ORIGINAL RESEARCH ARTICLE

Cardiovascular Therapeutics

Long-Term Safety of a Coordinated Delivery Tablet of Enteric-Coated Aspirin 325 mg and Immediate-Release Omeprazole 40 mg for Secondary Cardiovascular Disease Prevention in Patients at GI Risk

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SUMMARY

Introduction: In two, 6-month, randomized, double-blind Phase 3 trials, PA32540 (enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg) compared to aspirin alone was associated with fewer endoscopic gastric and duodenal ulcers in patients requiring aspirin therapy for secondary cardiovascular disease (CVD) prevention who were at risk for upper gastrointestinal (UGI) events. **Aims:** In this 12-month, open-label, multicenter Phase 3 study, we evaluated the long-term cardiovascular and gastrointestinal safety of PA32540 in subjects who were taking aspirin 325 mg daily for ≥3 months for secondary CVD prevention and were at risk for aspirin-associated UGI events. Enrolled subjects received PA32540 once daily for up to 12 months and were assessed at baseline, month 1, month 6, and month 12. **Results:** The overall safety population consisted of 379 subjects, and 290 subjects (76%) were on PA32540 for ≥348 days (12-month completers). Adverse events (AEs) caused study withdrawal in 13.5% of subjects, most commonly gastroesophageal reflux disease (1.1%). Treatment-emergent AEs occurred in 76% of the safety population (11% treatment-related) and 73% of 12-month completers (8% treatment-related). The most common treatment-related AE was dyspepsia (2%). One subject had a gastric ulcer observed on for-cause endoscopy. There were five cases of adjudicated nonfatal myocardial infarction, one nonfatal stroke, and one cardiovascular death, but none considered treatment-related. **Conclusions:** Long-term treatment with PA32540 once daily for up to 12 months in subjects at risk for aspirin-associated UGI events is not associated with any new or unexpected safety events.

Introduction

Patients who have experienced a cardiovascular event, such as myocardial infarction (MI) or ischemic stroke, or undergone interventional procedures such as angioplasty or bypass surgery are advised to begin aspirin therapy for the prevention of secondary cardiovascular events [1–3]. The use of aspirin therapy, however, has been associated with an increased risk of upper gastrointestinal (GI) bleeding [4–7] as well as clinically relevant symptoms such as dyspepsia and gastroesophageal reflux disease (GERD) [8–10]. Bleeding complications or upper GI symptoms may reduce the long-term compliance with aspirin therapy [8–11] and in turn increase the rate of adverse cardiovascular outcomes [11–14].

Patients at an increased risk of aspirin-associated adverse GI events include those with a history of previous gastric ulcer or upper GI bleeding [15–17]. Additionally, dual antiplatelet therapy, concurrent nonsteroidal antiinflammatory drug (NSAID) therapy, and increased age are also risk factors for upper GI events [5,6,15–18]. Aspirin users have an approximate 2-folder higher increased risk of upper GI complications, including bleeding [4,5,19–21]. In a recent case–control study, aspirin combined with the antiplatelet therapy increased upper GI bleeding risk from an odds ratio (OR)

of 1.8 (aspirin alone) to 6.7, and aspirin + NSAIDs had an OR of 3.6 [5]. Regarding aging, analysis from a systematic review found an approximate 3-fold increase in GI complications (peptic ulcer and/or GI bleeding) as patients age from 50–54 years to 70–74 years [18].

Proton pump inhibitor (PPI) therapy reduces the risk of aspirin-associated upper GI events and is recommended for patients at an increased risk [15,16]. However, several studies suggest that there are treatment gaps with the co-prescribed prophylactic PPI prescriptions and/or use [22–35]. Specifically, when PPIs are co-prescribed, adherence rates are often suboptimal, leaving patients at risk for adverse upper GI outcomes [27,28,32,33,35]. The development of these GI side effects may in turn lead to poor compliance and even discontinuation of aspirin therapy [8–11,36]. Discontinuation of aspirin therapy has been associated with a 40–60% increased risk of secondary cardiovascular events, including MI and stroke [12,13]. Beyond patient education through healthcare initiatives reinforcing the importance of medication persistence, an integrated delivery system that would ensure maximal adherence to PPI administration may be clinically helpful and result in better persistence of aspirin use and fewer therapy discontinuations.

