discriminate between delayed or immediate release with regard to efficacy. In addition, the proposed Yosprala label already contains a warning about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin. Therefore, these findings do not in my view warrant inclusion in the label, should this NDA be approved.

6. Clinical Microbiology

Not applicable to this review.

7. Clinical / Statistical - Efficacy

Dr. Zana Marks was the DGIEP medical officer who provided a review of the efficacy of Yosprala in preventing gastric ulcers and other secondary endpoints. The efficacy of omeprazole (Prilosec) in *preventing* gastric ulcers in the same at-risk population that was studied in the Yosprala trials had not been previously established; however Prilosec is indicated for (short-term) treatment of active gastric and duodenal ulcers. Dr. Mark's review focused primarily on evaluating the efficacy of Yosprala's proposed GI claims.

With regards to ASA, the applicant relied on the previous findings of efficacy for cardioprotection as described in the ASA monograph (21 CFR 343.80). The Division of Cardiovascular and Renal Drug

Products was consulted to provide input on the acceptability of the proposed dose of ASA within Yosprala (325mg and 81mg) and to review the clinical studies with regards to cardiovascular safety.

The discussion in this section is separated into two subsections, Prevention of Gastric Ulcers and Appropriateness of Proposed ASA Doses

7.1 Prevention of Gastric Ulcers

Refer to the clinical review by Dr. Zana Marks (signed 03/21/2014) for a detailed description of the clinical development program and regulatory history.

Two adequate and well-controlled trials, PA32540-301 and PA32540-302, were conducted to demonstrate the efficacy of the IR omeprazole 40 mg component of PA32540 in reducing gastric ulcer incidence (primary endpoint) compared to EC-aspirin 325 mg daily for 6 months. Study PA32540-303 was an open-label, one-year study of PA32540 in subjects with either a recent history of documented gastric or duodenal ulcer or who were over 55 years of age and expected to require daily aspirin therapy for at least 12 months.

The sponsor conducted a number of early phase studies supporting the potential benefit of IR-omeprazole 40 mg for protection against EC-aspirin 81 mg associated UGI mucosal damage. Refer to the clinical review for an overview of these studies.

Design of Efficacy Trials

Key elements of PA32540-301 and PA32540- 302 are described in this section.

Studies PA32540-301 and PA32540-302 were designed to enroll a population of subjects at risk for cardiovascular events that required daily use of aspirin and who were at risk of GI toxicity from the use of chronic aspirin. The diagnoses required for entry into the study included subjects with established cardiovascular disease (Table 8) and were taking daily aspirin 325 mg for 3 months and would require the use of daily aspirin 325 mg for the study period of 6 months.

Table 8. Conditions Required for Inclusion in Studies PA32540-301 and PA32540-302

Cardiac or cerebrovascular ischemic events:	• Confirmed or Suspected Myocardial Infarction • Ischemic Stroke • Transient Ischemic Attack
OR have Established coronary or vascular disease at high risk for surgical intervention or for major event if left untreated:	• Angina (Stable or Unstable) • Peripheral Arterial Disease • Aortic Atherosclerotic Disease • Carotid Artery Disease
OR History of a revascularization Procedure:	• Coronary Artery Bypass Grafting • Percutaneous Coronary Intervention with or without stent • Carotid Endarterectomy

Source: Applicant, Integrated Summary of Efficacy, Table 3, Section 2.3.5, page 29

These studies included subjects who were at risk for aspirin-associated gastric ulcer. Specifically, the inclusion criteria required that subjects be 55 years or older, if less than 55 years must have history of a documented, uncomplicated, gastric or duodenal ulcer within 5 years of the study enrollment. However, those with an active ulcer (≥ 3 mm diameter with depth) at screening were to be excluded. In addition, subjects who were *H. pylori* positive were excluded.

It should be noted that there is an error in the description of eligibility criteria within the initial clinical review dated 03/21/2014 (DARRTS Reference ID: 3475586), which prompted an addendum (signed 4/4/2014).

In both trials, subjects were randomized to either PA32540 or EC-aspirin 325 mg in 1:1 ratio and were stratified into three groups: 1) COX-2 users; 2) non-selective non-steroidal anti-inflammatory drug (NSAID) users; and, 3) use of neither. The comparator tablet of EC-aspirin 325 mg was formulated to be indistinguishable from PA32540 Tablets in size, shape, and color.

Study medication was taken in the morning, approximately 1 hour prior to the first meal of the day. NSAIDs were taken at least 2.5 hours after PA32540 or EC-aspirin. Subjects returned to the clinical research unit 1 month (Visit 4), 3 months (Visit 5), and 6 months (Final Visit) after the initiation of study drug for endoscopies, heartburn assessments, and safety assessments. Interim endoscopies were performed if clinically indicated. If a gastric, duodenal or esophageal ulcer was detected at Visits 4 or 5 or at any time during the trial, study drug was discontinued, and the subject was withdrawn from the study and placed on appropriate ulcer treatment.

In between clinic visits, subjects were contacted monthly by telephone. During each clinic visit and telephone interview, adverse events and concomitant medication use (including NSAID use) were assessed. Subjects were considered to have completed the study if they completed 6 months of treatment and had a 6-month endoscopy, or if the primary endpoint (gastric ulcer confirmed by endoscopy) had been reached prior to 6 months.

The primary efficacy endpoint was the cumulative incidence of gastric ulcers over six months of treatment. Assessment of the primary endpoint (gastric ulcers) was performed by endoscopists who were blinded to study drug and used a standard definition for ulcers, at least 3 mm in diameter with depth.

As noted by Dr. Mark's review with regards to the primary endpoint,

> "This endpoint has been used for assessment of UGI injury associated with the use of non-steroidal anti-inflammatory agents and aspirin, and is believed to have a strong correlation with the incidence of UGI complications (GI bleeding, perforations and obstruction) A recently approved combination product VIMOVO® (naproxen and esomeprazole magnesium) delayed release tablets 375mg/20mg (NDA 22511 approve April 30, 2010) used this ulcer definition as the primary endpoint."

The ordered key secondary efficacy and tolerability endpoint assessments included[6]:

[6] 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 gastric and/or duodenal ulcer;
2. The proportion of subjects with "Treatment Success", defined as those subjects without gastric ulcers and without pre-specified UGI AEs leading to discontinuation;
3. The proportion of subjects discontinuing the study due to pre-specified UGI AEs;
4. The proportion of subjects with heartburn resolution.

1. The cumulative incidence of gastric and/or duodenal ulcers at any time throughout the six months of treatment. A duodenal ulcer (DU) was defined as a mucosal break of at least 3 mm in diameter with depth. Duodenal ulcers were captured on the endoscopy electronic case report form, but were also considered adverse events.
2. Proportion of subjects with "Treatment Success", defined as those subjects without gastric ulcers and without pre-specified UGI AEs (determined prior to database lock and specified in the PA32540-301 and PA32540-302 SAP) leading to discontinuation.
3. The incidence of subjects discontinuing the study due to pre-specified UGI AEs at any time throughout 6 months of treatment,
4. Incidence of subjects with "Heartburn Resolution", defined as the answer "None" at the post-baseline heartburn symptom assessments.

[Reviewer comment: The "heartburn Resolution" endpoint is further described in the Study Report as "The proportion of subjects who had no heartburn at Months 1, 3, and 6 (regardless of the presence or absence of heartburn at baseline.]

The intent-to-treat (ITT) population consisted of all randomized subjects. Subjects who terminated early without a final endoscopic assessment were considered as ***not*** having an ulcer for the ITT analyses. The statistical team leader makes the following comment on this in her review:

> "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)."

Study Results

Refer to the clinical review for a detailed overview of the demographics and disposition of subjects. Across both studies, the demography of the analysis populations was balanced between the treatment groups. Subjects were predominantly white (non-hispanic) males.

