

Efficacy and Safety of PA, a Novel Combination of Enteric-Coated Aspirin and Immediate-Release Omeprazole

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BACKGROUND

- Approximately 795,000 people per year experience a new or recurrent stroke.¹
- Aspirin (ASA) 50-325 mg daily is recommended for the secondary prevention of stroke or TIA.²
- The antiplatelet effect of ASA, as measured by urinary 11-dehydro thromboxane B₂ (11-d-TXB₂), appears dose-related; higher doses suppress urinary 11-d-TXB₂ more than lower doses, and higher urinary 11-d-TXB₂ has been associated with an increased risk of cardiovascular (CV) events.^{3,4}
- ASA is associated with an increased risk of serious upper gastrointestinal (UGI) injury.^{5,6}
- For cardioprotection, physicians tend to prescribe lower doses of ASA (60% ASA 81 mg/day; 35% ASA 325 mg/day), prompted, in part, by tolerability and safety concerns with higher doses.⁷
- ASA dose reduction or use of modified release formulations does not appear to significantly lower the risk of UGI events.^{5,8} A meta-analysis of 13 placebo-controlled CV trials found no difference in major GI bleeding between ASA 75-162.5 mg [RR 2.22 (1.61-3.06)] and ASA 162.5-325 mg [RR 2.35 (0.98-5.66)].⁵
- Proton-pump inhibitors (PPIs) are the preferred agents for therapy and prophylaxis of NSAID- and ASA-associated GI injury,⁹ but long-term adherence to such co-therapy may be low.
- Novel approaches are needed to reliably reduce UGI toxicity and its complications.

PA PRODUCT DESCRIPTION

Figure 1a. Product Designation

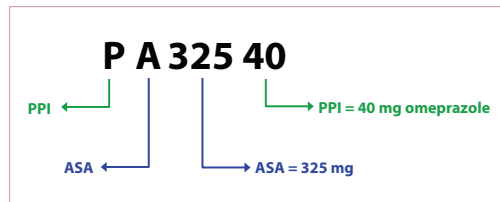
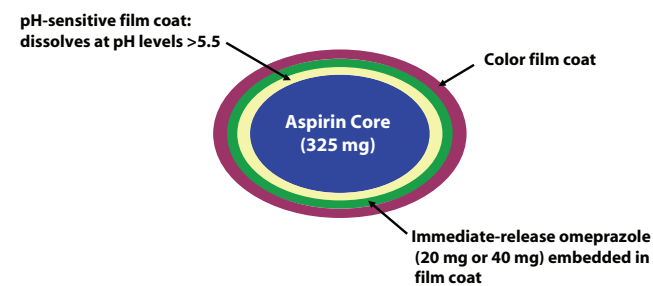


Figure 1b. Tablet Schematic (PA32520 or PA32540)



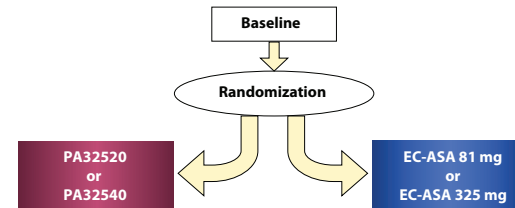
- Multilayer, coordinated-delivery system.
- IR omeprazole (protective agent) is released in the stomach prior to the dissolution of the ASA in the small intestine.

OBJECTIVES

- To compare via endoscopy the UGI mucosal effect of the fixed-dose combination tablet PA (enteric-coated [EC-ASA] and immediate-release [IR] omeprazole) with that of EC-ASA alone.
- To compare the antiplatelet effect of PA (which contains 325 mg of ASA) with that of EC-ASA 81 mg.
- To compare the bioequivalence of salicylic acid from PA vs EC-ASA alone.