PA32540 (enteric-coated aspirin 325 mg + immediate-release omeprazole 40 mg) is a coordinated delivery tablet consisting of an enteric-coated aspirin core surrounded by an outer layer containing immediate-release omeprazole, and the pharmacokinetics and pharmacodynamics have been previously published [37]. The efficacy of the coordinated delivery of a PPI has been tested in two randomized, double-blind 6-month clinical trials, demonstrating that PA32540 was associated with a significantly lower rate of endoscopic gastric and/or duodenal ulcers compared with aspirin therapy alone (3.4% vs. 11.6%, respectively; $P < 0.001$) [38].

As the value of effective aspirin therapy for cardiovascular protection/disease is dependent upon persistent use over time, this long-term, open-label study with PA32540 was conducted to simultaneously evaluate cardiovascular and GI safety for a period of 12 months.

Methods

Study Design and Patients

This was a Phase 3, open-label study that evaluated the 12-month use of PA32540 in adults requiring aspirin therapy for the secondary prevention of cardiovascular/cerebrovascular events. The study protocol and amendments were approved by a central Institutional Review Board (IRB) for all study sites except 2 that used their local IRB. The study was conducted in accordance with the Declaration of Helsinki and good clinical practice. All subjects provided written informed consent prior to undergoing any study procedures.

Eligible subjects were male or nonpregnant, nonbreastfeeding females taking aspirin 325 mg daily (defined as at least 5 days/week) for the secondary prevention of cardiovascular/cerebrovascular events for ≥3 months and who were expected to use daily aspirin 325 mg for ≥6 months. Subjects had to be ≥55 years old or between 18 and 54 years with a documented history of gastric or duodenal ulcer within the 5 years before the study enrollment. Subjects also had to have a diagnosis or history of at least one of the following: MI, ischemic stroke, transient ischemic attack (TIA), coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI) with or without stent, carotid endarterectomy, or established, clinically significant coronary and other atherosclerotic vascular disease (i.e., at high risk for surgical intervention or for MI, TIA, stroke, if left untreated), including angina (stable or unstable), peripheral arterial disease, atherosclerotic aortic disease, or carotid artery disease. Key exclusion criteria were participation in a previous PA32540 clinical research study, the known presence of current gastric, duodenal, or esophageal ulcer, H. *pylori*-positive stool antigen test at screening, history of a revascularization procedure (i.e., CABG, percutaneous transluminal coronary angioplasty, or carotid endarterectomy) <6 months prior to screening, history of serious upper GI event (e.g., bleeding, perforation, or obstruction), any GI disorder or surgery leading to impaired drug absorption, or the presence of any chronic or uncontrolled acute medical illness that would endanger the subject if he/she participated in the study.

Enrolled subjects were instructed to take 1 tablet of PA32540 each morning on an empty stomach with a glass of water approximately 1 h before eating. The tablet was to be swallowed whole and not crushed, chewed, or broken. Subjects taking concomitant NSAID therapy were instructed to take PA32540 at least 2½ h prior to NSAID dosing throughout the study [39] and were to self-report any NSAID use to study staff.

Following the baseline visit, subjects returned to the clinic for safety assessments at months 1, 6, and 12 (final visit). Safety assessments included adverse event (AE) collection, clinical laboratory tests, vital signs, and physical examination. In between clinic visits, subjects were contacted monthly by telephone by study personnel to reinforce compliance with the study medication and address any safety issues. Serious adverse events (SAEs) were monitored from the time of signed informed consent until 28 days following the participation in the study. Nonserious AEs were monitored from the start of study drug until the last day of participation in the study. AEs were coded using MedDRA (Medical Dictionary for Regulatory Activities) version 12.1 for preferred terms and classification of system organ class (SOC). Laboratory tests were analyzed by a central laboratory.