In both studies combined, approximately 5% of those assigned to the PA32540 treatment group and 7% of those subjects assigned to the EC-aspirin 325 mg treatment group had experienced a gastric or duodenal ulcer within 5 years of study start, however, approximately 10% of the EC-aspirin 325 mg and 9% of PA32540 had reported a gastric or duodenal ulcer at any time in the past. Concomitant NSAID use was reported as 9.3% and 9.6% by the PA32540 treatment group and the EC-aspirin 325 mg, respectively.

The medical histories of the treatment groups were balanced and consistent with the population under study and the prior cardiovascular medical histories were also balanced in the ITT population.

In PA32540-301, 82% of subjects assigned to PA32540 completed the study compared to 75% of those subjects assigned to EC-aspirin 325 mg. Similarly, in PA32540-302, 80% of subjects assigned to PA32540 completed the study compared to 76% of those subjects assigned to EC-aspirin 325 mg. As noted by the statistical reviewer, subjects with duodenal or

esophageal ulcers detected at any time during study drug treatment were not considered completers.

In PA32540-301 adverse events (AEs) were the reason for discontinuation in 7% of those assigned to PA32540 and 13% of those subjects assigned to EC-aspirin 325 mg. In PA32540-302 AEs were the reasons for discontinuation in 7% of those assigned to PA32540 and 10% of those subjects assigned to EC-aspirin 325 mg.

As noted by Dr. Marks in her review, in the combined population, more subjects "who took ECASA 325 mg discontinued due to pre-specified upper GI adverse events (16.8%) than those subjects who took PA32540 (4.8%). This was primarily due to discontinuation from gastric ulcer, dyspepsia, and duodenal ulcer."

The efficacy results from each study are presented in Table 9.

Table 9. Primary and Secondary Endpoints

	PA32540-301			PA32540-302		
Endpoint	**PA32540 n = 265**	**EC-Aspirin 325 mg n = 265**	**p-value[1]**	**PA32540 n = 259**	**EC-Aspirin 325 mg n = 260**	**p-value[1]**
Primary Endpoint						
Gastric Ulcer at 6 months	10 (3.8%)	23 (8.7%)	0.020	7 (2.7%)	22 (8.5%)	0.005
Secondary Endpoints						
Gastric and/or Duodenal Ulcers at 6 months	11 (4.2%)	31(11.7%)	0.002	7 (2.7%)	30 (11.5%)	<0.001
Treatment Success [2]	249 (94.0%)	220 (83.0%)	<0.001	250 (96.5%)	217 (83.5%)	<0.001
Discontinuation Due to UGI Events	6 (2.3%)	22(8.3%)	0.002	2 (0.8%)	21 (8.1%)	<0.001
Heartburn Resolution	198/214 (92.5%)	135/188 (71.8%)	<0.001	200/215 (93.0%)	152/190 (80.0%)	<0.001

[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] 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.

In study PA32540-301 the cumulative GU rates at 1 month were 1.1% vs. 3.8% in the PA32540 arm vs. ECASA 325mg arm, respectively. At 3 months the GU rates were 3.0% and 6.8%, respectively. In study PA32540-302 the cumulative GU rates at 1 month were 0.4% vs. 3.1% in the PA32540 arm vs. ECASA 325mg arm, respectively. At 3 months the GU rates were 0.4% and 6.5%, respectively. Because the statistical analyses did not adjust for multiplicity, I do not present p-values across all timepoints; however they are summarized in the clinical review.

However the term "heartburn resolution" is misleading and not strictly supported by the analysis, since the vast majority of subjects reported no heartburn at baseline (70% in Study PA32540-301 and 67% in Study PA32540-302). A subgroup analysis in those subjects who reported heartburn at baseline was not prespecified (b) (4)

In addition, there was discussion late in the review cycle regarding whether the endpoint "discontinued due to UGI events" was fully interpretable. The sponsor had prespecified 41 aspirin-associated UGI Adverse Events (see Table 10) but for the analysis of this endpoint only counted those events that resulted in discontinuation of treatment.

Table 10. Pre-Specified Aspirin-Associated UGI Adverse Events

Preferred Term	
abdominal discomfort	gastritis haemorrhagic
abdominal pain	gastroduodenitis
abdominal pain upper	gastrointestinal erosion
abdominal tenderness	gastrointestinal haemorrhage
duodenal haemorrhage	gastrointestinal inflammation
duodenal ulcer	gastrointestinal mucosal disorder
duodenal ulcer haemorrhage	gastrooesophageal reflux disease (GORD)
duodenitis	gastrooesophagitis
duodenitis haemorrhagic	haematemesis
dyspepsia	haematochezia
eosinophilic oesophagitis	hyperchlorhydria
epigastric discomfort	melaena
erosive duodenitis	nausea
erosive gastritis	oesophageal discomfort
erosive oesophagitis	oesophageal disorder
gastric haemorrhage	oesophageal haemorrhage
gastric mucosal lesion	oesophageal ulcer
gastric ulcer haemorrhage	oesophagitis
gastritis	reflux oesophagitis
gastritis atrophic	vomiting
gastritis erosive	

Source: Applicant, Clinical Study Report - PA32540-301, Table 4

Therefore, although AEs of gastric hemorrhage, gastric ulcer hemorrhage, and melena were reported (and as in the listing above) they were not counted for this analysis because they did not result in discontinuation. This raised some concerns about the interpretability of this secondary endpoint in light of the fact that it includes the (likely biased) determination by the investigator regarding whether or not the subject should be discontinued after having the reported AE. Labeling negotiations regarding this issue were ongoing at the time of finalization of my review.

Statistical Considerations

There were two statistical reviews submitted for this NDA, one from Milton C. Fan (primary reviewer) and Freda Cooner (the concurring reviewer) as well a separate review from Freda Cooner as the statistical Team Lead.

As noted by the primary statistical reviewer, in both studies the incidence of gastric ulcers were consistently lower (between ~5-8%) across all three sensitivity analyses[7] (analyses based on FDA Advice Letter dated Nov. 29, 2011) in the PA32540 group than in the EC aspirin 325 mg group. Although the treatment difference between treatment groups in the worst case analysis failed to achieve statistical significance, as noted by the primary statistical reviewer, the consistently lower absolute incidence of gastric ulcers with PA32540 observed in all 3 sensitivity analyses support the primary positive outcome of these studies.

In Study PA32540-301, results of subgroup analyses on the primary endpoint, outcomes were generally favorable for PA32540 in all subgroups, with the exception of Ulcer History = "yes." This finding was not replicated in the same subgroup in Study PA32540-302.

The statistical reviewer requested the applicant perform the following additional sensitivity analyses for primary efficacy endpoint for both studies:

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

In both studies, the observed-case analysis was still statistically significant; however the worst-case analyses were not. As noted by the statistical team leader, the results of these analyses, including the p-values, are exploratory only. With regard to Worst-case scenario #2 (above) the applicant explains this finding by noting that the most common reason for missing observations (endoscopies) was adverse events and subject withdrawal of consent. As noted previously, the prespecified plan was to count subjects with missing endoscopies as not having an ulcer (a conservative approach as noted by the statistical team leader) and therefore the clinical significance of this worst-case sensitivity analysis appears unclear. The statistical Team Leader notes in her review that "The statistical significance of the results should also be viewed with caution due to their exploratory nature." The primary statistical reviewer concludes that despite the worst-case analyses, 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.

The statistical Team Leader concludes the following in her review: "In summary, the two phase 3 studies (PA32540-301 and PA32540-302) showed statistically significant benefit of

[7] "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 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."

7.2 Appropriateness of Proposed ASA Doses

DCRP was consulted to provide input on two questions relevant to the efficacy of ASA in Yosprala. These were related to 1) whether the 10-15% lower exposure to aspirin for PA32540 tablets compared to Ecotrin® 325 mg is clinically meaningful and 2) to address the applicant's statement that "the relevant antithrombotic effects of aspirin have been demonstrated to occur over the dose range of 50-325mg, this observed small difference in acetylsalicylic acid exposure is not clinically meaningful."

The DCRP review provides an overview of literature and concludes that a "… 10-15% lower exposure to aspirin for PA32540 tablets compared to Ecotrin® 325 mg is not clinically meaningful as this change in aspirin plasma exposures at 325 mg does not affect platelet inhibition."

