

# PA32540 (a coordinated-delivery tablet of enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg) versus enteric-coated aspirin 325 mg alone in subjects at risk for aspirin-associated gastric ulcers: Results of two 6-month, phase 3 studies



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**Background** Discontinuations and/or interruptions in aspirin therapy for secondary cardioprotection due to upper gastrointestinal (UGI) complications or symptoms have been shown to increase the risk for subsequent cardiovascular events. PA32540 is a coordinated-delivery, combination tablet consisting of enteric-coated aspirin (EC-ASA) 325 mg and immediate-release (IR) omeprazole 40 mg.

**Methods** Two identically-designed, 6-month, randomized, double-blind trials evaluated PA32540 vs. EC-ASA 325 mg in a secondary cardiovascular disease prevention population taking aspirin 325 mg daily for  $\geq 3$  months and at risk for ASA-associated gastric ulcers (GUs). The combined study population was 1049 subjects (524 randomized to PA32540, 525 to EC-ASA 325 mg). The primary endpoint was the occurrence of endoscopically-determined gastric ulceration over 6 months. Safety outcomes included the rates of major adverse cardiovascular events (MACE) and UGI symptoms.

**Results** Significantly fewer PA32540-treated subjects (3.2%) developed endoscopic GUs vs. EC-ASA 325 mg-treated subjects (8.6%) ( $P < .001$ ). Overall occurrence of MACE was low (2.1%), with no significant differences between treatments in types or incidence of MACE. PA32540-treated subjects had significantly fewer UGI symptoms ( $P < .001$ ) and significantly fewer discontinuations due to pre-specified UGI adverse events (1.5% vs. 8.2%, respectively;  $P < .001$ ).

**Conclusions** PA32540 reduced the incidence of endoscopic GUs compared to EC-ASA 325 mg, but with a similar cardiovascular event profile. Due to fewer UGI symptoms, continuation on aspirin therapy was greater in the PA32540 treatment arm. (Am Heart J 2014;168:495-502.e4.)

Aspirin (ASA) use in patients with known cardiovascular (CV) disease can reduce the risk of a vascular event by approximately 25%,<sup>1</sup> but patient non-adherence rates for ASA therapy remain high.<sup>2</sup> Gastrointestinal (GI) issues, which range from symptoms such as heartburn

and dyspepsia to more severe conditions such as gastric and duodenal ulcer disease and complications such as bleeding, have been reported as reasons for discontinuation of ASA therapy.<sup>2,3</sup> As a result, patients may be at an increased risk for CV events after stopping ASA therapy.<sup>3,4</sup>

Current options used in attempt to reduce ASA-associated mucosal injury and symptoms have included the use of enteric-coated (EC) or buffered ASA products. However, studies have shown upper GI (UGI) toxicity is not reduced with these formulations; the rate of UGI ulcer bleeding remains the same.<sup>5,6</sup> For ASA-users, PPI therapy is recommended for patients at an increased risk for GI bleeding.<sup>7</sup> However, in daily practice, adherence to co-prescribed proton pump inhibitor (PPI) therapy has been reported to be less than 50%.<sup>8,9</sup>

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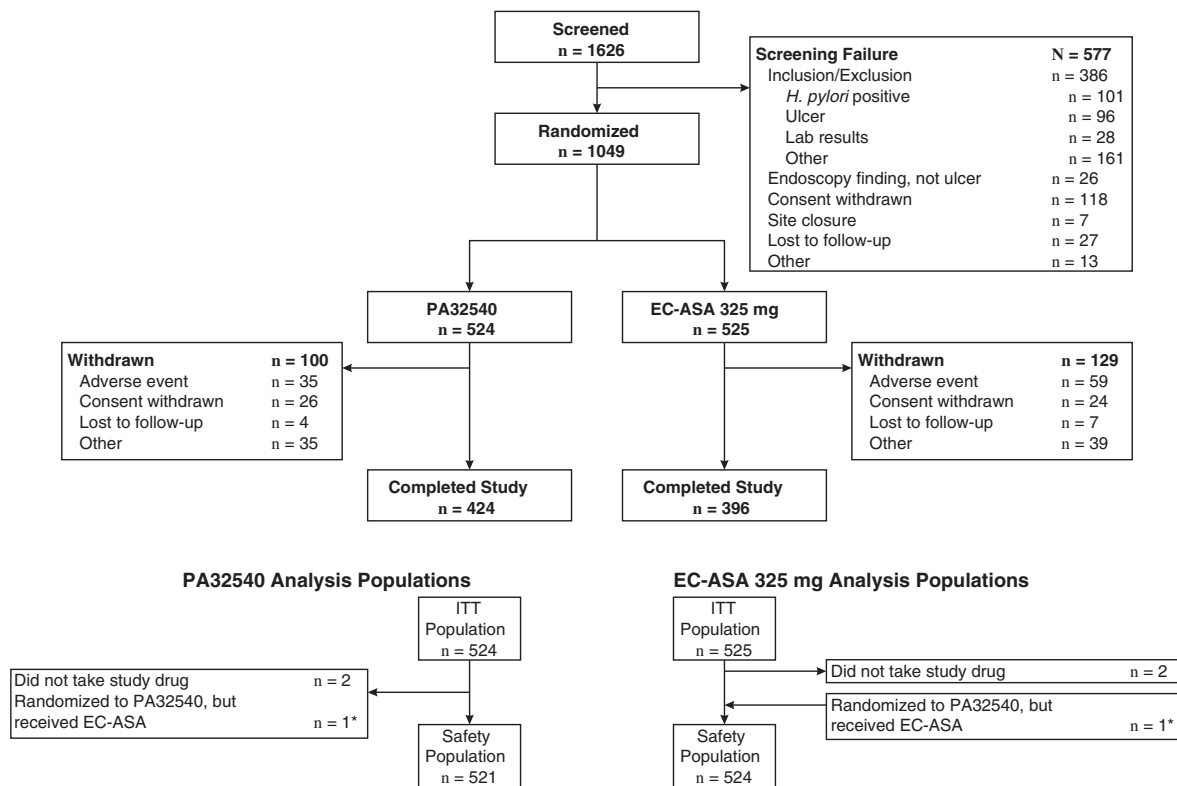
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Figure 1



Trial profile and analysis populations.