All investigator-reported potentially clinically significant upper GI events and cardiovascular events from the Phase 3 program (two double-blind trials [38] and the present open-label trial) were sent to either an independent GI Clinical Event Committee (authors: JG, AL, JS, GE, BC) or an independent Cardiovascular Review Committee (DW [author], CO, AM—see Acknowledgments) for adjudication based on *a priori* defined set of criteria as previously described [38]. For the purposes of blinding the committees, all potential events were reported without identifying from which of the three studies it originated. This ensured that all adjudicated events were assessed blinded to subject treatment and study.

Statistical Analysis

Data were summarized for categorical and ordinal measures by reporting the frequency and percentage of subjects in each category. Means, standard deviations (SD), medians, minimum, and

maximum were summarized for continuous measures. All statistical summaries were completed using SAS® version 9.1 (SAS Institute Inc., Cary, NC, USA) or higher.

Approximately 400 subjects were planned to ensure that approximately 300 enrolled subjects would have 6-month exposure to PA32540 and at least 100 subjects would have 12-month exposure to PA32540. All safety analyses were performed on the overall safety population (i.e., all enrolled subjects who received at least one dose of study drug) and the 12-month "completer" population (i.e., all subjects who were on study drug for at least 348 days). A subject who completed 12 months of therapy and all scheduled study assessments was considered to have "completed" the study. Compliance was assessed using pill counts and information provided by the subjects. Treatment compliance over the entire duration of study was defined as the percentage of drug days out of total days in the study.

Results

A total of 380 subjects enrolled in the study at 44 sites within the United States. The first subject enrolled on November 2, 2009, and the last subject completed on May 26, 2011. Of these subjects, 292 (76.8%) completed the study and 88 (23.2%) discontinued early (Table 1). The overall safety population consisted of 379 subjects (one subject did not take study drug and was not included in the safety population), and 290 subjects were included in the 12-month completer population (two subjects who discontinued from the study met the 12-month completer definition, while 4 subjects who completed the study did not meet the 12-month completer definition.). Baseline demographics and characteristics are shown in Table 2. The majority (70%) of subjects were males, and most (66%) of the study population was ≥65 years.

The median duration of exposure to PA32540 was 358 days in the overall safety population, 360 days in the 6-month completer population, and 361 days in the 12-month completer population. In the overall safety population, 84.2% were treated for more than 180 days (6 months). The median number of doses taken per subject was 354 in the overall safety population and 356 and 357 in the 6- and 12-month completer populations, respectively. The median number of doses per month was equivalent for all three populations (29.8), reflecting the once-daily dosing of PA32540 and few missed doses. The majority of subjects (98% overall safety population; 99% 6-month and 12-month completers) had ≥70% compliance.

The overall treatment-emergent adverse events (TEAE) rate was 76% in the overall safety population and 73% in the 12-month completer population. The most common events by SOC were infections and infestations (26% overall population, 30% 12-month completers) and GI disorders (24% overall population, 20% 12-month completers). The most frequent TEAEs in the infections and infestations class were bronchitis, upper respiratory tract infection (URTI), nasopharyngitis, and sinusitis. Each of these events occurred in 4% of the overall population and in 5–6% of the 12-month completers (Table 3). The most common

Table 1 Subject disposition and analysis populations

	PA32540 (N = 380) Number of subjects (%)
Number enrolled	380 (100)
Overall safety population[a]	379 (99.7)
6-months completers[b]	323 (85.0)
12-month completer population[c,d]	290 (76.3)
Completed study[d]	292 (76.8)
Discontinued early from study	88 (23.2)
Reasons for study discontinuation	
Adverse events	51 (13.4)
Protocol violations	14 (3.7)
Withdrew consent	7 (1.8)
Site closure	4 (1.1)
Lost to follow-up	2 (0.5)
Other[e]	10 (2.6)

Enrolled: met all inclusion/exclusion criteria and received treatment assignment. Completed: completed 12 months of therapy and all scheduled assessments. [a]All enrolled subjects who received at least one dose of study medication. [b]6-month completers: on study drug at least 168 days. [c]12-month completers: on study drug at least 348 days. [d]Two subjects discontinued from the study, but met the 12-month completers definition, while 4 subjects who completed the study did not meet the 12-month completers definition. [e]Other included investigator/sponsor request, need for medical procedure or change in medication, exclusion criteria met, moving out of state.