However, the consult review further questioned "whether anyone 'needs' high dose [325mg] maintenance aspirin, as was tested in this development program, for the secondary prophylaxis if CV events."

The DCRP consult review provides a thorough overview of published studies and current cardiovascular clinical practice guidelines. These data sources do appear to support DCRP's assertion that there is no clear advantage of high dose (i.e., 325mg vs. ≤100mg) aspirin for secondary cardioprotection.

DCRP makes the following summary conclusions in their review regarding the appropriateness of 325mg ASA for CV protection:

- *While there appears to be no incremental benefit in chronic administration of doses of ASA above 100 mg, it is generally accepted that there is a dose-related increase in bleeding – particularly gastrointestinal bleeding (nominally significant increase in GI bleeding demonstrated in both CURE and OASIS-7)*
- *The data about the relationship between aspirin dose and bleeding are persuasive despite essentially all of it coming from subjects who have not been randomized to the dose of aspirin (OASIS-7 randomized the aspirin dose)*
- *Finally, it should be noted that the patients for whom Pozen's ASA+omeprazole will be indicated is a subpopulation at higher risk for adverse gastrointestinal events than the population for whom ASA is indicated in the professional label, 21CFR 341.80. The draft label submitted by Pozen states its product is: "indicated for patients who require aspirin …* (b) (4) *in patients at risk for developing aspirin-associated gastric ulcers." Furthermore, not all patients on ASA for prevention of CV disease were eligible to enroll in the two pivotal trials but rather the eligibility*

criteria allowed enrollment only of a subpopulation at higher risk of gastric ulcers.

- *Given the lack of a dose-related increase in efficacy and a dose-related increase in harm, it seems to us that patients at sufficient risk for gastric ulceration to require chronic administration of a PPI should not be administered 325 mg of aspirin.*

DCRP's position regarding the most appropriate ASA dose is therefore discordant with the ASA Professional Labeling in 21 CFR 343.80, which recommends a dosage range that includes ASA 325mg. This issue was discussed between the review team and various representatives from the Office of New Drugs, ODEI, DCRP and ODE III. Although DCRP made a case for not approving a 325mg ASA dose, the current Professional Labeling for ASA still recommends this dose. In additional the applicant provided data that demonstrated that ASA 325mg is still prescribed for secondary cardioprotection. As a result of these discussions it was accepted by the review team that there were insufficient criteria to issue a Complete Response to the application because of the aspirin dose alone. However, the review team did feel that having a Yosprala tablet containing ASA 81mg + omeprazole 40mg available (in addition to a 325/40 tablet) would be a more optimal situation for patients and practitioners, as well as allow alignment with clinical practice guidelines where relevant.

(See the Clinical Pharmacology review for a detailed description of the PK data that was needed and obtained to support approval of the Yosprala 81/40 tablet.)

8. Safety

A total of 1221 subjects were exposed to PA32540 in the development program. Fifty-nine (59) of these subjects took PA32540 in combination with clopidogrel and 30 in combination with celecoxib. An additional 81 were exposed to PA32520 and 86 were exposed to PA8140. Another 803 subjects were exposed to EC-aspirin 325mg and 126 received EC-aspirin 81 mg.

In short (less than one month) phase 1 studies, 321 subjects were exposed to PA32540. These studies provide information on the effects of the study drugs on mucosal damage, pH, and drug-drug interactions. Some of these studies have been described previously in my review.

The long-term exposure occurred in the adequate and well-controlled trials PA32540-301 and PA32540-302 that exposed 521 subjects to PA32540 and 524 subjects to EC-aspirin 325mg up to 6 months each, and the open-label long-term safety study PA32540-303, which exposed 379 subjects to PA32540 for up to one year.

The applicant has defined 4 major safety populations:

1. Primary Safety Population (PSP)
    - The PSP consists of all subjects randomized in Studies PA32540-301 and PA32540-302. These studies enrolled identical populations treated with PA32540 or EC-aspirin 325 mg daily for 6 months
2. Long-term Safety Population (LSP)

- The LSP consists of all subjects who entered study PA32540-303 and received at least one dose of PA32540 drug in study PA32540-303.

3. Twelve-Month Population (TMP)
   - Twelve-Month Population (TMP) consists of subjects from study PA32540-303 that completed at least 348 days of treatment with PA32540.
4. Six- Month Population (SMP)
   - The SMP consists of subjects from studies PA32540-301, PA32540-302 and PA32540-303 who were on treatment at least 168 days.

In my review, primarily the results from the PSP and LSP groups are presented.

Subject dispositions across the safety populations are presented in Table 11.

Table 11. Subject Accountability and Disposition of Subjects in Study PA32540-303

	Enrolled n(%) (N=380)
Long-term Safety Population (LSP)	379 (99.7)
Six Month Population (SMP)[1]	323 (85.0)
Twelve Month Population (TMP)[2]	290 (76.3)
Completed Study	292 (76.8)
Premature Discontinuations	88 (23.2)
Reasons for Discontinuation:	
Adverse Event	51 (13.4)
Withdrew Consent	7 (1.8)
Lost to Follow up	2 (0.5)
Other	28 (7.4)

[1] Population (SMP): Includes subjects who were on study drug at least 168 days.
[2] Population (TMP): Includes subjects on study drug at least 348 days.
Source: Applicant, Table 9, page 61

Extent of exposures across safety populations within Study PA32540-303 are presented in Table 12.

Table 12. Exposure to Study Drug in the Long-Term Safety Population and the Twelve-Month Population

	Long-term Safety Population n(%) (N=379)	Twelve Month Population n(%) (N=290)
Days from First Dose to Last Dose[1]:		
N	379	290
Mean (std)	309.6 (108.4)	361.6 (7.5)
Median	358.0	361.0
Min, Max	1.0, 400.0	348.0, 400.0
Duration of Treatment (Days) [1]		
1 – 30	17 (4.5)	0
31 – 90	21 (5.5)	0
91 – 180	22 (5.8)	0
181 – 270	14 (3.7)	0
>270	305 (80.5)	290 (100)
Number of Doses per Subject		
N	379	290
Mean (std)	304.8 (108.9)	356.3 (21.1)
Median	354.0	357.0
Min, Max	1.0, 432.0	211.0, 432.0
Average Doses per Month		
N	379	290
Mean (std)	29.4 (2.2)	29.6 (1.7)
Median	29.8	29.8
Min, Max	16.0, 39.6	17.2, 36.7

[1] If the treatment duration and/or the number of doses taken were unknown, imputation rules defined in the statistical analysis plan were applied.

Source: Applicant, ISS, Table 22, Page 64

General AEs

Adverse event listings are presented in the Appendices. See Table 18, Table 19 & Table 20 for AEs across Studies PA325-401, PA32540-302 and PA32540-303, respectively.

In general, there were fewer observations of gastrointestinal damage in the PA32540 treatment group than in the EC-aspirin 325 mg group in both of the adequate and well controlled studies, and in long term open label study.

As expected there was a higher rate of esophagitis, gastritis, duodenitis and other GI related symptomatology in the ECASA arm compared to PA32540. The clinical reviewer did not identify other new safety concerns upon review of the application.

Serious Adverse Events (SAEs)

As noted by Dr. Marks, the rates of SAEs were similar between the treatment groups in the Primary Safety Population (7.5% of subjects taking PA32540 and 7.8% of subjects taking ECASA 325 mg). No specific or new serious safety concern was raised during the review of the observed data. See Table 13 for a description of GI bleeds considered to be SAEs.

Discontinuations Due to AEs

As discussed in Dr. Mark's review, in both of the studies 52 subjects (10.0%) in the combined analysis who took PA32540 discontinued participation compared to 104 (19.8%) subjects discontinued who took ECASA 325 mg. Dr. Marks noted that difference was primarily due to increased reporting of preferred terms in the SOC of Gastrointestinal Disorders in subjects who took ECASA 325 mg and included increases in discontinuations for gastric ulcer, dyspepsia, and duodenal ulcer.

