

Analgesic Doses of Aspirin Cause Significant Upper Gastrointestinal Damage: PA65020, a New Combination of Enteric-Coated Aspirin & Immediate-Release Omeprazole Significantly Reduces the Incidence of Gastroduodenal Ulcers

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INTRODUCTION

- The current labeling for aspirin (ASA) use in osteoarthritis (OA) is up to 3 g/day in divided doses.¹ While a broad range of effective doses has been suggested, the lowest effective ASA dose for OA is unknown.
- Higher doses of ASA are associated with greater toxicity, including upper gastrointestinal (UGI) mucosal damage, tinnitus and hearing loss.^{2,3}
- It has been suggested that there is a dose-response relationship for the clinical effect of ASA,⁴ with a ceiling analgesic effect of 1300 mg.⁵ ASA dosing intervals of 8 or 12 hours are usually sufficient to maintain plasma salicylate concentrations in the anti-inflammatory range.⁶ However, the large single doses required for twice daily (BID) dosing, for example, should be administered in a formulation that minimizes gastric injury. Modified-release ASA formulations do not appear to significantly lower the risk of UGI events.^{7,8}
- We hypothesize that PA65020 BID (total daily dose of ASA = 1,300 mg) will be a clinically useful analgesic regimen for multiple conditions (e.g., OA). In this first study, we evaluated safety and tolerability in normal, healthy volunteers.

PA PRODUCT CONCEPT

Figure 1a. Product Designation

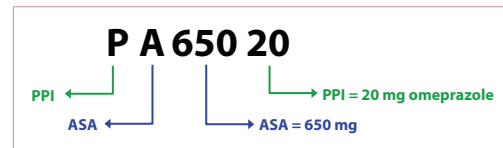
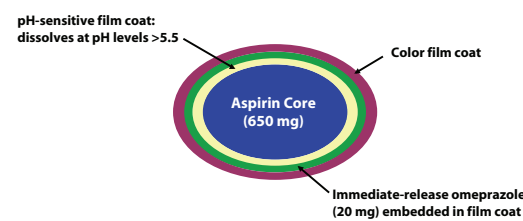


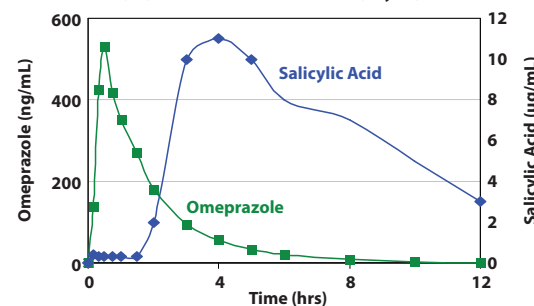
Figure 1b. Tablet Schematic—Multilayer, Coordinated Delivery System



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

PHARMACOKINETICS

Figure 2. Pharmacokinetic (PK) Release Profile of PA32520 (Day 13)

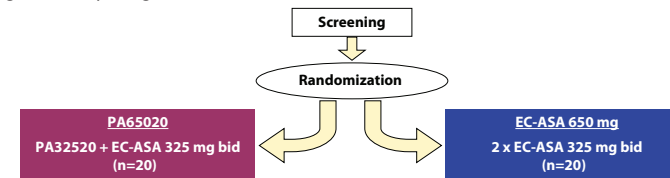


OBJECTIVE

- To compare via endoscopy the gastroduodenal mucosal effect of an analgesic dose of PA (a fixed-dose combination product of EC-ASA and IR omeprazole) with that of EC-ASA alone.

METHODS

Figure 3. Study Design



- Phase 1, randomized, double-blind, 4-week study in healthy adult volunteers (≥50 years and *Helicobacter pylori* negative) with normal endoscopy (Grade 0 Lanza score*) at baseline
 - PA65020 was administered as one tablet of PA32520 [a fixed-dose combination tablet of EC-ASA 325 mg and IR omeprazole 20 mg] + one tablet of EC-ASA 325 mg.
 - EC-ASA 650 mg was administered as 2 tablets of EC-ASA 325 mg.
 - Total daily ASA dose was 1300 mg.

Primary Endpoint

- Proportion of subjects with Grade 3 or Grade 4 Lanza scores at Day 28

Secondary Endpoints

- Proportion of subjects with gastric or duodenal ulcers (GU/DU) at Day 28
- Proportion of subjects with Grade 0 Lanza score at Day 28
- Heartburn assessment
- Assessment of dyspepsia-associated abdominal pain by mSODA (modified severity of dyspepsia assessment score, range 2–47)¹⁰

Statistical Analysis

- Treatments were compared for efficacy using Fisher's Exact test.

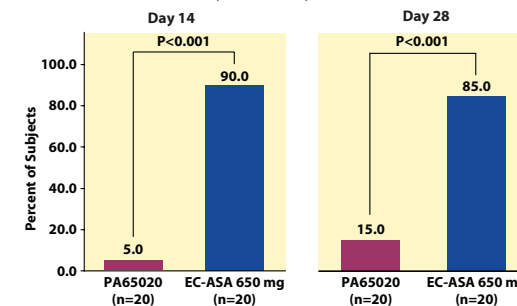
- Median time to maximum plasma concentration (T_{max}):
 - Omeprazole (from PA32520): Approximately 30 minutes for Days 1 and 13
 - Salicylic acid (from PA32520): Day 1, 4.5 hours; Day 13, 4.0 hours
 - EC-ASA 325 mg: Day 1, 5.0 hours; Day 13, 4.0 hours
- Plasma exposure of salicylic acid from PA32520 is similar to marketed EC-ASA 325 mg following both single-dose and repeat-dose administration of PA32520.
- IR omeprazole in PA32520 has no effect on the PK profile of salicylic acid.