Table 2 Baseline demographics and characteristics

	Overall safety population, N = 379	12-month completers, N = 290
Age (years)		
Mean (SD)	67.3 (7.8)	67.6 (7.7)
<55, n (%)	9 (2.4)	4 (1.4)
55–64, n (%)	121 (31.9)	89 (30.7)
≥65, n (%)	249 (65.7)	197 (67.9)
Male gender, n (%)	266 (70.2)	204 (70.3)
Race, n (%)		
White	347 (91.6)	265 (91.4)
Black/African American	17 (4.5)	11 (3.8)
American Indian/Alaska Native	10 (2.6)	10 (3.4)
Other	5 (1.3)	4 (1.4)
Ethnicity, n (%)		
Hispanic or Latino	27 (7.1)	21 (7.2)
Not Hispanic or Latino	352 (92.9)	269 (92.8)
Weight (kg), mean (SD)	90.1 (18.8)	89.9 (18.6)
BMI (kg/m^2), mean (SD)	30.5 (5.4)	30.4 (5.3)
History of gastric or duodenal ulcer, n (%)	39 (10.3)	27 (9.3)
History of ulcer within past 5 years, n (%)	13 (3.4)	9 (3.1)
History of diabetes, n (%)	136 (35.9)	101 (34.8)
History of MI, n (%)	141 (37.2)	105 (36.2)
History of stroke, n (%)	26 (6.9)	21 (7.2)
NSAID use during study (≥7 consecutive days), n (%)	68 (17.9)	55 (19.0)
Clopidogrel use at any time during the study, n (%)	71 (18.7)	48 (16.6)

MI, myocardial infarction.

Table 3 Treatment-emergent adverse events

Preferred term	Overall safety population, N = 379	12-month completers, N = 290
	Number of Subjects (%)	
Subjects with any TEAE	286 (75.5)	213 (73.4)
Most Common TEAEs[a]		
Diarrhea	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)
Dizziness	11 (2.9)	9 (3.1)
Peripheral edema	10 (2.6)	9 (3.1)
Subjects with any prespecified UGI AE	55 (14.5)	31 (10.7)
Dyspepsia	16 (4.2)	13 (4.5)
Nausea	16 (4.2)	7 (2.4)
Abdominal pain upper	9 (2.4)	3 (1.0)
Vomiting	7 (1.8)	4 (1.4)
Gastroesophageal reflux disease	7 (1.8)	2 (0.7)
Abdominal discomfort	5 (1.3)	2 (0.7)
Abdominal pain	1 (0.3)	1 (0.3)
Epigastric discomfort	1 (0.3)	1 (0.3)
Gastritis	1 (0.3)	1 (0.3)
Hyperchlorhydria	1 (0.3)	1 (0.3)
Gastric Ulcer	1 (0.3)	0
Esophagitis	1 (0.3)	0

UGI, upper gastrointestinal; TEAE, treatment-emergent adverse event.
[a]Events occurring in ≥3% of subjects.

GI events were diarrhea, dyspepsia, and nausea, which were each reported in 4–5% of the overall population and in 2–5% of the 12-month completers (Table 3). Gastroesophageal reflux disease was reported in 1.8% of the overall safety population and in 0.7% of the 12-month completers (Table 3). The incidence of TEAEs was higher in NSAID users versus nonusers (94% vs. 71% in the overall safety population, $P < 0.001$).

Onset of TEAEs by treatment window was determined for only those events with valid onset dates. There were a total of 876 such events, and, consistent with the above data, most were in the SOC of infections and infestations (135/876, 15.4%) and GI disorders (135/876, 15.4%). The majority of GI events, including symptoms such as nausea, dyspepsia, and gastroesophageal reflux disease, occurred in the first 30 days of the study (46/876, 5.3%), with an overall event rate of 8.6% in the first 90 days of the study. In total, the incidence of GI events was 10.3% in the first 6 months of the study and 5.1% in the last 6 months.

