CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205103Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 205103	Submission Date(s): 03/14/2016, 5/2/2016, 7/20/2016
Submission Type; Code	Resubmission
Brand Name	Yosprala
Generic Name	Aspirin Delayed Release/Omeprazole Immediate Release
Reviewer	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Sponsor	POZEN, Inc
Formulation; Strength(s)	Tablet, 81 mg or 325 mg Aspirin/40 mg Omeprazole
Proposed Indication	Use in the secondary prevention of cardiovascular and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers
Proposed Dosing Regimen	Once Daily tablet
PDUFA Goal Date:	09/14/2016

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1 Executive Summary

This is a 505(b)(2) application for Yosprala (Delayed Release Aspirin/Immediate Release omeprazole) tablets referencing Ecotrin® (EC-Aspirin) and Prilosec® (EC-Omeprazole). The proposed product is an oral fixed dose combination product containing 81 mg or 325 mg aspirin in the inner enteric coated core (delayed release) surrounded by 40 mg omeprazole in the immediate-release film coat to release the active ingredients in a sequential fashion.

The original application was submitted on 03/25/2013. A full clinical pharmacology review was conducted during the 1st review cycle and application was acceptable from clinical pharmacology perspective. Please see Clinical Pharmacology review dated 04/18/2014. However, this application was issued a Complete Response (CR) action letter on 04/25/2014 due to facility inspection deficiencies at (b) (4) manufacturing facility, which was a supplier to aspirin drug substance used to manufacture Yosprala tablets. There were no deficiencies from clinical pharmacology perspective.

The sponsor submitted a response to the Complete Response action letter (resubmission) on June 30, 2014. There was no new clinical pharmacology study in that submission. Please see clinical pharmacology review dated 11/24/2014. That submission was issued another Complete Response (CR) action letter on 12/16/2014 due to facility inspection deficiencies at aspirin substance supplier (b) (4) manufacturing facility again.

In this 3rd submission, the sponsor submitted another response to Complete Response action letter (resubmission) on March 14, 2016. In this submission, in order to address its manufacturing facility deficiency, the sponsor had changed the supplier for aspirin (b) (4) component from the previous supplier (b) (4) to a new supplier (b) (4) (also referred to as (b) (4)) (b) (4) The omeprazole for Yosprala Tablets and the manufacturing process for Yosprala Tablets remain completely unchanged. To support these changes in aspirin supplier, in addition to in-vitro testing, the sponsor submitted two relative BA/BE study comparing the aspirin components of PA32540 and PA8140 (b) (4) (b) (4)

1.1 Recommendation

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

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Aspirin Supplier Comparison:

In this submission, the sponsor changed API aspirin supplier source from (b) (4) to (b) (4) (also referred to as (b) (4)). In addition, aspirin

from this new supplier [redacted]

BA/BE study:
Aspirin components of PA8140 and PA32540 from the new supplier [redacted] was bioequivalent to that of previous supplier [redacted] based on two separate BE studies (PA8140-104 and PA32540-119) that had used partial reference-replicate3-way study design with a reference-scaled average BE approach.

OSI inspection:
An inspection for bioequivalence (BE) studies PA8140-104 and PA32540-119 for both clinical site and bioanalytical site was requested on 06/21/2016. However, the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection [redacted] as OSIS recently inspected these sites and the inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Relative BA of omeprazole component of PA8140 vs Prilosec :
Based on bridged cross-study comparisons, the plasma exposure of IR omeprazole 40 mg from PA8140 was lower than that of Prilosec 40 mg, Prilosec®. Cmax and AUC of IR omeprazole 40 mg from PA8140 were estimated to be 90% and 75%, respectively, of that from an EC formulation omeprazole 40 mg, Prilosec 40 mg following a repeat dose administration for 7 days.