Deaths

Dr. Marks states in her review that there were 6 deaths reported in any of the studies that comprise this application.

Three subjects who took PA32540 died during the study:

- Subject 302-499/3015 was an 87-year old Hispanic female who died of a cerebrovascular accident on day 149 of the study
- Subject 302-572/4254 was a 66-year old white male who had a cardiac arrest after being struck by an automobile
- Subject 303-612/5232 was a 60-year old white male with a cerebrovascular accident with infarction.

Two subjects who took EC-aspirin 325 mg died during the study:

- Subject 301-887/2639 sustained a cardiac arrest after bouts of angina
- Subject 302-876/4580 died of renal cancer.

Additionally, the sponsor was made aware of one post-study death from Study PA32540-303 that occurred 75 days after the subject took her last dose of study drug (pancreatic cancer).

Adjudication of Major Adverse Gastrointestinal Events (MAGIEs)

An independent Gastrointestinal Clinical Event Committee (GICEC) performed a blinded review and adjudication of potential clinically significant major adverse gastrointestinal events (MAGIEs). The GICEC consisted of 5 board certified gastroenterologists who had staff level experience or privileges as a gastroenterologist at a medical institution (or had

obtained equivalent eligibility in their country or region). These were classified as the following:

- Bleeding of gastroduodenal origin
- Overt UGI bleeding
- Presumed upper gastrointestinal bleeding of unknown location:
- Occult gastrointestinal bleeding
- Symptomatic gastroduodenal ulcer
- Persistent pain of presumed gastrointestinal origin with underlying multiple erosive disease
- Obstruction
- Perforation

There were 3 subjects in the adequate and well controlled studies with adjudicated MAGIE. There was 1 adjudicated MAGIE in each treatment group consistent with bleeding of gastroduodenal ulcers. One subject in the PA32540 group experienced an obstruction in the small bowel.

There was only 1 preferred term consistent with GI haemorrhage in the open-label study. One subject experienced a non-TEAE MAGIE of occult bleeding of unknown GI origin.

In addition, I went through the AE data tables in the Study Reports for PA32540-301 and -302 and tabulated the following AEs that appeared to be consistent with or related to GI bleeds:

Table 13. Adverse Events in Controlled Trials Consistent with GI Bleed

System Organ Class / Preferred Term	PA32540	ECASA 325
Study PA32540-301	**3/264 (1%)**	**9/265 (3%)**
Gastric hemorrhage	1 (0.4%)	3 (1.1%)
Gastric ulcer haemorrhage†	1 (0.4%)	0
Hematochezia	1 (0.4%)	0
Duodenal ulcer hemorrhage†	0	1 (0.4%)
Gastritis hemorrhagic	0	1 (0.4%)
Intestinal haemorrhage†	0	1 (0.4%)
Melena	0	1 (0.4%)
Rectal haemorrhage	0	2 (0.8%)
Study PA32540-302	**1/257 (0.4%)**	**1/259 (0.3%)**
Gastric hemorrhage	0	1 (0.3%)
Large intestinal haemorrhage†	1 (0.4%)	0

† Serious Adverse Event
Source: Applicant, the Study Reports for PA32540-301 and -302, Table 14.3.1.1

The data in Table 13 speak to the fact that PPIs do not completely eliminate the risk of GI bleeds from aspirin, either from the upper GI tract or elsewhere.

Adjudication of Major Adverse Cardiovascular Events (MACE)

An independent Cardiovascular Review Committee (CRC), consisting of 3 board certified cardiologists, performed a blinded review and adjudication of major adverse cardiovascular events (MACE).

521 subjects on PA32540 treatment in studies PA32540-301 and PA32540-302 reported 9 events that were adjudicated as MACE and 524 subjects on EC-aspirin 325 mg treatment, reported 14 events (13subjects) that were adjudicated as MACE (1.7% and 2.5%, respectively).

Table 14 presents all subjects from the two adequate and well controlled studies that were identified with events adjudicated as MACE.

Table 14. Adjudicated Major Cardiovascular Adverse Events in Primary Safety Population (PSP)

MACE Category	Adverse Event Preferred Term
PA32540	
CAD	Non-Cardiac Chest Pain
Non fatal MI	Myocardial Infarction
Non fatal MI	Myocardial Infarction
Non fatal MI	Acute Myocardial Infarction
Non fatal MI	Acute Myocardial Infarction
Non fatal MI	Acute Myocardial Infarction
Planned Coronary Artery Bypass Graft	Arteriosclerosis Coronary Artery
TIA	Reversible Ischaemic Neurological Deficit
Heart Failure	Cardiac Failure Congestive
EC-aspirin 325 mg	
Non fatal MI	Acute Myocardial Infarction
Non fatal MI	Acute Myocardial Infarction
Non fatal MI	Acute Myocardial Infarction
ACS	Coronary Artery Occlusion
ACS	Angina Pectoris
ACS	Angina Pectoris
TIA	Transient Ishchaemic Attack
TIA	Transient Ishchaemic Attack
CV Death	Sudden Cardiac Death
ACS	Coronary Artery Disease
ACS	Angina Pectoris
TIA	Transient Ishchaemic Attack
TIA	Reversible Ischaemic Neurological Deficit
Heart Failure	Cardiac Failure Congestive

Source: Applicant, ISS, Table 55, page 128

A total of 16 adjudicated MACE were identified in subjects who entered PA32540-303 based on a review of SAE and AEs reported by investigators over 12 months in 379 subjects (4.2%).

Table 15. Adjudicated MACE in Subjects Who Entered PA32540-303

MACE	Adverse Event Preferred Term
CV death-stroke	Cerebral Infarction
Non-fatal MI	Angina Pectoris
Non-fatal MI	Myocardial Infarction
Non-fatal MI	Coronary Artery Disease
Non-fatal MI	Myocardial Infarction
Non-fatal MI	Myocardial Infarction
ACS	Angina Unstable
ACS	Angina Pectoris
ACS	Cardiac Failure Congestive
Ischemic Stroke	Thalamic Infarction
Heart Failure	Angina Unstable
Unplanned PCI	Angina Unstable
Unplanned PCI	Myocardial Ischemia
Heart Failure	Cardiac Failure Congestive
Other CV Event	Carotid Artery Stenosis
Unplanned CABG	Coronary Artery Disease

Source: Applicant, ISS, Table 58, page 131

Impact of Clopidogrel Use

Subjects who took PA32540 or EC-aspirin 325 mg and did not take clopidogrel had less than 1% rate of MACE (1 event in 404 subjects and 4 in 409, respectively). Subjects who took PA32540 and clopidogrel had an incidence of MACE of 3.4% (4 events in 117 subjects). See Table 16 for a presentation of MACE events stratified by clopidogrel use.

Table 16. Proportion of Subjects with Pre-Specified Major Cardiovascular Adverse Events by Concomitant Use of Clopidogrel in the Primary Safety Population from Studies PA32540-301 and PA32540-302

	Clopidogrel Use = Yes[1]				Clopidogrel Use = No	
	PA32540 n(%) (N=117)		EC-Aspirin 325 mg n(%) (N=115)		PA32540 n(%) (N=404)	EC-Aspirin 325 mg n(%) (N=409)
	Any Time	Within 7 Days	Any Time	Within 7 Days		
Subjects with Any Major CV AE	4 (3.4)	4 (3.4)	0	0	1 (0.2)	4 (1.0)
Non-Fatal Stroke	0	0	0	0	0	0
Non-Fatal Myocardial Infarction	4 (3.4)	4 (3.4)	0	0	1 (0.2)	3 (0.7)
CV Death	0	0	0	0	1 (0.2)	1 (0.2)

[1]'Any Time' columns include subjects on clopidogrel at any time during the treatment period. 'Within 7 Days' columns include only MACE Adverse Events that occurred following at least 7 consecutive days of clopidogrel use.
Source: Applicant, ISS, Table 56, page 129

The use of clopidogrel during treatment occurred in 71 (18.7%) subjects in the LSP. MACE were analyzed based on clopidogrel use (PA32540-303). For this analysis, clopidogrel use was defined as subjects on clopidogrel at least 7 consecutive days prior to the MACE. Five (5) subjects experienced MACE consistent with CV death, non-fatal MI and non-fatal stroke. Of these, 3 subjects did not take clopidogrel and 2 subjects did take clopidogrel. Of those subjects with MACE not on clopidogrel (n=3), 2 subjects did not take clopidogrel at any time during treatment and 1 subject was started on clopidogrel after the MACE.