Table 4 Treatment-emergent adverse events leading to study drug discontinuation and serious adverse events by system organ class[a]

System organ class	Overall safety population, N = 379	12-month completers, N = 290
	Number of subjects (%)	
Any adverse event leading to study discontinuation	51 (13.5)	1 (0.3)
Gastrointestinal disorders	15 (4.0)	0
Gastroesophageal reflux disease	4 (1.1)	0
Abdominal pain upper	3 (0.8)	0
Diarrhea	2 (0.5)	0
Dyspepsia	2 (0.5)	0
Neoplasms: benign, malignant, and unspecified	7 (1.8)	1 (0.3)
Cardiac disorders	6 (1.6)	0
Investigations	6 (1.6)	0
Any serious adverse event	55 (14.5)	34 (11.7)
Cardiac disorders	20 (5.3)	12 (4.1)
Respiratory, thoracic, and mediastinal disorders	7 (1.8)	3 (1.0)
Neoplasms: benign, malignant, and unspecified	6 (1.6)	2 (0.7)
Gastrointestinal disorders	5 (1.3)	4 (1.4)
Nervous system disorders	5 (1.3)	3 (1.0)
General disorders and administration site conditions	4 (1.1)	2 (0.7)
Infections and infestations	4 (1.1)	4 (1.4)
Vascular disorders	4 (1.1)	1 (0.3)
Musculoskeletal and connective tissue disorders	3 (0.8)	3 (1.0)

[a]Only events occurring in ≥1% of subjects by system organ class are displayed.

Adverse events considered to be treatment-related by the study investigators were reported for 11% of subjects in the overall safety population and in 8% of subjects in the 12-month completer population. Dyspepsia was the most frequent treatment-related, treatment-emergent individual adverse event (2% in both populations) and the only individual TEAE related to study treatment that occurred in ≥2% of subjects. Treatment-related GERD was reported for 3 subjects (0.8%) in the overall safety population and in 1 subject (0.3%) of the 12-month completers.

Gastrointestinal events were the most common reason for study discontinuation due to AEs (Table 4). Of the 51 subjects (13.5%) who discontinued from the study due to AEs, 15 (4%) were due to GI disorders. Gastroesophageal reflux disease was the most frequent of these events (four subjects, 1.1%) and the only event to have occurred in >1% of subjects; in two subjects (0.5%), the investigator considered GERD to be treatment-related. Abdominal upper pain caused study discontinuation in 3 subjects (0.8%) and was considered treatment-related by the investigator in 2 (0.5%) of the subjects. Dyspepsia caused study discontinuation in two subjects (0.5%), and in one subject (0.3%), the investigator considered the event to be treatment-related.

A total of 55 subjects (15%) in the overall safety population and 34 subjects (12%) in the 12-month completer population reported at least one SAE. Only SAEs categorized as cardiac disorders occurred in ≥2% of subjects—5% in the overall population and 4% in the 12-month completers (Table 4). One subject with a history of previous MI, triple bypass surgery, hypertension, and hyperlipidemia died of a cerebrovascular accident with infarction after 2 weeks on study drug; the event was considered unlikely related to study treatment by the investigator.

While a total of eight potential events in the present study were sent to the GI Clinical Event Committee for adjudication as potential bleeding events, only one met predefined endpoints; the subject presented with documented melena, with no site of bleeding identified. Additionally, one subject with bright red blood per rectum and abdominal pain had a gastric ulcer observed on for-cause endoscopy; no bleeding was noted, and the patient did not meet the predefined endpoint for a significant upper GI event. A total of 14 subjects were adjudicated by the Cardiovascular Review Committee to have events that met the predefined endpoints for a major adverse cardiovascular event (MACE), and none were considered treatment-related (Table 5). Considering events typically reported as serious vascular events in cardiovascular outcome trials, there were 5 cases of nonfatal myocardial infarction, one case of nonfatal stroke, and one cardiovascular death.