PA32540 is a coordinated-delivery tablet consisting of an inner core of enteric-coated aspirin (EC-ASA) 325 mg surrounded by an outer layer of immediate-release (IR) omeprazole 40 mg. The IR-omeprazole is embedded within a film coat where it is available for instantaneous dissolution, while ASA release occurs only after GI tract pH is >5.5.

The clinical benefits of PA32540 were studied in 2 separate and identically-designed, long-term, double-blind, active-control studies, and each trial was analyzed separately. The data from these trials are presented as a pooled analysis for this publication.

## Methods

Two independent, randomized, double-blind, active-control, parallel group comparator studies were conducted within the United States. Study 301 (N = 530) was conducted in 78 centers from November 2009 to January 2012 and Study 302 (N = 519) in 75 centers from October 2009 to January 2012. In each study, subjects were stratified into 3 groups according to baseline nonsteroidal anti-inflammatory drug (NSAID) use (non-specific NSAID, COX-2 inhibitor NSAID [celecoxib], no NSAID) and then

randomized in a 1:1 ratio within each strata to either PA32540 or EC-ASA 325 mg. Each study treatment was taken once daily in the morning for up to 6 months. The studies were conducted in accordance with the principles of the Declaration of Helsinki. The study protocols were approved by the institutional review board at each participating center, and each subject provided signed, written informed consent before any screening procedures were performed (<http://clinicaltrials.gov>, identifiers NCT00960869 and NCT00961350).

Eligible subjects were male or female adults with established CV or cerebrovascular disease who had been taking ASA 325 mg daily for  $\geq 3$  months and were expected to continue daily ASA for  $\geq 6$  months. Aspirin for secondary prevention is recommended in doses of up to 325 mg.<sup>10,11</sup> Approximately 35% of aspirin users in the United States take doses of 325 mg or greater.<sup>12</sup> Subjects also had to be at risk for ASA-associated gastric ulceration, defined in the protocol as either  $\geq 55$  years-of-age or 18 to 54 years old with a documented history of gastric or duodenal ulcer within the 5 years before study enrollment. Key exclusion criteria included UGI ulcer  $\geq 3$  mm in diameter with depth at the screening/baseline endoscopy, positive *H. pylori* (via stool antigen testing) at screening, history of serious

**Table 1.** Baseline demographics and characteristics (ITT populations)

	PA32540 (n = 265)	EC-ASA 325 mg (n = 265)	PA32540 (n = 259)	EC-ASA 325 mg (n = 260)	PA32540 (n = 524)	EC-ASA 325 mg (n = 525)
Baseline characteristics	Study 301		Study 302		Combined Populations	
Age, mean (range), years	66.3 (41-88)	65.8 (51-88)	66.2 (41-87)	65.6 (39-86)	66.3 (41-88)	65.7 (39-88)
Males, n (%)	188 (70.9)	190 (71.7)	187 (72.2)	184 (70.8)	375 (71.6)	374 (71.2)
Race, n (%)						
White	245 (92.5)	228 (86.0)	225 (86.9)	245 (94.2)	470 (89.7)	473 (90.1)
Black	19 (7.2)	31 (11.7)	30 (11.6)	11 (4.2)	49 (9.4)	42 (8.0)
Asian	0	4 (1.5)	2 (0.8)	4 (1.5)	2 (0.4)	8 (1.5)
Other	1 (0.4)	2 (0.8)	2 (0.8)	0	3 (0.6)	2 (0.4)
Ethnicity, n (%)						
Not Hispanic or Latino	241 (90.9)	246 (92.8)	237 (91.5)	238 (91.5)	478 (91.2)	484 (92.2)
Body mass index, mean (SD), kg/m <sup>2</sup>	31.0 (6.3)	31.1 (6.0)	31.0 (5.4)	31.2 (6.0)	31.0 (5.9)	31.1 (6.0)
Hx of gastric/duodenal ulcer (GU/DU), n (%)	20 (7.5)	32 (12.1)	33 (12.7)	31 (11.9)	53 (10.1)	63 (12.0)
Recent Hx (within past 5 years) of GU/DU, n (%)	13 (4.9)	13 (4.9)	12 (4.6)	19 (7.3)	25 (4.8)	32 (6.1)
Hx of previous MI, n (%)	115 (43.4)	100 (37.7)	99 (38.2)	99 (38.1)	214 (40.8)	199 (37.9)
Hx of PVD, n (%)	40 (15.1)	32 (12.1)	22 (8.5)	29 (11.2)	62 (11.8)	61 (11.6)
Hx of cerebrovascular disease, n (%)	56 (21.1)	64 (24.2)	46 (17.8)	49 (18.8)	102 (19.5)	113 (21.5)
Lipid-lowering therapy, n (%) <sup>*</sup>	226 (85.6)	211 (79.6)	213 (82.9)	219 (84.6)	439 (84.3)	430 (82.1)
Clopidogrel, n (%)	58 (21.9)	54 (20.4)	53 (20.5)	56 (21.5)	111 (21.2)	110 (21.0)
NSAIDs, n (%)	20 (7.5)	24 (9.1)	24 (9.3)	25 (9.6)	44 (8.4)	49 (9.3)

Abbreviation: DU, duodenal ulcer.