DCRP Consult Review

The DCRP Consult review made the following Conclusions to our Consult Question:

Q.1 Applicant has provided an Integrated Summary of Safety of data from Studies 301 and 302 that includes an analysis of Cardiovascular Events of Special Interest (Section 2.4.2). MACE were observed in both studies and applicant also provides an analysis of MACE in patients who received clopidogrel concomitantly. Do the adjudicated and unadjudicated analyses presented by the sponsor, including the analysis of MACE in subjects who took clopidogrel, warrant inclusion in the label? Do these analyses suggest a new safety concern?

DCRP Conclusions for Question 1:

- *"The number of events is too small and the duration of exposure too short to draw reliable conclusions about cardiac safety. Rather than including Table 59 [Table 16 in my CDTL review] above that demonstrates these small numbers (with more unadjudicated MACE events and fewer adjudicated MACE events with this drug), we suggest including a statement that simply states that the number of adjudicated MACE events was similar between the groups, but number of events is too small and the duration of exposure too short to draw reliable conclusions about cardiac safety.*

- *Even in this small dataset, all MACE events in clopidogrel-treated patients occurred in the group receiving omeprazole (as PA32540). Given the well-known interaction between clopidogrel and omeprazole, the label for PA32540, if approved, should reflect the warning regarding clopidogrel and omeprazole as is currently included in the omeprazole label."*

Although the DGIEP consult request asked DCRP whether any of the MACE data should be included in the label, in my view it probably isn't warranted since there doesn't appear to be specific new safety concerns raised within the DCRP review. In addition, the omeprazole interaction with clopidogrel is well known and will be described within the label regardless (including in the clopidogrel and Prilosec labels). Although there are small numerical imbalances between the clopidogrel use subgroups with respect to MACE, it does not to me suggest a signal of concern; the label will contain suitable warning about concomitant clopidogrel use anyway.

5. Advisory Committee Meeting

An Advisory Committee Meeting was not held for this NDA.

6. Pediatrics

The Pediatric and Maternal Health Staff (PMHS) was consulted during the NDA review to assist with Pediatric Review Committee (PeRC) preparation (Pediatric Team) and to provide input on labeling for the Pediatric Use, Pregnancy and Nursing Mothers sections of labeling (Maternal Health team).

Since the approval of Prilosec® (omeprazole), the RLD, FDA became aware of data indicating that use of esomeprazole in pregnancy may cause fetal harm with changes in bone morphology and physeal dysplasia in pre- and postnatal developmental toxicity studies in rats (from studies conducted under NDA 202342, esomeprazole strontium). Adverse effects were also seen on maternal bone in pregnant and lactating rats. Based on these animal data, DGIEP invoked FDAAA to request safety labeling changes in the Pregnancy, Nursing Mothers and Pediatric Use section for all esomeprazole and omeprazole products. PMHS labeling recommendations for Yosprala (aspirin/omeprazole) include the recent recommendations based on this animal data; the proposed Yosprala label has been revised accordingly.

Pediatric Review Committee (PeRC)

This application triggered PREA as this NDA proposed a new indication for the components of this combination product. The PeRC met on September 25, 2013 and agreed to the full waiver on the grounds that studies would be impossible or highly impractical, "because the proposed indication in the pediatric population is rare, therefore the incidence of aspirin associated gastric ulcers would also expected to be rare."

7. Other Relevant Regulatory Issues

Clinical Inspections

Two sites were selected because they had the largest number of enrollees per study (Study PA3245-301 and Study PA3245-302). Many sites had less than 15 subjects enrolled. The two sites inspected were classified as NAI. The data generated at both sites were deemed acceptable to the OSI reviewers and could be used in support of the NDA.

The two clinical sites selected and inspection results are presented in Table 17.

Table 17

Name of CI, Location and Site #	Protocol # and # of Subjects	Inspection Date	Final Classification
Sabine Hazan-Steinberg, M.D. Ventura Clinical Trials 1746 S. Victoria Ave., Suite 230 Ventura, CA 93003 Site 0776	PA32540-301 31 Subjects	July 10-15, 2013	NAI
Neal Secrist, M.D. Professional Research Network of Kansas 345 Riverview Street, Suite 400 Wichita, KS 67203 Site 0671	PA32540-302 22 Subjects	July 15-18, 2013	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

505(b)(2) Related Issue(s)

This application was cleared for action from a 505(b)(2) team perspective with one item requiring resolution prior to approval:

1) [redacted] (b) (4) . Therefore, it was the aspirin professional labeling (b) (4) that was relied upon for including that statement within the Yosprala label.

8. Labeling

Proprietary Name Review

DMEPA previously reviewed three proposed proprietary names, [redacted] (under IND 078747) [redacted] (under this NDA) [redacted] (OSE Review #2011-3141 dated January 18, 2012), [redacted] (OSE Review # 2012-901 dated October 2, 2012), and [redacted] (OSE Review # 2013-355) were found to be unacceptable.

Applicant initially proposed the proprietary name [redacted] within the NDA. The Division of Medication Error Prevention & Analysis (review dated 6/21/2013) found that the proposed proprietary name is acceptable from a promotional perspective but not acceptable from a safety perspective. The proposed name is vulnerable to name confusion [redacted]

The Applicant then proposed the proprietary name, Yosprala for review under the NDA and it was found to be acceptable from both a promotional and safety perspective.

Label

The proposed label was a combined label that incorporated data from omeprazole (Prilosec) and from the aspirin monograph (21 CFR 343.80). Efficacy and safety data from the two clinical trials have been incorporated into relevant sections.

Indication Statement

The proposed indication statement was revised, but otherwise remained similar to that originally proposed in adherence to the aspirin monograph. A limitation of use sections was added to indicate that reduction in risk of GI bleeds due to aspirin has not been demonstrated.

Safety Sections

As noted previously, the animal data recently incorporated into the approved omeprazole and esomeprazole labels has been added to the proposed labeling for Yosprala. Warnings and Precautions relies heavily on the approved omeprazole and aspirin labeling, however minor reorganization was done to improve clarity.

Efficacy / Clinical Studies Sections

The description of clinical studies was modified. Proposed results of primary and secondary were modified to a minor extent. [redacted]

9. Recommendations / Risk Benefit Assessment

Recommended Regulatory Action

Complete Response; the Office of Compliance has issued an overall "*Withhold*" recommendation for the inspection of one of the manufacturing facilities.

Risk Benefit Assessment

Both active ingredients, omeprazole and aspirin, are FDA approved drugs, albeit in a variety of different formulations. There is also FDA precedent in combining immediate release PPIs with NSAIDS to prevent gastric ulcers (Vimovo, which is esomeprazole + naproxen).

Acetylsalicylic acid is the active moiety of aspirin, through which it exerts its antiplatelet effect that results in cardioprotective benefit. The bioequivalence of aspirin between the proposed products (PA32540 and PA8140) and the reference products (Ecotrin® 81 mg and 325 mg) were established based on demonstration of bioequivalence of acetylsalicylic acid. These facts support approval of Yosprala for the indications provided to aspirin within the professional labeling (21 CFR 343.80).