Discussion

Aspirin is recommended for all patients with coronary artery disease unless contraindicated [1], but the occurrence of bleeding complications or significant GI symptoms prevents some patients from adhering to this recommendation [8–11]. Germane to this study, discontinuation of aspirin based on symptoms may in turn increase the risk of subsequent cardiovascular events [8–10,12–14]. Proton pump inhibitor therapy is recommended for the prophylaxis of upper GI events in patients at risk for aspirin-associated GI injury [15,16]. The risk factors that warrant PPI therapy in aspirin users include the history of ulcer (bleeding or nonbleeding), GI bleeding, dual antiplatelet therapy, or concomitant anticoagulation or NSAID therapy [15,16]. In the absence of any of the above GI bleeding risk factors, PPI therapy is also recommended for aspirin users who meet at least two of the following criteria: dyspepsia or GERD symptoms, age ≥60 years, or corticosteroid use [15].

Table 5 Adjudicated major cardiovascular events

Major adverse cardiovascular event (MACE)[a]	Number of subjects (%), N = 379
Subjects with any MACE[b]	14 (3.7)
Cardiovascular death	1 (0.3)
Nonfatal myocardial infarction	5 (1.3)
Acute coronary syndrome	3 (0.8)
Unplanned PCI	2 (0.5)
Unplanned CABG	1 (0.3)
Confirmed ischemic stroke	1 (0.3)
Heart failure	1 (0.3)
Other cardiovascular event	1 (0.3)

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft. [a]All events were considered treatment-emergent adverse events, except 1 case of nonfatal myocardial infarction that occurred after study treatment discontinuation. No event was considered treatment-related. [b]One subject had two events (one nonfatal myocardial infarction and one acute coronary syndrome).

Drawing from the literature evaluating co-prescribed PPI therapy with NSAID therapy, it is well documented that adherence to co-prescribed acid reduction therapy appears to be suboptimal [31,33,35,40] and adherence to co-prescribed gastroprotective medications significantly declines over time leading to increasing risk of upper GI events [35,40]. A practical approach to address this issue of nonadherence has been the development of fixed-dose formulations consisting of an NSAID and an acid-suppressive agent (e.g., diclofenac/misoprostol [41], naproxen/esomeprazole [42], ibuprofen/famotidine [43]). Given the efficacy of PPIs in reducing gastric mucosal injury, extending the concept of fixed dosing to aspirin and a PPI for patients in need of aspirin prophylaxis for cardiovascular events has clinical face validity [44–46]. PA32540 with its novel coordinated delivery of 325 mg of aspirin and 40 mg of immediate-release omeprazole [37] applies this concept to the large at-risk population of patients who clinically require long-term aspirin therapy [38]. Additionally, studies suggest that PPI therapy has the potential to increase adherence to aspirin therapy in patients requiring long-term treatment with aspirin for the prevention of secondary cardiovascular events [28,47–49].

The unique nature of this study is its focus on a clinically relevant population at increased risk of upper GI events (i.e., age ≥55 years or age <55 years with a history of ulcer within 5 years before study enrollment) who required long-term aspirin therapy for secondary cardiovascular/cerebrovascular prevention. Given the long-term clinical necessity of aspirin therapy in this population, this study was designed to evaluate the overall safety of PA32540 tablets, including GI and cardiovascular events, for a 12-month period. Beyond upper GI events such as bleeding, a major deterrent to long-term aspirin utilization can be the development of dyspepsia and/or GERD-like symptoms [8–10], which are often controlled with PPI therapy. In the Phase 3 double-blind trials, the incidence of dyspepsia was 11% with PA32540 versus 30% with aspirin alone ($P < 0.001$), while the combined events of GERD, esophagitis, erosive esophagitis, or reflux esophagitis were reported in 6.1% of PA32540-treated subjects versus 23.9% of aspirin-treated subjects ($P < 0.001$ for the difference between groups) [38].

Of the 380 enrolled subjects, 76% completed the study and took PA32540 for at least 348 days. The remaining subjects left the study due to AEs (13%) or other reasons. The most common AE leading to study withdrawal was GERD, which occurred in 4/379 subjects (1.1%). All remaining events leading to study discontinuation occurred in <1% of subjects.