Hx, History. There were no statistically significant differences in baseline parameters between the individual studies or between treatment groups in the combined study populations. <sup>\*</sup> Data represent use of lipid-modifying agents at anytime during the study based on the safety population. Study 301: n = 264 for PA32540 and n = 265 for EC-ASA 325 mg; study 302 (n = 257 for PA32540 and n = 259 for EC-ASA 325 mg; for the combined populations: n = 521 for PA32540 and n = 524 for EC-ASA 325 mg.

UGI event/disorder or surgery leading to impaired drug absorption, or recent (<6 months prior to screening) coronary revascularization procedure. Subjects taking non-aspirin NSAIDs at baseline were allowed to continue therapy if use was chronic and expected to continue through the study period. Subjects were instructed to take their NSAID ≥2.5 hours after study treatment and report any change to the study investigator.

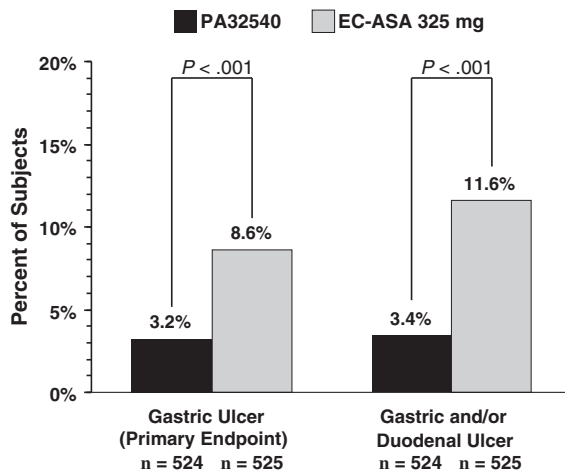
Endoscopy was performed at screening/baseline, and after 1, 3, and 6 months of treatment. All attempts were made to have all endoscopies for a given subject performed by the same endoscopist. If a gastric, duodenal, or esophageal ulcer was detected, study drug was discontinued, and the subject was withdrawn from the study. Duodenal and esophageal ulcers were considered adverse events. However, endoscopic gastric ulceration was the primary efficacy endpoint, and as such GUs were not considered as adverse events.

Other evaluations at follow-up (months 1, 3, and 6) included assessments of heartburn and safety (including adverse events and laboratory analyses). 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 was reached prior to 6 months.

The primary efficacy endpoint was the cumulative proportion of subjects developing endoscopically-determined gastric ulceration throughout 6 months of treatment. A gastric ulcer was defined as a mucosal break

of ≥3 mm in diameter with depth.<sup>13,14</sup> Secondary efficacy and tolerability endpoints included endoscopically-determined gastric and/or duodenal ulcers at 6 months, “Treatment Success” (defined as those subjects without endoscopic GUs and without pre-specified UGI adverse events leading to study discontinuation), discontinuations due to pre-specified UGI adverse events (online [Appendix A: List of pre-specified UGI adverse events](#)), and heartburn resolution. Heartburn resolution (ie, the absence of heartburn) was analyzed regardless of the presence or absence of heartburn at baseline. The incidence of heartburn (defined as a burning feeling rising from the stomach or lower part of the chest towards the neck) was obtained using a standardized questionnaire in which subjects were asked to rate their heartburn symptoms (none, mild, moderate, or severe) over the 7 days before each study visit.<sup>15</sup>

Two independent adjudication committees blinded to study treatment evaluated all investigator-reported serious CV events and potential UGI events based on reported symptoms, laboratory values, and/or endoscopic findings found at scheduled or for-cause evaluations and endoscopies. The major adverse cardiovascular events (MACE) criteria (see online [Appendix B](#)) included CV death, acute coronary syndrome (including non-fatal or fatal myocardial infarction), ischemic stroke, heart failure, and unplanned coronary artery bypass graft or percutaneous coronary intervention.<sup>16</sup> The results of the adjudicated findings were

**Figure 2**

Cumulative rate of upper gastrointestinal injury over 6 months. Significantly ( $P < .001$ ) fewer subjects treated with PA32540 vs. EC-ASA 325 mg developed gastrointestinal injuries, including endoscopic gastric ulcers, over the 6-month study.

tabulated. The GI Events Committee developed pre-defined criteria for UGI ulcer complications (see online [Appendix C](#)).

### Statistical analyses

The primary efficacy analysis was conducted on the intention-to-treat population, defined as all randomized subjects. All safety analyses were conducted on the safety population, defined as all randomized subjects who took  $\geq 1$  dose of study medication, and these subjects were analyzed according to the actual treatment taken. All statistical tests were two-sided with significance at the 5% level. All analyses were done using SAS Version 9.2 (SAS Inc, Cary, NC).

A Cochran-Mantel-Haenszel (CMH) test stratified by NSAID use at randomization was used to test the null hypothesis that there was no difference between treatment groups with regard to the primary endpoint. This test was also used for evaluation of endoscopic GUs at month 1 and month 3 as well as for the secondary endpoints, and for the comparison of subjects who discontinued from the study for any reason or due to any adverse event. (For heartburn resolution, the CMH test was stratified by baseline heartburn severity and NSAID use [Yes/No] at randomization.) A post hoc analysis reviewed gastric ulcer size using the largest ulcer diameter. The cumulative proportion of subjects in each treatment group with endoscopic GUs of  $\geq 5$  mm in diameter was compared using a CMH test stratified by NSAID use (COX-2/Other NSAID/No NSAID). The post hoc analysis of treatment-emergent adverse event-preferred terms was compared using a Fisher exact test.

The sample sizes for the individual studies were based on the assumption that 13% of EC-ASA 325 mg-treated subjects would develop an endoscopic gastric ulcer over 6 months vs. 5% of subjects taking PA32540.<sup>17-19</sup> The Fisher's exact test, with a two-sided significance level of 5% and 86% power, required 250 subjects per treatment arm in each study to detect the difference between PA32540 and EC-ASA 325 mg. This sample size also provided adequate power to test the secondary endpoints.