The results of the two clinical trials established the efficacy of the omeprazole 40mg IR component in Yosprala to prevent gastric ulcers (GU), including other claims within the label as discussed previously, associated with administration of the EC aspirin 325mg component. (b) (4)

There were no adequate and well controlled trials that evaluated the efficacy of the ASA 81mg + IR omeprazole 40mg Yosprala tablet (PA8140). However, effectiveness of the PA8140 tablet is supported by the following lines of evidence:

1. The applicant provided PK data (relative bioavailability study) demonstrating that the BA of omeprazole in PA8140 is somewhat higher (27%) than that in PA32540. These data therefore support the conclusion that the pharmacodynamic effect of omeprazole in PA8140 is at least as good as that from the omeprazole in PA32540. Further, OCP has concluded that co-administration of aspirin and omeprazole does not affect each other's PK profiles. One can therefore conclude that the pharmacodynamic effect of the omeprazole component of the two formulations, i.e., to raise gastric pH, should be very similar, particularly when taking daily.
2. The risks of developing gastric ulcers from ASA 325mg is *at least as great* as that from ASA 81mg and there is no reasonable expectation that ASA 81mg would have a greater risk of GU.

Therefore, the review team was able to conclude that the omeprazole component in PA8140 would be effective in reducing the occurrence of gastric ulcers known to be associated with ASA 81mg.

The DGIEP review team understands DCRP's concerns regarding the clinical use of ASA 325mg for secondary cardioprotection and has successfully worked with the applicant to submit data to support the PA8140 tablet so that it can be marketed. However, given that the Professional Labeling provides for a range of ASA doses across a number of indications, the demonstrated lower incidence of gastric ulcers with PA32540 compared to ASA 325mg alone, plus the known prevalence of clinical use of ASA 325mg, it is not clear what the grounds would be not to approve the PA32540 tablet.

There are a number of known safety issues with omeprazole that led to revisions to the proposed Yosprala label. These have been discussed in my review and include new animal safety data and pregnancy warnings for omeprazole, as well as a description of an interaction (DDI) with clopidogrel.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS is not recommended.

Recommendation for other Postmarketing Requirements and Commitments

None at this time since this application will receive a Complete Response. However Biopharmaceutics had recommended PMCs prior to determination that this NDA would receive a Complete Response.

Recommended Comments to Applicant

Within the CR Letter, the team is considering attaching the negotiated labeling such that the applicant can provide a more complete label should they submit a response to the CR.

10. Appendices

Table 18. Treatment Emergent Adverse Events with Incidence of 2% or More in Study PA32540-301

System Organ Class / Preferred Term[1]	PA32540 n(%) (N=264)	EC-Aspirin 325 mg n(%) (N=265)
Number of Events	498	801
Subjects with Any Adverse Event	193 (73.1)	224 (84.5)
Gastrointestinal Disorders	155 (58.7)	206 (77.7)
Gastritis	46 (17.4)	44 (16.6)
Dyspepsia	35 (13.3)	90 (34.0)
Gastritis Erosive	27 (10.2)	82 (30.9)
Hiatus Hernia	27 (10.2)	26 (9.8)
Duodenitis	15 (5.7)	46 (17.4)
Diarrhoea	9 (3.4)	8 (3.0)
Nausea	8 (3.0)	7 (2.6)
Oesophagitis	8 (3.0)	31 (11.7)
Gastroesophageal Reflux Disease	7 (2.7)	15 (5.7)
Oesophageal Disorder	7 (2.7)	2 (0.8)
Reflux Oesophagitis	4 (1.5)	7 (2.6)
Erosive Duodenitis	2 (0.8)	25 (9.4)
Duodenal Ulcer	1 (0.4)	9 (3.4)
Erosive oesophagitis	1 (0.4)	15 (5.7)
Infections and Infestations	28 (10.6)	40 (15.1)
Upper respiratory tract infection	5 (1.9)	10 (3.8)
Nasopharyngitis	4 (1.5)	6 (2.3)
Bronchitis	3 (1.1)	9 (3.4)
General Disorders and Administration Site Conditions	17 (6.4)	16 (6.0)
Non-cardiac chest pain	8 (3.0)	3 (1.1)
Musculoskeletal and Connective Tissue Disorders	17 (6.4)	21 (7.9)
Arthralgia	2 (0.8)	6 (2.3)
Nervous System Disorders	16 (6.1)	14 (5.3)
Dizziness	4 (1.5%)	6 (2.3)
Skin and Subcutaneous Tissue Disorders	10 (3.8)	17 (6.4)
Petechiae	3 (1.1)	10 (3.8)

[1] Note: Events are summarized in decreasing order based on the occurrence rate in the PA32540 group.

Source: Applicant, Integrated Summary of Safety, Table 26, page 73

Table 19. Treatment Emergent Adverse Events with Incidence of 2% or More in Study PA32540-302

System Organ Class / Preferred Term[1]	PA32540 n(%) (N=257)	EC-Aspirin 325 mg n(%) (N=259)
Number of Events	474	621
Subjects with Any Adverse Event	178 (69.3)	211 (81.5)
Gastrointestinal Disorders	124 (48.2)	178 (68.7)
Gastritis	45 (17.5)	40 (15.4)
Gastritis erosive	33 (12.8)	56 (21.6)
Dyspepsia	24 (9.3)	68 (26.3)
Hiatus hernia	19 (7.4)	30 (11.6)
Duodenitis	14 (5.4)	24 (9.3)
Nausea	9 (3.5)	5 (1.9)
Oesophagitis	9 (3.5)	32 (12.4)
Acquired oesophageal web	6 (2.3)	7 (2.7)
Diarrhoea	6 (2.3)	4 (1.5)
Gastric polyps	6 (2.3)	1 (0.4)
Erosive duodenitis	5 (1.9)	12 (4.6)
Reflux oesophagitis	2 (0.8)	10 (3.9)
Erosive oesophagitis	1 (0.4)	18 (6.9)
Duodenal ulcer	0	10 (3.9)
Infections and Infestations	40 (15.6)	39 (15.1)
Bronchitis	6 (2.3)	5 (1.9)
Urinary tract infection	6 (2.3)	5 (1.9)
Nasopharyngitis	3 (1.2)	6 (2.3)
Musculoskeletal and Connective Tissue Disorders	22 (8.6)	17 (6.6)
Arthralgia	6 (2.3)	4 (1.5)
Cardiac Disorders	18 (7.0)	12 (4.6)
Angina pectoris	5 (1.9)	6 (2.3)

[1] Note: Events are summarized in decreasing order based on the occurrence rate in the PA32540 group.

Source: Applicant, Integrated Summary of Safety, Table 28, page 76

Table 20. Treatment Emergent Adverse Events Reported by ≥ 2% of Subjects in the Long-Term Safety Population (LSP) and the Twelve Month Population (TMP)

Preferred Term[1]	LSP N=379 Number of Subjects (%)	TMP N=290 Number of subjects (%)
Diarrhoea	20 (5.3)	14 (4.8)
Back pain	16 (4.2)	15 (5.2)
Bronchitis	16 (4.2)	15 (5.2)
Dyspepsia	16 (4.2)	13 (4.5)
Nausea	16 (4.2)	7 (2.4)
Upper respiratory tract infection	16 (4.2)	16 (5.5)
Nasopharyngitis	15 (4.0)	14 (4.8)
Sinusitis	14 (3.7)	13 (4.5)
Muscle spasms	13 (3.4)	9 (3.1)
Pain in extremity	13 (3.4)	10 (3.4)
Angina pectoris	12 (3.2)	6 (2.1)
Cough	12 (3.2)	12 (4.1)
Dyspnea	12 (3.2)	8 (2.8)
Constipation	11 (2.9)	7 (2.4)
Dizziness	11 (2.9)	9 (3.1)
Headache	11 (2.9)	8 (2.8)
Hypertension	11 (2.9)	8 (2.8)
Anaemia	10 (2.6)	4 (1.4)
Fatigue	10 (2.6)	8 (2.8)
Peripheral edema	10 (2.6)	9 (3.1)
Abdominal pain upper	9 (2.4)	3 (1.0)
Arthralgia	9 (2.4)	7 (2.4)
Hemoglobin decreased	9 (2.4)	3 (1.0)
Chronic obstructive pulmonary disease	8 (2.1)	7 (2.4)
Carotid artery stenosis	6 (1.6)	6 (2.1)
Urinary tract infection	7 (1.8)	6 (2.1)
Renal impairment	7 (1.8)	6 (2.1)

[1] Note: Events are summarized in decreasing order based on overall occurrence rate.