STUDY DESIGN & METHODS

Figure 2. Endoscopy Trials

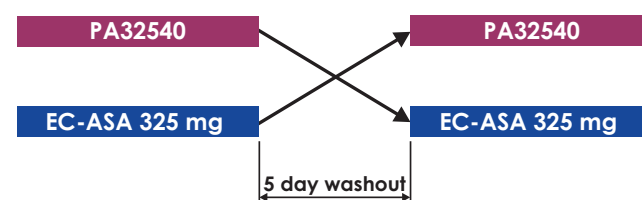


- Three, randomized, investigator-blinded, 4-week studies in healthy adult volunteers with normal endoscopy (Grade 0 Lanza score¹⁰) at baseline
 - PA32520 vs. EC-ASA 325 mg (Study 1)
 - PA32520 vs. EC-ASA 81 mg (Study 2) (Urinary 11-d-TXB₂ measured)
 - PA32540 vs. EC-ASA 325 mg (Study 3)
- Each tablet was taken once-daily for 4 weeks.

Study Endpoints

- Proportion of subjects with Grade 3 or 4 Lanza scores at Day 14.
- Proportion of subjects with Grade 3 or 4 Lanza scores at Day 28.
- Concentration of urinary 11-d-TXB₂ after 4 weeks of therapy.

Figure 3. Bioequivalence Study



- Single-dose, open-label, crossover study in 36 healthy adult volunteers (mean age 32 yrs).
- PA32540 vs. EC-ASA 325 mg.
- Bioequivalence requires that the 90% CI for the ratios of the geometric least squares mean (LSM) of area under the concentration-time curve (AUC_{0-∞}) and maximum plasma concentration (C_{max}) are between 80%–125%.

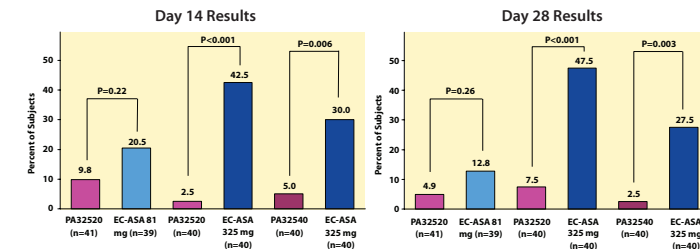
RESULTS

Endoscopy Trials

Table 1. Baseline Demographics

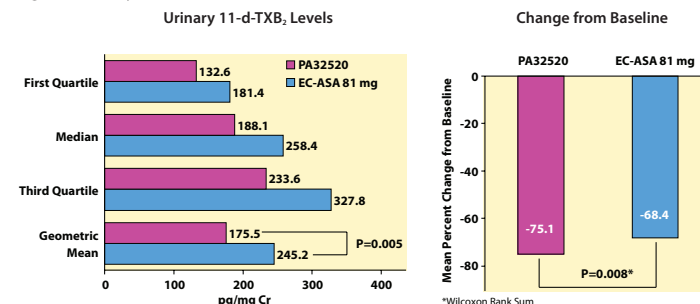
Characteristic	Study 1		Study 2		Study 3	
	PA32520 (n=40)	EC-ASA 325 mg (n=40)	PA32520 (n=41)	EC-ASA 81 mg (n=39)	PA32540 (n=40)	EC-ASA 325 mg (n=40)
Age, mean (SD), y	57.6 (6.6)	58.1 (6.6)	57.4 (6.9)	57.9 (6.6)	58.5 (5.6)	58.1 (6.2)
Gender, n (%)						
Male	27 (67.5)	19 (47.5)	27 (65.9)	30 (76.9)	20 (50.0)	27 (67.5)
Female	13 (32.5)	21 (52.5)	14 (34.1)	9 (23.1)	20 (50.0)	13 (32.5)
Race, n (%)						
Caucasian	40 (100)	40 (100)	38 (92.7)	38 (97.4)	39 (97.5)	40 (100)
Black			2 (4.9)	0	1 (2.5)	
Other			1 (2.4)	1 (2.6)		
H-pylori, n (%)						
Negative	30 (75.0)	28 (70.0)	30 (73.2)	29 (74.4)	40 (100.0)	40 (100.0)
Positive	10 (25.0)	12 (30.0)	11 (26.8)	10 (25.6)		

Figure 4. Comparison of the Incidence of Grade 3 or 4 Lanza Scores



- At Day 14 and at Day 28, subjects taking PA32520 or PA32540 had significantly less UGI damage compared with subjects taking EC-ASA 325 mg (P≤0.006).