For purposes of this publication, a pooled analysis was performed. Pooling was deemed appropriate given that the clinical design was identical, study populations were similar, and analysis was consistent with the individual study results.

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## Results

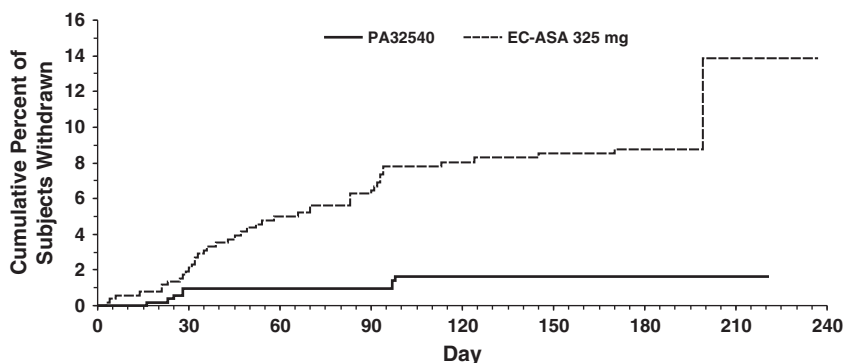
For the two studies, 1626 subjects were screened, and 577 were screen failures ([Figure 1](#)). A total of 96 of (5.9%) 1626 screened subjects were not eligible for enrollment due to the finding of a gastric, duodenal, and/or esophageal ulcer at the screening endoscopy.

Of the 1049 eligible subjects, 524 were randomized to PA32540 and 525 to EC-ASA 325 mg; this was the intention-to-treat population. A total of 820 subjects completed the studies (424 in the PA32540 group [80.9%] and 396 in the EC-ASA group [75.4%]) ([Figure 1](#)), and 229 discontinued (100 in the PA32540 group [19.1%] and 129 in the EC-ASA group [24.6%];  $P = .034$  for the difference between treatments). For both treatments, the most common reason for early discontinuation was adverse events (6.7% for PA32540 and 11.2% for EC-ASA 325 mg;  $P = .010$  for the difference between treatments). Among clopidogrel-users, study discontinuation was 17.1% in the PA32540 group and 28.2% in the EC-ASA group. Baseline demographics and medical history are shown in [Table I](#). The mean age of the study population was 66 years; approximately 20% of subjects were  $< 60$  years old and 2% were  $< 55$  years old.

### Primary endpoint

After 6 months of treatment, endoscopic GUs were observed in 3.2% of PA32540-treated subjects and 8.6% of EC-ASA 325 mg-treated subjects ( $P < .001$ ) ([Figure 2](#)). A significant difference between treatments was observed as early as the first post-baseline visit (month 1), and remained significant ( $P < .001$ ) throughout the trial. Median gastric ulcer size was 3 mm (range 3-8 mm) in the PA32540 group and 5 mm (range 3-30 mm) in the EC-ASA group. Endoscopic GUs that were  $\geq 5$  mm in diameter

**Figure 3**



Kaplan-Meier estimates of the cumulative percent of subjects who discontinued over time due to pre-specified upper gastrointestinal adverse events. The observed incidence of discontinuation over 6 months was 1.5% for PA32540 and 8.2% for EC-ASA 325 mg ( $P < .001$ ).

were observed in 1.3% of PA32540 subjects and 4.4% of EC-ASA subjects ( $P = .003$ ). The primary endpoint was also met in both individual studies. In Study 301, endoscopic GU at Month 6 was 3.8% for PA32540 and 8.7% for EC-ASA ( $P = .020$ ), and in Study 302, 2.7% for PA32540 and 8.5% for EC-ASA ( $P = .005$ ).

Among NSAID-users at baseline, the cumulative rates of endoscopic GU at Month 6 were 4.5% (2/44) for PA32540 and 10.2% (5/49) for EC-ASA 325 mg vs. 3.1% (15/480) for PA32540 and 8.4% (40/476) for EC-ASA 325 mg among those not taking NSAIDs.

### Secondary endpoints

Significantly fewer subjects treated with PA32540 developed an endoscopic gastric and/or duodenal ulcer over the 6-month study period compared with EC-ASA 325 mg (3.4% vs. 11.6%, respectively;  $P < .001$ ) (Figure 2), and 95.2% of PA32540 subjects had treatment success compared with 83.2% EC-ASA subjects ( $P < .001$ ). The Kaplan-Meier estimates of subjects discontinued overtime due to pre-specified UGI adverse events is shown in Figure 3. Over the 6-month study period, 1.5% of PA32540 subjects compared with 8.2% of EC-ASA 325 mg subjects discontinued due to pre-specified UGI adverse events ( $P < .001$ ). Beginning at Month 1 and continuing throughout the study, significantly ( $P < .001$ ) more PA32540-treated subjects were heartburn-free than EC-ASA 325 mg-treated subjects (Figure 4). Similar significant results were observed in each individual trial.

### Safety

#### Adjudicated events

**Cardiovascular.** A total of 22 subjects (2.1% of the study population) were adjudicated to have had MACE over the 6-month study period, and the overall event rate was similar with both treatments (1.7% for PA32540 and 2.5% for EC-ASA 325 mg) (Table II). The most common

MACE was non-fatal myocardial infarction, which occurred in 5 subjects taking PA32540 and 3 subjects taking EC-ASA 325 mg.

Among subjects who reported clopidogrel use at baseline, adjudicated MACE occurred in 6.3% (7/111) of PA32540-treated subjects and in 3.6% (4/110) EC-ASA 325 mg-treated subjects;  $P = .366$ .