2 Question Based Review

2.1 What are the differences in aspirin API from the two suppliers?

In this submission, the sponsor changed API aspirin supplier source from [redacted] to [redacted] (also referred to as [redacted]). In addition, aspirin from this new supplier [redacted]

Table 1: Comparison of ASA [redacted] Sourced From [redacted] (Current Source) and [redacted] (New Source)

[redacted]

Table 2: Comparison of PA8140 Aspirin Core Tablet Formulation [redacted]

Components	Quantity per unit (mg/tablet)	

(b) (4)

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Table 3: Comparison of PA32540 Aspirin Core Tablet Formulation (b) (4)

(b) (4)

(b) (4)

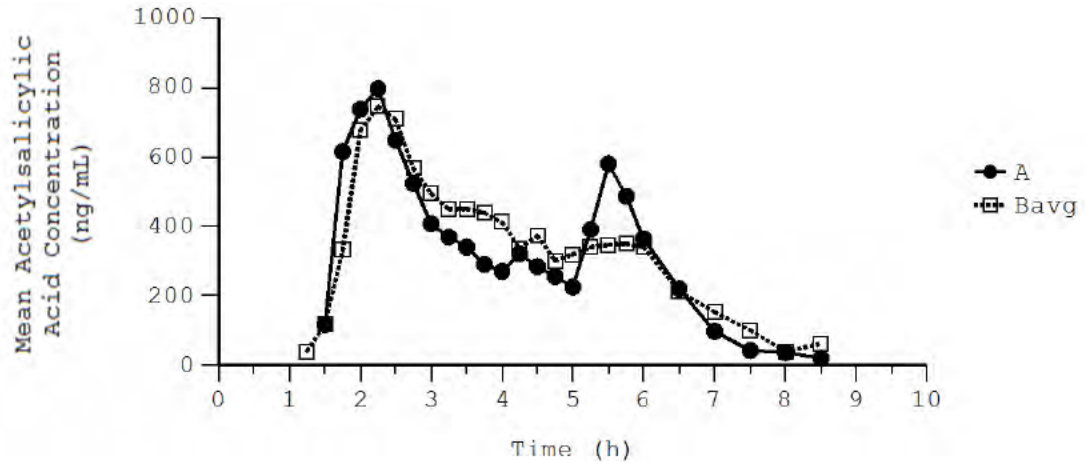
2.2 Is the aspirin (acetylsalicylic acid) component of Yosprala from the two suppliers bioequivalent at the proposed dosages?

Yes, aspirin components of PA8140 and PA32540 from the new supplier [redacted] (b) (4) was bioequivalent to that of previous supplier [redacted] (b) (4) based on two separate BE studies (PA8140-104 and PA32540-119) that had used partial reference-replicate3-way study design with a reference-scaled average BE approach.

Bioequivalence for Aspirin component for PA8140:

Study PA8140-104 compared relative bioavailability of aspirin component of Yosprala tablets PA8140 produced from [redacted] (b) (4) aspirin. This study was designed as an open-label, randomized, single-center, single-dose, 3-way crossover study in 36 healthy adult subjects comparing two aspirin formulations [redacted] (b) (4) of PA8140 using the partial reference replicated 3-way design. Each subject was to receive the reference product (Treatment B), 3 tablets of PA8140 (dosed concurrently) as Formulation 1 [redacted] (b) (4) twice, and the test product (Treatment A), three tablets (dose concurrently) of PA8140 [redacted] (b) (4) as Formulation 2, once in a randomized crossover fashion over 3 treatment periods based on the treatment sequence of BBA, BAB, or ABB. The study drugs were administered following an overnight fasting of at least 10 hours prior to dosing. Subjects received a standardized breakfast an hour after the dosing. The study drug was to be swallowed as whole and was not to be broken, crushed, or chewed. There was at least a 4- day of washout period between the treatments. PK blood samples were collected for up to 8.5 hours in each treatment period to determine the plasma concentrations of acetylsalicylic acid.

Figure 1: Mean Plasma Acetylsalicylic Acid Concentration vs. Time Curves (Treatment A and Average of Treatments B1 and B2)



A=Test product: three tablets (dosed concurrently) of PA8140 [redacted] (b) (4) (Formulation 2). B_{avg}=average concentration of Treatment B1 (first occurrence) and Treatment B2 (second occurrence) for subjects who had completed both B1 and B2, reference product of PA8140 [redacted] (b) (4).