Source: Applicant, ISS, Table 33, page 85.

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/s/

ROBERT FIORENTINO
04/25/2014

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 205103

Submission Date(s): March 25, 2013

Applicant: POZEN

Product: YOSPRALA

Reviewer: Zana Marks, MD, MPH

Date of Review: April 14, 2013

Covered Clinical Study (Name and/or Number): PA32540-301; PA32540-302

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: _____		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 230		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: **N/A**	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A**	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The sponsor has disclosed the financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. There is no indication that any investigators are sponsor employees.

One investigator was disclosed under Form 3455. The basis of this disclosure was based on box #2 which reads "any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria"
The investigator , (b) (6) participated as a clinical investigator in the submitted study (b) (6). Details of (b) (6) disclosable financial arrangements and interests are provided below.

The inclusion of (b) (6) as a clinical investigator in the study has not affected the approvability of the application.

[1] See [web address].

NDA # 205103
Non-Grant-Payment Investigator Compensation

Clinical Studies: (b) (6)

Investigator	Description
	(b) (6)

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/s/

ZANA H MARKS
04/16/2014

Cross-Discipline Team Leader Review

Date	December 12, 2014
From	Robert P. Fiorentino, M.D., M.P.H. Division of Gastroenterology & Inborn Errors
Subject	Cross-Discipline Team Leader Review
NDA#	205103
Applicant	POZEN, Inc.
Date of Submission	June 30, 2014 (Class 2)
PDUFA Goal Date	December 30, 2014
Proprietary Name / Established (USAN) Names	Yosprala / Omeprazole and aspirin
Dosage forms / Strength	81 mg/40 mg and 325 mg/40 mg
Proposed Indications	YOSPRALA is a combination of aspirin, an anti-platelet agent, and omeprazole, a proton pump inhibitor (PPI), indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers. The aspirin component of YOSPRALA is indicated for: • reducing the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, • reducing the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, • reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris, • use in patients who have undergone revascularization procedures (Coronary Artery Bypass Graft [CABG] or Percutaneous Transluminal Coronary Angioplasty [PTCA]) when there is a pre-existing condition for which aspirin is already indicated. The omeprazole component of YOSPRALA is indicated for decreasing the risk of developing aspirin associated gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers due to age (≥ 55) or documented history of gastric ulcers.
Recommended:	Complete Response

Table of Contents

1. Introduction

Yosprala tablets are a multilayer orally administered tablet consisting of an enteric-coated (EC) aspirin core (81 mg or 325 mg), and an immediate release (IR) omeprazole 40 mg film coat. This allows for a sequential release, first of omeprazole followed by aspirin (b) (4) The tablets are intended for once daily use to provide the benefits of aspirin with the upper gastrointestinal (UGI) protection of omeprazole, a proton pump inhibitor (PPI).

The original 505(b)(2) NDA was submitted by POZEN Inc. on March 25, 2013. The NDA received a Complete Response (CR) action on April 25, 2014 because the Office of Compliance had issued an overall "*Withhold*" recommendation for the (b) (4) manufacturing facility where the aspirin component of the tablet is manufactured.

This CDTL Memo serves as a summary review for the Resubmission.

The following primary reviews and memoranda are summarized in my CDTL review:

Chemistry
- Zhengfang Ge, Ph. D., review dated 12/09/2014

Nonclinical
- Tamal Chakraborti, Ph.D., review signed 11/21/2014

Clinical Pharmacology
- Dilara Jappar, Ph.D., review signed 11/24/2014

Biopharmaceutics
- Banu Sizanli Zolnik, Ph.D., review signed 11/25/2014

Division of Medication Error Prevention and Analysis (DMEPA)
- Labeling Review: Sherly Abraham, R.Ph., review signed 10/08/2014
- Proprietary Name Review: Sherly Abraham, R.Ph, signed 9/29/2014

Division of Medical Policy Programs (DMPP)
- Karen Dowdy, RN, BSN, review signed 11/19/2014

DGIEP Regulatory Project Manager Memorandum
- CDR Stacy Barley, R.N., M.S.N., M.H.A, signed 12/09/2014

2. Background

The following was the primary reason for a CR as noted in the action letter dated April 25, 2014 for the Yosprala NDA:

> During a recent inspection of the (b) (4). manufacturing facility for this application, the field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Despite this, the results of the two clinical trials submitted during the first review cycle established the efficacy of the omeprazole 40mg IR component in Yosprala to prevent gastric ulcers (GU), including other claims discussed in clinical and summary reviews from the first review cycle. Although there were no adequate and well controlled trials that evaluated the efficacy of the ASA 81mg + IR omeprazole 40mg Yosprala tablet (PA8140), effectiveness of the PA8140 tablet was supported by a number of considerations also discussed in prior clinical and summary reviews.

Therefore, at the time of the previous action (CR), the only remaining deficiency was the Withhold recommendation from the Office of Compliance.

It should also be noted that labeling recommendations were provided to the sponsor within the CR Letter on April 25, 2014 (and labeling revisions continued through this review cycle).

3. CMC

General Product Quality Considerations
The reader is referred to the previous cycle's CMC review in regards to general product quality considerations, which were deemed to be acceptable from the CMC standpoint.

Facilities Inspection
As noted in the CMC review the Office of Compliance (OC) issued an overall "*Withhold*" recommendation on December 09, 2014 for the inspections of the manufacturing facilities; this was the same site that led to OC's Withhold recommendation during the prior review cycle [i.e., the (b) (4) facility].

Therefore, the following language for the CR Letter was recommended by OC this cycle:

> During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

4. Nonclinical Pharmacology / Toxicology

The Applicant did not submit any nonclinical study report in this submission and from nonclinical's perspective, this NDA resubmission was again recommended for approval.

In his labeling review, the nonclinical reviewer noted that the Applicant deleted the duplicated sentence, "Animal reproduction studies (b) (4)….human dose of 40 mg") from the beginning of the fourth paragraph on page 16 of the draft label (Section 8.1 Pregnancy) in the revised label version dated October 30, 2014 because this sentence was duplicated in the second paragraph of Section 8.1 of the label. The Applicant's deletion of the above sentence and the proposed version was deemed acceptable to the nonclinical reviewer.

5. Clinical Pharmacology / Biopharmaceutics

Clinical Pharmacology
There were no new clinical pharmacology studies in this resubmission. Therefore, this application is acceptable from the clinical pharmacology perspective provided that mutual agreement can be reached regarding the labeling. However, because of the pending CR, the clinical pharmacology reviewer deferred completion of their labeling review to the next cycle.

Biopharmaceutics
From the biopharmaceutics perspective, the original NDA was recommended for approval. In this submission, there were no new biopharmaceutics study/data included for review. Therefore, this Application was deemed to be "acceptable" from the biopharmaceutics

perspective; however note that there are two PMCs recommended by biopharmaceutics. During the first cycle of the Biopharmaceutics Review, the dissolution method was found acceptable, however, the dissolution acceptance criteria for both strengths were found acceptable in an interim basis. The Applicant had previously agreed (b) (4)

[redacted]

6. Clinical Microbiology

Not applicable to this review.

7. Clinical / Statistical: Efficacy

No new clinical efficacy data was submitted in this resubmission. A clinical review was completed last review cycle by Zana H. Marks, MD, MPH (review signed 3/21/2014, addendum signed 4/04/2014). The reader is referred to her review and other summary reviews (a CDTL and Division Director review) in which the effectiveness of both doses is extensively discussed.

8. Safety

In the resubmission, the applicant submitted an appended document to the Integrated Summary of Safety (ISS) section of the NDA describing the safety findings from a single phase 1 study. This study, PA10040-102, was conducted in 18 healthy volunteers and had not been previously reported to the NDA. The purpose of this study is not entirely clear to me but it appears to have been done to support a tablet that contains ASA 100mg, which is a commonly used aspirin dosage for secondary CV protection outside the United States. All other studies conducted by POZEN have been reported in the NDA.