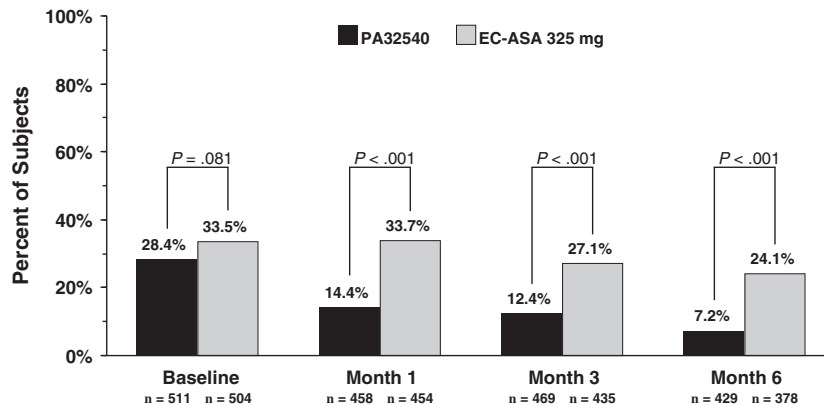
**Investigator-Reported Adverse Events.** As expected, most adverse events were GI-related (Table III). Of note, dyspepsia occurred in 30% of EC-ASA-treated vs. 11% of PA32540-treated subjects ( $P < .001$ ). Also, the combined events of gastroesophageal reflux disease, esophagitis, erosive esophagitis, or reflux esophagitis was significantly ( $P < .001$ ) less in PA32540-treated subjects (6.1%) vs. EC-ASA 325 mg-treated subjects (23.9%). Serious adverse events were reported in 7.5% of PA32540 subjects and in 7.8% of EC-ASA subjects, and these included 4 deaths (all judged as not related to study treatments by the investigators)—2 in the PA32540 group and 2 in the EC-ASA group.

### Discussion

In the studies presented here, use of PA32540, which provides coordinated delivery of 325 mg of EC-ASA and 40 mg of immediate-release omeprazole, was associated with a significantly reduced incidence of endoscopic GUs without a difference in MACE between the two treatment arms. During the 6 months of treatment, discontinuation of study medication for pre-specified UGI adverse events or for any reason was significantly less in the PA32540-treated subjects.

A reduction in the incidence of endoscopic GUs in patients taking ASA randomized to enteric-coated PPIs (esomeprazole) vs. placebo has been reported previously.<sup>13,14</sup> In addition, the COGENT study<sup>20</sup> evaluated a fixed-dose combination of clopidogrel

Figure 4



Presence of heartburn as reported on the standardized questionnaire. Throughout the study, heartburn was present in significantly fewer subjects treated with PA32540 vs. EC-ASA 325 mg ( $P < .001$ ).

and omeprazole vs. clopidogrel alone, and patients in both treatment arms were also taking ASA. Although this publication provided valuable information about the GI benefits of omeprazole in a CV population on dual anti-platelet therapy, the study results are limited given that the trial was terminated before completion. In the above-mentioned trials, ASA dosing was not controlled. The present randomized controlled trials provide information about the use of a combination product of ASA with an immediate-release (IR) formulation of omeprazole, which has distinct pharmacokinetic and pharmacodynamic properties compared to an enteric-coated (EC) formulation of omeprazole.<sup>21</sup> The concern is that with degradation of the immediate-release PPI by the acidic environment of the stomach, the subsequent level of acid control would be insufficient to reduce the risk of developing endoscopic GUs. However, IR-omeprazole 40 mg (from PA32540) has demonstrated adequate intragastric pH control,<sup>21</sup> comparable to acid suppression with EC-omeprazole 20 mg.<sup>22</sup> The application of this level of intragastric pH control was further demonstrated in the present studies by the significant reduction in the rate of endoscopic GUs and other UGI mucosal injuries.

The types and incidence of MACE events were similar in the PA32540 and EC-ASA groups. Although the sample size, trial duration, and total event numbers were smaller than in most CV outcome trials, the long-term CV benefit of PA32540 is suggested by the bioequivalence of PA32540 to EC-ASA 325 mg. To date, published data have demonstrated that PA32540 is bioequivalent to Ecotrin 325 mg (enteric-coated aspirin, GlaxoSmithKline Consumer Healthcare, Moon Township, PA) based on salicylic acid, the major pharmacological moiety derived from ASA in systemic circulation.<sup>21</sup>

The FDA currently recommends avoiding the concomitant use of clopidogrel and omeprazole.<sup>23</sup> Gurbel

and colleagues<sup>24</sup> observed that inhibition of platelet aggregation was significantly higher for PA32540 when dosed 10 hours apart from clopidogrel compared with synchronous dosing of EC-ASA, clopidogrel, and EC-omeprazole ( $P = .004$ ). The lack of difference in MACE events between treatment arms in the studies reported here is noteworthy given concerns that PPIs may interfere with the anti-platelet properties of clopidogrel, thus decreasing its effectiveness. While *ex vivo* studies in patients and healthy subjects have supported an interaction with PPIs and clopidogrel, clinical studies in patients have shown mixed results.<sup>25</sup>

Similar concerns have been raised regarding interference with the platelet-inhibiting properties of ASA when prescribed alongside a PPI. An increased risk of future CV events among ASA-treated patients who received PPI therapy was observed in a retrospective cohort study that evaluated patients who survived 30 days following their index myocardial infarction.<sup>26</sup> In contrast, a pharmacodynamic study has shown no such link in healthy subjects taking co-administered esomeprazole and ASA.<sup>27</sup> In the Gurbel study described above,<sup>24</sup> there was no difference between treatment arms in arachidonic acid-induced platelet aggregation. Both the pharmacokinetic<sup>21</sup> and pharmacodynamic<sup>24</sup> data do not suggest a drug-drug interaction with the ASA and PPI components of the PA32540 product, as specifically studied in subjects receiving PA32540.