Table 4: Summary of Acetylsalicylic Acid Pharmacokinetic Parameters

Treatment	Statistics	C_{max} (ng/mL)	t_{max}* (hr)	t_{lag}* (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL	$t_{½}$ (hr)
	n	31	31	31	31	31	31

A	Mean*	2377.00	3.05	1.57	2551.22	2572.60	0.40
PA8140 (b) (4)	%CV	54	43	60	38	38	30
	GeoMean	2079.91	3.25	ND	2346.99	2373.37	0.38
	Min	647	1.75	0.00	592.14	615.69	0.27
	Max	5400	6.50	5.25	4777.49	4789.75	0.79
	n	32	32	32	32	30	30
B1	Mean*	2185.59	4.00	1.88	2491.13	2564.43	0.39
PA8140	%CV	41	43	57	36	36	15
First Dose	GeoMean	2023.50	3.55	2.37	2327.49	2399.79	0.38
	Min	929	1.75	1.25	735.44	747.74	0.29
	Max	4590	7.00	6.50	4963.52	4987.27	0.54
	n	34	34	34	34	33	33
B2	Mean*	2095.65	3.29	2.25	2488.95	2469.96	0.37
PA8140	%CV	42	44	56	33	32	15
Second Dose	GeoMean	1922.50	3.50	2.29	2335.90	2327.10	0.37
	Min	863	1.50	0.50	790.43	805.21	0.29
	Max	3990	7.53	6.50	4080.23	4095.16	0.55
	n	31	31	31	31	28	28
Average of	Mean*	2067.88	3.74	2.29	2450.29	2459.87	0.38
B1 and B2	%CV	36	38	50	33	30	11
	GeoMean	1955.02	3.47	2.28	2314.21	2342.37	0.37
	Min	1045.79	1.73	0.79	770.36	770.36	0.31
	Max	4148.80	7.26	6.50	4413.32	4413.32	0.46

GeoMean = geometric mean. *: Median for tmax.and tlag., na = not applicable

The Swr (intra-subject variability) value for Cmax of acetylsalicylic acid for the reference treatment (Treatment B) was determined using the Referenced-Scaled Average Bioequivalence (RSABE) evaluable population (N=28), who had adequate blood sampling to assess the PK parameters for acetylsalicylic acid for both Cmax and AUC values for all three periods. The Swr value for Cmax was 0.384, indicating a "highly variable" drug product for this parameter. Therefore, reference-scaled average bioequivalence (RSABE) approach was used for comparison of acetylsalicylic acid Cmax.

The Swr values for AUC0-t and AUC0-inf of acetylsalicylic acid for the reference treatment (Treatment B) were determined in 31 subjects and 28 subjects, respectively, using the BE evaluable population and whose both periods of Treatment B were measurable. The Swr values for AUC0-t and AUC0-inf were below 0.294, (0.261 and 0.270, respectively). Therefore, average bioequivalence approach was used for comparison of AUC0-t and AUC0-inf of acetylsalicylic acid.

Table 5: Summary of Statistical Analysis Results of Acetylsalicylic Acid PK Parameters:

	Referenced Scaled Average Bioequivalence (RSABE)

C_{max} (N=28)	S_{WR} [>=0.294]	Point Estimate [0.80, 1.25]	Critical Bound [<=0]
USE RSABE: Criteria Met	0.384	1.0292	-0.0650

	Average Bioequivalence (ABE)			
AUC_{0-t} (N=35)	S_{WR} [<0.294]	Ratio (%)	90% CI Lower	90% CI Upper
USE UNSCALED ABE: S_{WR} < 0.294	0.261	99.75	90.59	109.84

	Average Bioequivalence (ABE)			
AUC_{0-inf} (N=35)	S_{WR} [<0.294]	Ratio (%)	90% CI Lower	90% CI Upper
USE UNSCALED ABE: S_{WR} < 0.294	0.270	99.44	90.32	109.49

***Reviewer's Comment*:**

- *The within-subject standard deviation (Swr) of acetylsalicylic acid PK parameters from the reference product, PA8140, was estimated to be:*
  - *0.384 (38.4%) for Cmax, appropriate for reference-scaled average bioequivalence approach,*
  - *0.261 (26.1%) for AUC0-t and 0.270 (27.0%) for AUC0-inf, appropriate for average bioequivalence approach, not for* (RSABE).
- *Cmax: The reference-scaled average bioequivalence assessment showed that the point estimate of the geometric least squares mean ratios, PA8140 (b) (4) vs. PA8140, for Cmax of acetylsalicylic acid were within the interval of 0.80-1.25. In addition, the upper bound (critical bound) of the 95% confidence interval for the difference between PA8140 (b) (4) and PA8140 treatments, adjusted for the estimated intrasubject variability of the PA8140 treatment was less than zero, indicating that PA8140 (b) (4) is bioequivalent to PA8140 in terms of Cmax of acetylsalicylic acid*
- *AUC: The average bioequivalence assessment showed that the 90% confidence interval for the geometric least squares mean ratios, PA8140 (b) (4) vs. PA8140, for AUC0-t and AUC0-inf of acetylsalicylic acid were within the bioequivalence interval of 80%-125% indicating that PA8140 (b) (4) is bioequivalent to PA8140 in terms of AUC of acetylsalicylic acid.*
- *Overall, PA8140- (b) (4) is bioequivalent to PA8140 in terms of Cmax, AUC0-t and AUC0-inf of acetylsalicylic acid.*