RESULTS

Table 1. Baseline Demographics

Characteristic	PA65020 (n=20)	EC-ASA 650 mg (n=20)
Age, mean (SD), y	59.6 (8.1)	59.9 (6.5)
Gender, n (%)		
Male	16 (80.0)	16 (80.0)
Female	4 (20.0)	4 (20.0)
Race, n (%)		
Caucasian	20 (100.0)	20 (100.0)

Figure 4. Grade 3 or 4 Lanza Score at Day 14 and Day 28



- Grade 3 or Grade 4 Lanza scores were significantly lower in the PA65020 treatment group compared with the EC-ASA 650 mg treatment group at both Day 14 and Day 28 (P<0.001).

SAFETY AND TOLERABILITY

Table 2. Adverse Events

Adverse Event	PA65020 (n=20)	EC-ASA 650 mg (n=20)
Any*	6 (30.0)	8 (40.0)
All Gastrointestinal (GI)	3 (15.0)	4 (20.0)
Individual GI events†		
Stomach discomfort	0 (0)	3 (15.0)
Abdominal discomfort	0 (0)	2 (10.0)
Dyspepsia	2 (10.0)	2 (10.0)
Abdominal pain upper	1 (5.0)	0 (0)
Constipation	1 (5.0)	0 (0)

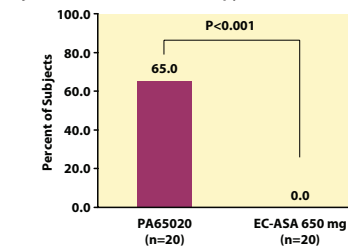
* No serious adverse events were reported.

† Individual GI adverse events occurring in ≥5% of subjects in either treatment group.

Dyspepsia-associated Abdominal Pain by mSODA (range = 2–47)

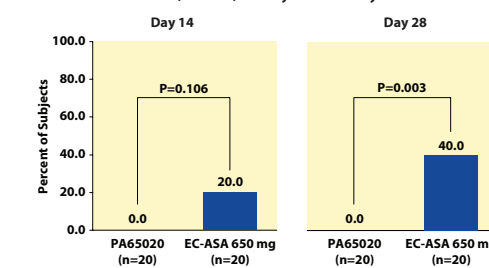
- At baseline, subjects in both treatment groups had a mean mSODA score of 2.0. After 28 days of therapy, the mean change from baseline in mSODA was 0 in the PA65020 group vs. 0.7 in the EC-ASA 650 mg group (P=0.32).

Figure 5. Percent of Subjects with Normal Endoscopy (Grade 0 Lanza score) at Day 28



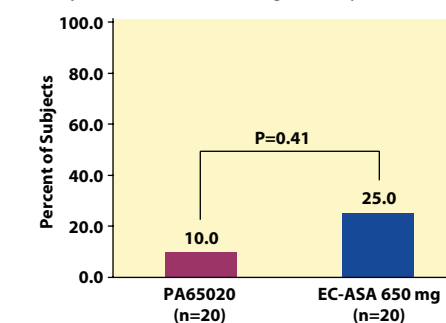
- After 28 days of therapy, 65% of subjects in the PA65020 group had no endoscopic evidence of gastroduodenal injury.
- In contrast, gastroduodenal mucosal damage was present in all subjects (100%) in the EC-ASA 650 mg group at Day 28.

Figure 6. Gastric or Duodenal Ulcer (GU/DU) at Day 14 and Day 28



- No gastric or duodenal ulcers were identified for subjects in the PA65020 treatment group at either Day 14 or Day 28.
- After 28 days of therapy, the incidence of GU/DU was significantly lower for subjects in the PA65020 group vs. the EC-ASA 650 mg group (P=0.003).

Figure 7. Percent of Subjects with Heartburn During the Study



- Heartburn was reported by 10% of PA65020 subjects and 25% of EC-ASA 650 mg subjects, representing a 60% relative decrease with PA65020 treatment.

SUMMARY

After 28 days of therapy:

- Grade 3 or 4 Lanza score was 15% in the PA65020 treatment group vs. 85% in the EC-ASA 650 mg treatment group (P<0.001).
- 65% of subjects in the PA65020 treatment group had Grade 0 Lanza score (no visible GI lesions).
- All subjects (100%) in the EC-ASA 650 mg treatment group had at least 1 erosion or hemorrhage on endoscopy.
- GU/DU was 0% in the PA65020 treatment group vs. 40% in the EC-ASA 650 mg treatment group (P=0.003).
- No cases of heartburn were reported by 90% of PA65020 subjects vs. 75% of EC-ASA 650 mg subjects.

CONCLUSIONS

- Analgesic doses of over-the-counter EC-ASA produced significant gastroduodenal damage in most subjects following 1 month of treatment.
- PA65020 was associated with a significantly decreased risk of GI mucosal damage.
- PA65020 may provide an important therapeutic option for at-risk patients who require analgesic doses of ASA.

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