In a recent meta-analysis assessing medication adherence for CV disease prevention, non-adherence to ASA therapy for the secondary prevention of CV disease was found to be approximately 35% (2 studies, N = 16,207), presumably driven by the issues of GI tolerability with continued use.<sup>28</sup> It is of clinical relevance that in our trial, subjects receiving PA32540 reported significantly less ASA-associated dyspepsia and heartburn compared with

**Table II.** Adjudicated MACEs (safety population)\*

MACE	PA32540	EC-ASA 325 mg
	(n = 521)	(n = 524)
	Number of Subjects (%)	
Subjects with any MACE <sup>†</sup>	9 (1.7%)	13 (2.5%)
Cardiovascular death	0 (0%)	1 (0.19%)
Nonfatal myocardial infarction	5 (0.96%)	3 (0.57%)
Confirmed ischemic stroke	0 (0%)	0 (0%)
Acute coronary syndrome <sup>‡</sup>	0 (0%)	4 (0.76%)
Transient ischemic attack	1 (0.19%)	4 (0.76%)
Congestive heart failure	1 (0.19%)	1 (0.19%)
Other, mild coronary artery disease	1 (0.19%)	0 (0%)
Other, planned CABG	1 (0.19%)	0 (0%)

\* Number of subjects based on actual treatment taken.

<sup>†</sup> Total number of subjects (%) with any adjudicated MACE: 22 (2.1%).

<sup>‡</sup> One subject had 2 events of acute coronary syndrome.

subjects randomized to EC-ASA 325 mg alone; dyspepsia was reported by 11% of subjects taking PA32540 and 30% of subjects taking EC-ASA ( $P < .001$ ). We believe that this difference in symptoms in part explains the significantly reduced discontinuation rate of study medication due to pre-specified UGI adverse events (1.5% for PA32540 vs. 8.2% with EC-ASA 325 mg alone;  $P < .001$  for the difference between treatments) and the overall discontinuation of study medication (19.1% for PA32540 vs. 24.6% for EC-ASA 325 mg;  $P = .034$ ).

### Limitations

While a low CV event rate and improved GI tolerability were clearly demonstrated in these studies, the short follow-up duration (6 months) prevented examination of the long-term efficacy/effectiveness of PA32540. An additional limitation was that all subjects entering the studies were taking ASA for  $\geq 3$  months before trial entry. As such, the study sample may have been biased for subjects who were likely tolerant to ASA therapy, and the generalizability of the study results might be questioned. Nevertheless, subjects in both treatment arms were at an increased risk for GUs, and the lower rates of UGI symptoms and injuries with PA32540 demonstrated the benefit of immediate-release PPI therapy. These studies did not address a comparison of the combination product to the individual components.

### Conclusion

By providing a coordinated delivery of 325 mg of EC-ASA and 40 mg of immediate-release omeprazole, PA32540 significantly reduced the cumulative incidence of endoscopic GUs at 6 months (primary endpoint of the studies) vs. 325 mg of EC-ASA alone. Additionally, troublesome GI symptoms were reduced within the

**Table III.** Most common treatment-emergent adverse events (safety population)\*

Parameter	PA32540	EC-ASA 325 mg
	(n = 521)	(n = 524)
	Number of subjects (%)	
Any TEAE	374 (71.8)	446 (85.1)
Any GI-related TEAE	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)
Nausea	17 (3.3)	12 (2.3)
Esophagitis	17 (3.3)	63 (12.0)
Erosive duodenitis	7 (1.3)	37 (7.1)
GERD	7 (1.3)	20 (3.8)
Reflux esophagitis	6 (1.2)	17 (3.2)
Erosive esophagitis	2 (0.4)	33 (6.3)
Duodenal ulcer	1 (0.2)	19 (3.6)

GERD, Gastroesophageal reflux disease; TEAE, treatment-emergent adverse event.

\* Investigator-reported TEAEs by preferred term occurring in  $\geq 3\%$  of subjects in either treatment group.

population of patients receiving the study medication. Although limited by sample size, low overall event rate, and short follow-up period, there were no significant CV safety signals. Tolerability and treatment continuation with ASA therapy was significantly better with PA32540 than with EC-ASA alone, and this has implications for improved adherence and subsequent long-term ASA efficacy/effectiveness in secondary CV disease patients at risk for ASA-associated UGI injuries.

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## Appendix A. List of pre-specified upper GI adverse event preferred terms

Preferred Terms
abdominal discomfort
abdominal pain
abdominal pain upper
abdominal tenderness
duodenal hemorrhage
duodenal ulcer
duodenal ulcer hemorrhage
duodenitis
duodenitis hemorrhagic
dyspepsia
eosinophilic esophagitis
epigastric discomfort
erosive duodenitis
erosive gastritis
erosive esophagitis
gastric hemorrhage
gastric mucosal lesion
gastric ulcer hemorrhage
gastritis
gastritis atrophic
gastritis erosive
gastritis haemorrhagic
gastroduodenitis
gastrointestinal erosion
gastrointestinal hemorrhage
gastrointestinal inflammation
gastrointestinal mucosal disorder
gastroesophageal reflux disease
gastroesophagitis
hematemesis
hematochezia
hyperchlorhydria
melaena
nausea
esophageal discomfort
esophageal disorder
esophageal hemorrhage
esophageal ulcer
esophagitis
reflux esophagitis
vomiting

## Appendix B. MACE definitions

### Cardiovascular events and definitions

#### 1. Cardiovascular death

- Sudden cardiac death (SCD): An unexpected death in a previously stable patient. Patients in this category should have had recent human contact before the event. This includes patients who after attempted resuscitation, were comatose and then died. Patients who have been out of contact for a prolonged or unknown period of time should be classified as unknown.