Bioequivalence for Aspirin component for PA32540:

Study PA32540-119 compared relative bioavailability of aspirin component of Yosprala tablets PA32540 produced from (b) (4) aspirin. This study was designed as an open-label, randomized, single-center, single-dose, 3-way crossover study in 48 healthy adult subjects comparing two aspirin formulations (b) (4) of PA32540 using the partial reference replicated 3-way design. Each subject was to receive the reference product (Treatment B), PA32540 as Formulation 1 (b) (4), twice, and the test product (Treatment A), PA32540-(b) (4) as Formulation 2, once in a randomized crossover fashion over 3 treatment periods based on the treatment sequence of BBA, BAB, or ABB. The study drugs were administered following an overnight fasting of at least 10 hours prior to dosing and an additional 4 hours of fasting post-dose. The study drug was to be swallowed as whole and was not to be broken, crushed, or

chewed. There was at least a 4- day of washout period between the treatments. PK blood samples were collected for up to 10 hours in each treatment period to determine the plasma concentrations of acetylsalicylic acid.

Figure 2: Mean Plasma Acetylsalicylic Acid Concentration vs. Time Curves (Treatment A and Average of Treatments B1 and B2)

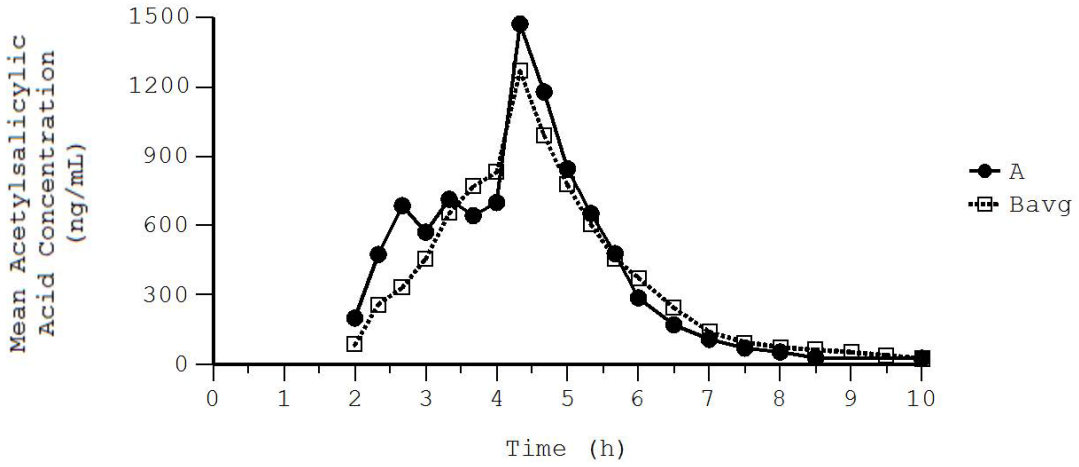


Table 6: Summary of Acetylsalicylic Acid Pharmacokinetic Parameters

Treatment	Statistics	C_{max} (ng/mL)	t_{max}* (hr)	t_{lag}* (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	$t_{½}$ (hr)
	n	47	47	47	47	46	46
A	Mean*	3034.09	4.33	2.67	3323.83	3380.04	0.40
PA32540 (b) (4)	%CV	54	32	29	44	43	24
	GeoMean	2446.94	4.22	2.48	2945.69	3011.98	0.39
	Min	227	2.00	1.50	467.07	497.72	0.29
	Max	6540	9.50	4.33	7529.72	7542.91	0.88
	n	48	48	48	48	46	46
B1	Mean*	2645.63	4.33	2.52	2973.79	3059.22	0.46
PA32540	%CV	60	35	44	48	45	54
First Dose	GeoMean	1991.25	4.35	ND	2433.41	2633.54	0.42
	Min	121	2.33	0.00	88.05	378.15	0.28
	Max	5780	10.00	8.00	5697.51	5709.12	1.80
	n	48	48	48	48	47	47
B2	Mean*	2631.44	4.40	2.68	3078.07	3122.77	0.44
PA32540	%CV	50	33	35	45	45	34
Second Dose	GeoMean	2237.64	4.53	2.55	2688.55	2732.46	0.42
	Min	548	2.00	0.75	596.88	607.34	0.27
	Max	5760	10.05	4.33	6089.81	6107.11	1.22
	n	48	48	48	48	45	45
Average of	Mean*	2479.22	4.46	2.66	2903.62	3019.53	0.43