PA10040-102 was a randomized, open-label, 2-way cross-over, single-center study in 18 healthy adult volunteers. The study design consisted of two 7-day treatment periods. The first treatment period was followed by a washout period of at least 7 days.

There are no new safety concerns generated by this trial and no meaningful conclusions can be drawn given the small number of healthy subjects enrolled. No new changes to the label are warranted based on the results of this small trial.

The applicant states that they have not performed any new safety analyses or integrated the data from study PA10040-102 with other safety data on the PA32540 and PA8140 tablet

strengths previously provided in the NDA, “as this new safety information is minimal and does not impact the analysis presented in the ISS.”

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this resubmission or for the original NDA.

10. Pediatrics

The original application triggered PREA as this NDA proposed a new indication for the components of this combination product. The PeRC met on September 25, 2013 and agreed to the full waiver on the grounds that studies would be impossible or highly impractical, "because the proposed indication in the pediatric population is rare, therefore the incidence of aspirin associated gastric ulcers would also expected to be rare."

The reader is referred to the previous cycle reviews regarding the incorporation into the draft label of data indicating that use of esomeprazole in pregnancy may cause fetal harm with changes in bone morphology and physeal dysplasia in pre- and postnatal developmental toxicity studies in rats (from studies conducted under NDA 202342, esomeprazole strontium).

11. Other Relevant Regulatory Issues

No new regulatory issues were discussed during the review of this resubmission.

12. Labeling

Proprietary name
DMEPA reviewed the proposed proprietary name, Yosprala, and concluded that this name is acceptable. This decision was communicated to the Applicant in a communication dated 10/03/2014. The proprietary name was also found to be acceptable during the previous cycle review.

Carton and immediate container label
During the review of the original NDA, the Division of Medication Error Prevention and Analysis (DMEPA)’s comments on carton and container labels were communicated to the sponsor (on March 29, 2013). The applicant resubmitted revised labeling on July 28, 2014, in response to recommendations that DMEPA made during the previous label and labeling review. Based on DMEPA’s review this cycle, the revised container label and carton labeling were deemed to be acceptable from a medication error perspective.

Physician labeling
During this review cycle, a number of revisions were made by the review team to the negotiated label that had been provided to the applicant in the 04/25/2014 Complete Response letter. The sponsor accepted many of the proposed revisions. This effort during the current review cycle did not add new data or revise claims previously described in the label provided in the Complete Response letter. Rather, the intent was to provide additional clarity and improvements in the information presented in the label.

As noted in the memo by Stacy Barley (RPM) dated 12/09/2014, Clinical Pharmacology reviewers deferred review of the sponsor's proposed revisions to Section 12 of the draft label. The applicant had reworded this section during the current review cycle; should these revisions be resubmitted by the applicant in the future, they will require review by Clinical Pharmacology.

In addition, the safety labeling language issued by way of FDAAA Safety Label Change notification letters on October 31, 2014 to the Sponsors of approved Proton Pump Inhibitors has not been included in this to-be-marketed label. This language will need to be included in the Yosprala label during the next review cycle.

Patient labeling/Medication guide
Due to outstanding manufacturing deficiencies and pending Complete Response, the Division of Medical Policy Programs (DMPP) deferred comment on the Applicant's patient labeling at this time, including the proposed Medication Guide. A final review will be performed by DMPP after the Applicant submits a complete response to the Complete Response letter.

13. Recommendations / Risk Benefit Assessment

Recommended Regulatory Action

Complete Response.

Risk Benefit Assessment

The Risk Benefit Assessment has not changed since my summary review during the previous cycle. Refer to the CDTL memo dated 04/25/2014.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS is not recommended.

Recommendation for other Postmarketing Requirements and Commitments

None at this time since this application will receive a Complete Response. However Biopharmaceutics continues to recommended PMCs should the application ultimately be approved.

Recommended Comments to Applicant

None. The label will not be attached to the CR Letter this review cycle; however negotiations had been ongoing with the applicant at the time an action was taken.

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/s/

ROBERT FIORENTINO
12/12/2014

Clinical Review Addendum
NDA 205103

The purpose of this addendum is to correct an error in the description of the eligibility criteria in the Clinical Review (pages 30 – 32) that was electronically submitted and signed on 03/21/2014 (DARRTS Reference ID: 3475586). The description of the inclusion criteria for both studies PA32540-301 and PA32540-302 should read the following:

A subject was eligible for inclusion in this study if all of the following criteria applied:

1A. Males or non-pregnant, non-breastfeeding females who had been on daily (at least 5 days per week) aspirin 325 mg for at least 3 months and who were expected to use daily aspirin 325 mg for at least 6 months,

AND, who were:

- 55 years of age and older;

or

- 18-54 years of age with a history of a documented gastric or duodenal ulcer within the past 5 years.

2A. Aspirin was used for the secondary prevention of the following cardiovascular or cerebrovascular events:

Diagnosis or history of:

- Confirmed or suspected myocardial infarction (MI);
- Ischemic stroke; or
- Transient ischemic attack (TIA).

Or established, clinically significant coronary and other atherosclerotic vascular disease (i.e., high risk for surgical intervention or for MI, TIA, stroke, if left untreated), including:

- Angina (stable or unstable);
- Peripheral arterial disease;
- Atherosclerotic aortic disease; or
- Carotid artery disease.

Or history of:

- Coronary artery bypass graft (CABG);
- Percutaneous coronary intervention (PCI) with or without stent; or
- Carotid endarterectomy.

3A. Female subjects were eligible if they were of:

a) non-childbearing potential (i.e., physiologically incapable of becoming pregnant); or,
b) childbearing potential, and had a negative pregnancy test at Screening and at least one of the following applied or was agreed to by the subject:

- Female sterilization or sterilization of male partner;
- Use of hormonal contraception by oral route, implant, injectable, or vaginal ring;

- Use of any intrauterine device with published data showing that the lowest expected failure rate was less than 1% per year;
- Use of double-barrier method (2 physical barriers or 1 physical barrier plus spermicide);
- Use of any other contraceptive method with published data showing that the lowest expected failure rate was less than 1% per year.

4. Ability to understand and comply with study procedures required and ability and willingness to provide written informed consent prior to any study procedures being performed.

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/s/

ZANA H MARKS
04/04/2014

ROBERT FIORENTINO
04/04/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 205103 Applicant: POZEN,Inc. Stamp Date: 3/27/2013

Drug Name: aspirin and omeprazole NDA/BLA Type:

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			Multiple sections of the PI have been abstracted directly from the currently approved labeling (21CFR 343.80) or Prilosec Prescribing Information and are annotated to those documents
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			There are no specific nonclinical studies to support PA Tablets. No nonclinical information is provided in Module 2.6. A full review and summary of the pertinent non-clinical literature is provided in module 2.4
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?			x	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505(b)(2).The reference drugs are Ecotrin and Prilosec
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title:			x	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: Arms: Location in submission:				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 PA32540-301 Indication: To demonstrate that PA32540 caused fewer gastric ulces in subjects at risk for developing aspirin-associated gastric ulcers compare to enteric-coated (EC) aspirin 325mg Pivotal Study #2 PA32540-302 Indication: To demonstrate that caused fewer gastric ulces in subjects at risk for developing aspirin-associated gastric ulcers compare to enteric-coated (EC) aspirin 325mg	x			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		x		
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			The sponsor requested a waiver from the requirement to conduct pediatric studies in pts 18 y/o and younger on the basis that the product is intended for secondary prevention of cardiovascular and cerebrovascular events that are due to arteriosclerosis
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___yes_____

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

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

Zana Marks, MD MPH 4/26/13

Reviewing Medical Officer Date

Robert Fiorentino, MD, MPH

Clinical Team Leader Date

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

/s/

ZANA H MARKS
05/13/2013

ROBERT FIORENTINO
05/13/2013