- Fatal myocardial infarction (MI): Death from a cardiac event within 28 days of acute MI (including sudden, unexpected cardiac death involving cardiac arrest, often with symptoms suggestive of myocardial ischemia and accompanied by presumably new ST elevation or new left bundle-branch block (LBBB), and/or evidence of fresh thrombus by a coronary angiography and/or autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood).
- Pump failure death: Death involving a substantive worsening of heart failure symptoms and/or signs resulting in augmentation or addition of heart failure therapies. (Reference: O'Connor CM, Miller AB, Blair JE, et al. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) program. *Am Heart J* 2010;159:841-9. Erratum in: *Am Heart J*. 2012 May;163(5):900.)
- Death due to stroke: Death involving cerebral hemorrhage, cerebral infarct or cerebral embolism, in the absence of an MI.
- Cardiac procedural death: Death within 30 days of and related to a cardiac procedure.
- Other cardiovascular: Death in which there is evidence of a primary cardiovascular etiology that cannot be classified as definite sudden death, MI, pump failure, stroke, or procedure-related (e.g., ruptured aortic aneurysm, aortic dissection, pulmonary embolism, cardiac tamponade).

#### 2. Non-fatal MI

Non-fatal MI will be defined as presentation in a clinical setting consistent with myocardial ischemia with evidence of myocardial necrosis, and alive 7 days after the index event. Non-fatal MI will also be characterized by Type as per UDMI\* criteria (See Appendix B, page 5).

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia
  - Electrocardiogram (ECG) changes indicative of new ischemia (new ST-T changes or new LBBB)
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- For percutaneous coronary interventions (PCI) in subjects with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL have been designated as defining PCI-related MI. A

subtype related to a documented stent thrombosis is recognized. Stent thrombosis will be adjudicated according to Academic Research Consortium (ARC) criteria. Events judged as “definite” and “probable” stent thrombosis will meet this definition.

- For coronary artery bypass grafting (CABG) in subjects with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.
- Subjects presenting after randomization for routine evaluation or other reasons and who are found to have evidence of interval prior MI will be defined to have had non-fatal MI. Any one of the following criteria meets the diagnosis for prior MI:
  - o Development of new pathological Q waves with or without symptoms.
  - o Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of non-ischemic cause.
  - o Pathological findings of a healed or healing MI.

### 3. Confirmed ischemic stroke

Stroke is defined as a rapidly developing loss of brain function that is non-reversible and due to an interruption in the blood supply to all or part of the brain, and that persists for more than 24 hours, together with a diagnostic imaging study.

### 4. Unplanned Coronary Artery Bypass Graft Surgery

### 5. Unplanned percutaneous coronary intervention

- Any unplanned PCI, including any mechanical catheter-based revascularization techniques such as stenting, balloon angioplasty, coronary atherectomy or laser therapy.
- Other surgical-based cardiac revascularization techniques (e.g., transmyocardial revascularization).

### 6. Acute coronary syndromes (ACS)

- Acute coronary syndromes are defined as a group of clinical syndromes compatible with acute myocardial ischemia, ranging from ST-segment elevation myocardial infarction (MI) to non-ST-segment elevation MI and unstable angina. ACS without biological marker (unstable angina without detectable myocyte necrosis) is defined as non-ST-segment elevation ACS not accompanied by the release of markers of cell death (troponin and CK-MB), and is typically characterized by ECG changes of ST-segment depression or T-wave inversion or transient ST-elevation. (Reference: Fox KA. Management of acute coronary syndromes: an update. *Heart* 2004;90:698-706.)

### 7. Other adverse cardiovascular events

- Heart failure or signs and symptoms of heart failure requiring hospital admission or emergency room visit and requiring intravenous therapy.
- Transient ischemic attack less than 24 hours old, defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. (Reference: Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* 2009;40:2276-93).

### 8. Non-cardiovascular deaths

- Death due to causes such as infection, bleed, pulmonary, renal, cancer or other non-cardiovascular etiologies.
- Unknown death, defined as confirmed death, but without data to support mode of death.
- Death outside of the hospital without adequate source documentation or medical records will require a case narrative to be submitted by the investigator.

### Clinical classification of different types of myocardial infarctions

(Reference: Thygesen K, Alpert JS, White HD, et al. Universal definitions of myocardial infarction. *Circulation* 2007;116:2634-2653.)

#### Type 1

Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as a plaque erosion and/or rupture, fissuring, or dissection.

#### Type 2

Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply (eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension).

#### Type 3

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

**Type 4**

Myocardial infarction associated with PCI.

**Type 4b**

Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy.

**Type 5**

Myocardial infarction associated with CABG.

## Appendix C. Major Adverse Gastrointestinal Events (MAGIE) Classifications and Definitions

### 1. Bleeding of gastroduodenal origin

Gastroduodenal bleeding manifested by melena and/or hematemesis, with confirmation of a gastroduodenal ulcer or erosion by endoscopy or radiography.

There should be endoscopic or radiographic evidence of gastroduodenal ulceration (mucosal break with definite depth) or erosion (mucosal break without depth) or other likely causative lesion as deemed by the GI Clinical Event Committee (CEC) and clinical evidence of hemorrhage.

The lesion itself does not have to be bleeding at the time of the endoscopy. Clinical evidence of bleeding may include hematochezia (instead of just melena and/or hematemesis), although in the presence of hematochezia alone there should be additional confirmation (such as findings of hemodynamic status commensurate with bleeding, hemoglobin drop, stigmata or hemorrhage on the ulcer base or blood in the stomach) to support the gastroduodenal origin of the bleeding.

### 2. Overt upper (UGI) bleeding

Documented hematemesis or nasogastric aspirate with blood or coffee grounds material, or documented melena or hematochezia with an UGI lesion considered responsible for the GI bleeding. Clinical evidence of bleeding may include hematochezia (instead of just melena and/or hematemesis), although in the presence of hematochezia alone there should be additional confirmation (such as findings of hemodynamic status commensurate with bleeding, hemoglobin drop) to support the diagnosis of clinically significant bleeding.