B1 and B2	%CV	51	26	35	45	42	28
	GeoMean	2110.85	4.44	ND	2557.80	2729.01	0.42
	Min	438.62	2.33	0.00	353.94	736.59	0.28
	Max	5125	7.32	5.66	5708.72	5722.88	0.87

The Swr values for Cmax and AUC0-t of acetylsalicylic acid for the reference treatment (Treatment B) were determined using the 47 subjects who had adequate plasma concentrations to assess the PK parameters for acetylsalicylic acid for both Cmax and AUC0-t values for all three periods (RSABE1 evaluable population). The Swr value for AUC0-inf of acetylsalicylic acid for the reference treatment (Treatment B) was determined in 43 subjects who had adequate plasma concentrations to assess the PK parameters for acetylsalicylic acid for AUC0-inf values for all three periods (RSABE2 evaluable population).

Intrasubject standard deviation (Swr) values for C_{max}, AUC_{0-t} and AUC_{0-inf} of acetylsalicylic acid for the Reference treatment (Treatment B) were greater than 0.294, indicating that EC-Aspirin PK parameters qualify for the reference-scaled average BE approach to establish bioequivalence of AUCs and Cmax between two formulations.

Table 7: Summary of Statistical Analysis Results of Acetylsalicylic Acid PK Parameters:

	Referenced Scaled Average Bioequivalence (RSABE)		
	S_{wr} [>=0.294]	Point Estimate [0.80, 1.25]	Critical Bound [<=0]
C_{max} (N=47)	0.677	1.1760	-0.2055
AUC_{0-t} (N=47)	0.588	1.1669	-0.1386
AUC_{0-inf} (N=43)	0.475	1.1675	-0.0785

Swr: within-subject standard deviation of the PK parameter from the Reference product.

***Reviewer's Comment*:**

- *The within-subject standard deviation of acetylsalicylic acid pharmacokinetic parameters from the reference product PA32540 was estimated to be 0.677 for Cmax and 0.588 for AUCt and 0.475 for AUC0-inf, which are all greater than 0.294, confirming that EC-aspirin formulations are considered to be highly variable drug products and EC-Aspirin PK parameters qualify for the reference-scaled average BE procedure to establish bioequivalence of AUCs and Cmax between two formulations.*
- *The reference-scaled average bioequivalence assessment showed that the point estimates of the geometric least squares mean ratios, PA32540 (b) (4) vs. PA32540, for all bioavailability parameters of acetylsalicylic acid were within the interval of 0.80-1.25. In addition, the upper bound (critical bound) of the 95% confidence interval for the difference between PA32540 (b) (4) and PA32540 treatments (adjusted for the estimated intrasubject variability of PA32540) was less than zero.*
- *PA32540 (b) (4) is bioequivalent to PA32540 in terms of Cmax, AUC0-t and AUC0-inf of acetylsalicylic acid based on the reference-scaled average bioequivalence approach for highly variable drug products.*

2.3 What is the relative bioavailability of omeprazole in PA8140 compared to reference product Prilosec?

Based on cross-study comparison, Cmax and AUC of IR omeprazole 40 mg from PA8140 following repeat dose administration for 7 days were 90% and 75%, respectively, of that from an EC formulation of omeprazole 40 mg from Prilosec 40 mg.

In all submission for NDA 205103 thus far, the exposure of omeprazole from PA8140 has not been directly compared with Prilosec 40 mg. The sponsor had compared the exposure of omeprazole from PA32540 with Prilosec 40 mg in study PA32540-112 on Day 1, 5 and 7 (also in study PA32540-113 only on Day 1) and compared the exposure of omeprazole from PA32540 to that of PA8140 in study PA8140-103 on Day 7 only. Please refer to clinical pharmacology review d Clinical Pharmacology review dated 04/18/2014 for further details on this omeprazole exposure comparison.