Treatment-related AEs were reported for approximately 10% of subjects, and the most common event was dyspepsia, which occurred in 2% (8/379) of subjects. However, treatment-related dyspepsia was the cause of study discontinuation in only 1/379 (0.3%) subjects. This rate of occurrence is significantly lower than previously reported with aspirin [8–10]. Additionally, treatment-related GERD was reported in 3/379 (0.8%) subjects and resulted in study discontinuation in 2/379 (0.5%) subjects. Again, this is a

lower rate than that reported previously in patients receiving aspirin [8–10]. In the Phase 3 double-blind endoscopic pivotal trials with PA32540, the incidence of dyspepsia was significantly lower with PA32540 versus aspirin alone [38]. Likewise, reflux and esophagitis events were also significantly lower with PA32540 [38].

While these data support the benefit of long-term acid suppression in reducing aspirin-associated symptoms, PPIs also impact the rate of upper GI complications such as bleeding and are recommended by evidence-based consensus guidelines to minimize the risk of GI bleeding in at risk patients [15,16]. Previous studies on aspirin and NSAID users have demonstrated that lack of adherence to acid suppression therapy increases the rate of upper GI events [28,33,35], which may be circumvented by the use of an integrated formulation.

A limitation of the present study is its open-label design and lack of a control arm, which provide less rigorous results than those from a randomized, double-blind trial. In particular, the Phase 3 double-blind studies were designed to more specifically collect upper GI symptoms compared to the present open-label study, and therefore, they more accurately reflect the observed difference between subjects on PA32540 versus control (EC-ASA 325 mg alone). Additionally, eligible subjects had been on aspirin for ≥3 months before enrollment and during that time frame reported no clinically significant GI issues precluding participation in this study. As such, there may be some level of tolerance within the study population, leading to lower events as reported. The strength of this study, however, is its duration (providing up to 12 months of data on safety and tolerability) and its large clinically relevant sample. However, subjects with a revascularization procedure <6 months before enrollment as well as those who were *H. pylori* positive or had a history of prior significant upper GI event were not eligible for study enrollment. Therefore, our findings may not be generalized to subjects at higher CV and/or GI risk, and future study in these higher-risk populations is required. As good clinical practice dictates, physicians should carefully monitor newly diagnosed ischemic heart disease patients initiating aspirin therapy.

Conclusion

No new or unexpected safety concerns were identified following treatment with PA32540 once daily for up to 12 months in subjects at risk for aspirin-associated gastric injury. The type and pattern of AEs emerging in this one-year study were consistent with prior experience with aspirin and omeprazole administered as single agents.

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Conflict of Interest

JLG is a GI Clinical Event Committee member and consultant to POZEN, Inc. and has received research funding from Pfizer, Exact Sciences, Alvine Pharmaceuticals, Synergy Pharmaceuticals, Sanofi Pasteur, and Novo Nordisk. DJW is a Cardiovascular Review Committee member and has received research funding from Medtronic and ResMed. JMS is a GI Clinical Event Committee member and consultant to POZEN, Inc., Sanofi, Iroko Pharmaceuticals, Pfizer, and Takeda Pharmaceuticals. BLC is a GI Clinical Event Committee member and consultant to Iroko Pharmaceuticals, McNeil Consumer Healthcare, Ritter Pharmaceuticals, Sucampo Pharmaceuticals, Inc., and Takeda Pharmaceuticals. GME is a GI Clinical Event Committee member, speaker for Ferring, Salix, and Takeda Pharmaceuticals, and consultant to Endo CDX. AL is a GI Clinical Event Committee member and advisory board member to POZEN, Inc. and has served as an advisory board member and speaker to Bayer, and received research funding from Bayer. JGF is an employee and stockholder of POZEN, Inc. and has stock options in POZEN, Inc.

Author contributions

Author contributions: JLG, JMS, BLC, and JGF were involved in the conception and design of the study. All authors were involved in the analysis or interpretation of data. JLG, DJW, BLC, and JGF were involved in the drafting of the manuscript. All authors were involved in the critical review and revision of the manuscript. All authors approved the final version of the manuscript, including the authorship list.

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