### 3. Presumed UGI bleeding of unknown location

Documented hematochezia or melena associated with no or inconclusive endoscopic or imaging studies assessing the GI tract. Additional clinical evidence of bleeding may be needed for confirmation. Clinical evidence of bleeding may include hematochezia (instead of just melena and/or hematemesis), although in the presence of hematochezia alone there should be additional confirmation (such as findings of hemodynamic status commensurate with bleeding, hemoglobin drop) to support the diagnosis of clinically significant bleeding.

This is acute bleeding in the GI tract, manifested by melena and/or hematemesis, without confirmed identification of a GI lesion by endoscopy or radiography.

This definition excludes acute lower GI bleeding that

has been effectively identified by colonoscopy or radiography. This definition also excludes cases of hematochezia (bright red blood per rectum) with a negative UGI evaluation.

Surveys of acute UGI bleeding show that approximately one quarter do not have a bleeding source identified on initial endoscopy. This often occurs because the patient is late in presenting to the emergency room. (References: Vreeberg EM, Snel P, de Bruijne JW, Bartelsman JF, Rauws EA, Tytgat GN. Acute upper gastrointestinal bleeding in the Amsterdam area: incidence, diagnosis, and clinical outcome. *Am J Gastroenterol* 1997;92:236-43.

Zaltman C, Souza HS, Castro ME, Sobral Mde F, Dias PC, Lemos V Jr. Upper gastrointestinal bleeding in a Brazilian hospital: a retrospective study of endoscopic records. *Arg Gastroenterol* 2002;39:74-80.)

### 4. Occult gastrointestinal bleeding

Hemoglobin drop  $\geq 2$  g/dL or hematocrit decrease of at least 10% (absolute) compared to Screening hemoglobin or hematocrit, respectively, with no other identifiable cause within 2 weeks of stopping study drugs. Events reported after 2 weeks will be censored as causation will be questioned.

This decrease in hemoglobin or hematocrit occurs without a presumed identified bleeding source confirmed by endoscopic or radiographic evidence and in the absence of an alternative source or origin.

The 10% change in hematocrit represents an absolute change, not a relative change. For example, a decrease from 42% to 32% represents an absolute change of 10% and would constitute an event, whereas a decrease of 42% to 37% (>10% relative change, but only 5% absolute) would not constitute an event.

A case of bleeding of presumed occult GI origin can only be determined by adjudication by the GI CEC. It is not an automatic diagnosis based on single hemoglobin or hematocrit value.

Proper evaluation of changes in hemoglobin and hematocrit may include repeat hemoglobin and hematocrit, ferritin, mean corpuscular volume (MCV), and other red blood cell indices to exclude non-GI causes of anemia. Endoscopy will be appropriate when the findings are consistent with a possible GI source of anemia.

Even with esophagogastroduodenoscopy and colonoscopy, not all cases will have a clear diagnosis. As in the case of acute UGI bleeding, delays in conducting the elective procedure or imprecision in the diagnostic tests may lead to difficulty in identifying the source. In the event the GI CEC cannot make a determination based on the available clinical information, the GI CEC will not confirm such an event under this category.

Here the adjectives “presumed” and “occult” refer to the absence of overt signs of bleeding at the time that endoscopy or additional evaluation is scheduled. The evaluation is prompted by the anemia, not hematemesis, melena, or dyspepsia. If further evaluation effectively

identifies a bleeding source, then the case will still meet endpoint criteria if it is gastroduodenal in origin. In some of these cases, the ulcer and erosion will not be acutely bleeding, but it should still meet endpoint criteria since intermittent bleeding is common. In a few cases, both upper and lower GI pathology will be identified. These should count towards the endpoint if the UGI lesion is considered clinically relevant.

#### 5. Symptomatic gastroduodenal ulcer

Evidence of a GI tract ulcer (defined as at least 3 mm in greatest diameter with unequivocal depth) confirmed by endoscopy, imaging, surgery or autopsy in a subject with at least one clinical symptom that is consistent with an ulcer (e.g., abdominal pain) and in whom the procedure that identified the ulcer was performed due to the subject's symptoms.

It is anticipated that the GI symptoms will include dyspepsia and epigastric pain of sufficient magnitude to warrant endoscopy. The term unequivocal means "apparent", "obvious."

#### 6. Persistent pain of presumed gastrointestinal origin with underlying multiple erosive disease

Pain in the UGI region of presumed GI origin that persists for  $\geq 3$  days, with confirmation of 5 or more gastroduodenal erosions (defined as a mucosal break of any diameter without depth) by endoscopy.

It is anticipated that the GI symptoms will include dyspepsia and epigastric pain of sufficient magnitude to warrant endoscopy.

#### 7. Obstruction

Documented GI tract obstruction confirmed by endoscopy, imaging, surgery or autopsy in a subject with clinical presentation of obstruction (e.g., nausea/vomiting, abdominal pain, abdominal distention, lack of bowel movement).

This is GI obstruction occurring anywhere in the stomach, duodenum, jejunum or ileum, with confirmation by endoscopy or radiography.

The jejunum and ileum are included because, in this definition, small intestinal obstruction and perforation can be caused by aspirin. (Reference: Leong RW, Chan FK. Drug-induced side effects affecting the gastrointestinal tract. *Expert Opin Drug Saf* 2006;5:585-92).

Obstruction caused by sources in the lower GI tract (such as colon cancer, diverticulitis, or adhesions from prior surgery) should not be included.

#### 8. Perforation

Documented GI perforation confirmed by endoscopy, surgery, radiography or autopsy in a subject with clinical presentation consistent with a GI perforation (e.g., abdominal pain, peritoneal signs) or autopsy.

This is GI perforation occurring anywhere in the stomach, duodenum, jejunum or ileum, with confirmation by endoscopy or radiography.

The jejunum and ileum are included because, in this definition, small intestinal obstruction and perforation can be caused by aspirin.

Perforation caused by sources in the lower GI tract (such as colon cancer and diverticulitis) should not be included.