Table 8: Cross-study Comparison of Omeprazole Exposure from PA8140, PA32540 and Prilosec 40 mg on Day 7

Treatment	Statistics	Cmax (ng/mL)	AUC0-24 (hr*ng/mL)	Source (study #)
PA8140	N Mean %CV GeoMean	30 1488 71 1094	30 3063 101 1920	PA8140-103
PA32540	N Mean %CV GeoMean	30 1385 73 1051	30 2288 91 1513	PA8140-103
PA32540	n Mean %CV GeoMean	26 1196 71 903	26 2187 88 1446	PA32540-112
Prilosec 40 mg + Ecotrin 325 mg	n Mean %CV GeoMean	26 1345 44 1218	26 2985 59 2558	PA32540-112

With this available cross-study data, the agency requested the sponsor to approximate the geometric mean ratio and its associated confidence interval comparing Cmax and AUC of omeprazole from PA8140 to Prilosec 40. The requested analysis compared omeprazole exposure from one tablet of PA8140 administered once daily for 7 consecutive days on Day 7 in study PA8140-103 to one tablet of EC-ASA (Ecotrin®) 325 mg and one capsule EC omeprazole (Prilosec®) 40 mg administered once daily for 7 consecutive days on Day 7 in study PA32540-112 utilizing cross-study data. Please note that the PK studies used in this cross-study

comparison of exposure of omeprazole were conducted by same sponsor with similar bioanalytical method at the same bioanalytical site (b) (4)

The relative bioavailability of omeprazole from PA8140 to Prilosec® was estimated by performing a parametric analysis of variance (ANOVA) using a mixed-effects model based on natural log transformed PK parameters for plasma omeprazole (C_{max}, AUC_{0-t} and AUC_{0-24}). The mixed-effects model included a fixed effect for treatment and a random effect of subject-within-treatment. A 90% confidence interval (CI) around the geometric least-squares mean ratio of C_{max}, AUC_{0-t} and AUC_{0-24} was calculated for each pairwise comparison (test vs. reference) as summarized in Table 2 below. Statistical Team leader Dr. Yeh-Fong Chen stated that the statistical approach was reasonable.

Table 9: Geometric Mean Ratios and 90% Confidence Intervals for C_{max}, AUC_{0-t}, and AUC_{0-24} of Omeprazole from PA8140 to Prilosec® on Day 7 based on Bridged Cross-Study Comparisons

Parameter	**PA8140[1] vs Prilosec 40 mg[2] on Day 7 GLSM Ratio % (90% Confidence Interval)**
C_{max} (ng/mL)	89.76 (64.79-124.36)
AUC_{0-t} (hr*ng/mL)	74.97 (50.92-110.36)
AUC_{0-24} (hr*ng/mL)	75.05 (51.00-110.44)

GLSM = geometric least-squares mean.

1: PA8140 is from study PA8140-103 Treatment A: One tablet of PA8140 (delayed-release aspirin 81 mg and immediate release omeprazole 40 mg) administered once daily for 7 consecutive days.

2: Prilosec 40 mg is from study PA32540-112 Treatment B: One tablet of EC-ASA (Ecotrin®) 325 mg and one capsule EC omeprazole (Prilosec®) 40 mg administered once daily for 7 consecutive days.

Reviewer's Comment:

- *Based on bridged cross-study comparisons, the plasma exposure of IR omeprazole 40 mg from PA8140 was lower than that of Prilosec 40 mg, Prilosec®. Cmax and AUC of IR omeprazole 40 mg from PA8140 were 90% and 75%, respectively, of that from an EC formulation of omeprazole 40 mg, Prilosec 40 mg following repeat dose administration for 7 days.*
- *Based on result of study PA32540-112 with direct head-to-head comparison, Cmax and AUC of IR omeprazole 40 mg from PA32540 were 74% and 57%, respectively, of that from an EC formulation of omeprazole 40 mg, Prilosec 40 mg following repeat dose administration for 7 days.*
- *Based on result of study PA8140-103 with direct head-to-head comparison, omeprazole exposure (AUC) from PA8140 was 27% higher than that of PA32540 where the Cmax was very similar between PA8140 and PA32540 following repeat dose administration for 7 days.*