Figure 5. Urinary 11-d-TXB₂ after 4 weeks of Treatment



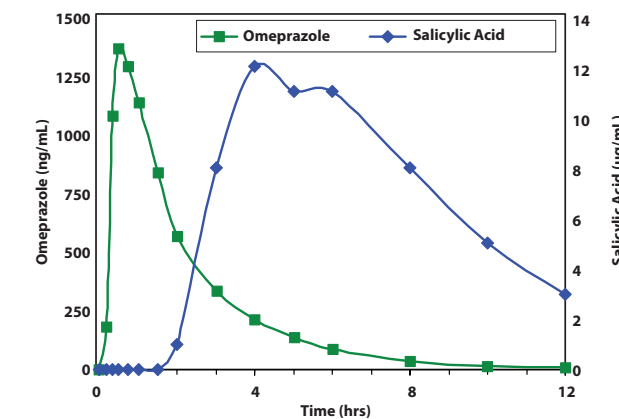
Pharmacokinetics

Table 2. Bioequivalence Study Results — Salicylic Acid Pharmacokinetics

PK Parameter	Geometric LSM		PA32540/EC-ASA 325 mg Geometric LSM Ratio (90% CI)
	PA32540	EC-ASA 325 mg	
AUC _{0-∞} (hr*µg/mL)	104.4	95.4	1.095 (0.967, 1.239)
C _{max} (µg/mL)	17.4	16.1	1.077 (0.959, 1.209)

- The 90% CI of the geometric LSM ratios for AUC_{0-∞} and for C_{max} for salicylic acid were between 80%–125%, thus meeting the criteria for bioequivalence.

Figure 6. Release Profile of PA32540 (Day 13, Study 3)



- Median time to maximum plasma concentration (T_{max}):
 - Omeprazole (from PA32540): Approximately 30 minutes for Days 1 and 13
 - Salicylic acid (from PA32540): Day 1, 4.0 hours; Day 13, 4.5 hours
 - EC-ASA 325 mg: Day 1, 4.0 hours; Day 13, 4.5 hours
- Plasma exposure of salicylic acid from PA32540 is similar to marketed EC-ASA 325 mg following both single-dose and repeat-dose administration of PA32540.
- IR omeprazole in PA32540 has no effect on the PK profile of salicylic acid.

Table 3. Adverse Events (Pooled Data)*

Adverse Event	PA32540 (n=40)	PA32520 (n=81)	EC-ASA 81 mg (n=39)	EC-ASA 325 mg (n=80)
	Number of Patients (%)			
Any	10 (25.0)	20 (24.7)	13 (33.3)	26 (32.5)
All Gastrointestinal (GI)	2 (5.0)	11 (13.6)	3 (7.7)	14 (17.5)
Individual GI Events [†]				
Nausea	1 (2.5)	3 (3.7)	0	4 (5.0)
Diarrhea	0	2 (2.5)	1 (2.6)	4 (5.0)
Abdominal pain	1 (2.5)	0	0	3 (3.8)
Other GI events	3 (7.5)	13 (16.0)	3 (7.7)	10 (12.5)

* Pooled data from Study 1, Study 2, and Study 3; GI disorders were the most frequently reported adverse events. There were 3 cases of epistaxis (1 in the PA32520 group, 2 in the EC-ASA 325 mg group) and no reported cases of upper or lower GI bleeding.

[†] Individual GI adverse events occurring in >3% of patients in any treatment group.

SUMMARY

- EC-ASA alone was associated with a high incidence of UGI damage.
- PA, the fixed-dose combination of EC-ASA 325 mg and IR omeprazole, was associated with a significant reduction in gastroduodenal injury.
- PA32520 produced significantly greater inhibition of in vivo thromboxane generation, as measured by urinary 11-d-TXB₂, compared to EC-ASA 81 mg.
- PA32540 demonstrated the least gastroduodenal damage and fewer overall GI adverse events.
- PA32540 exhibited the same rate and extent of absorption as EC-ASA 325 mg in terms of salicylic acid pharmacokinetics.

CONCLUSIONS

- PA is associated with a significant improvement in UGI safety and is bioequivalent to EC-ASA alone.
- In the secondary prevention of stroke and TIA, PA may allow for higher ASA dosing, which is associated with greater thromboxane inhibition.

References

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