3 Appendix

3.1 Individual reviews

3.1.1 Study PA32540-119

TITLE: **A Single-Dose Randomized Crossover Study to Assess the Intrasubject Variability of Acetylsalicylic Acid from Administration of PA32540 and to Evaluate the Relative Bioavailability of Two Formulations of PA32540 with the Partial Reference-Replicated 3-Way Design and the Reference-Scaled Average Bioequivalence Approach**

STUDY SITE:

Sponsor:	POZEN Inc. Chapel Hill, NC
Clinical Site:	PPD, Phase I Clinic, Austin, Texas 78744
Analytical Site:	(b) (4)
Study Data:	1/28/2016 through 2/17/2016

PHASE OF STUDY: Phase 1 study

OBJECTIVE:
Primary: The primary objective was to assess the intrasubject variability of acetylsalicylic acid following repeated single-dose administration of PA32540 as Formulation 1 and evaluate the relative bioavailability/bioequivalence of two PA32540 formulations (Formulation 1 and Formulation 2) with the partial reference replicated 3-way design and the reference-scaled average bioequivalence approach.
Secondary: To evaluate the safety of each of the treatments.

Background:
The current study was performed to determine the relative bioavailability of ASA from two formulations of PA32540. The formulations differed (b) (4)

STUDY DESIGN:
- **Treatment A (Test product)**: One (1) tablet of PA32540 (b) (4) (Formulation 2)
- **Treatment B (Reference Product)**: One (1) tablet of PA32540 (Formulation 1),

This study was an open-label, randomized, single-center, single-dose, 3-way crossover study in 48 healthy adult subjects (16/treatment sequence) evaluating two PA32540 formulations. There was at least a 4-day of washout period between the treatments. Each subject was to receive the reference product (Treatment B), PA32540 as Formulation 1, twice, and the test product (Treatment A), PA32540 (b) (4) as Formulation 2, once in a randomized crossover fashion over 3 treatment periods based on the treatment sequence of BBA, BAB, or ABB.

Treatment Sequences

Sequence	Number of Subjects	Treatment Period 1	Treatment Period 2	Treatment Period 3

I	16	A	B	B
II	16	B	A	B
III	16	B	B	A

The study drug(s) was administered with 240 mL of water in the morning following an overnight fasting of at least 10 hours prior to dosing and an additional 4 hours of fasting post-dose. The tablets were not to be broken, crushed or chewed. Subjects received standardized meals at appropriate times during the study, which were scheduled at the same time in each treatment period of the study. Pharmacokinetic (PK) blood samples were collected for up to 10 hours in each treatment period to determine the plasma concentrations of acetylsalicylic acid.

Study Population: The study included healthy males and non-pregnant, non-lactating female ages between 18-55 with good health with a BMI between 19-29 kg/m^2. This study had 48 healthy volunteers enrolled and all of them completed the study as planned by completing all three treatments periods.

Key exclusion criteria:

- Ingestion of any PPIs, H2-receptor antagonists, anticholinergics, over-the-counter anti-ulcer medications, gastric-altering compounds, ASA or salicylate-containing products, or selective serotonin reuptake inhibitors within 14 days prior to the first dose in Treatment Period 1 until after the last blood draw in the last Treatment Period.
- Significant history of acid-related GI symptoms, including peptic ulcer disease.
- Known allergy, hypersensitivity or intolerance to omeprazole or other PPIs (e.g., lansoprazole).
- Any GI disease, abnormality or gastric surgery that may have interfered with gastric emptying, motility, or drug absorption.
- Known allergic reaction, hypersensitivity or intolerance to ASA, and any subject in whom ASA or non-aspirin NSAIDs induce the symptoms of asthma, rhinitis and nasal polyps.
- Ingestion of grapefruit or grapefruit juice within the 10 days of dosing or during the study.

Concomitant Therapy

The following medications were not permitted within 14 days prior the treatment and throughout the study: antibiotics, Pepto Bismol, PPIs or gastroprotective agents, (including H2-receptor antagonists, misoprostol-containing preparations, sucralfate, and antacids), ASA or non-aspirin NSAIDs (including cyclooxygenase-2 selective and non-selective agents), bisphosphonates, steroids, anticoagulants, anticholinergic agents, and selective serotonin reuptake inhibitors.

Pharmacokinetic:

PK Blood Samples:

PK blood samples (2mL) were collected in each treatment period at pre-dose and at 0.75, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, and 10 hours post dose to determine the plasma concentration of only acetylsalicylic acid.

PK Analysis:

Pharmacokinetic parameter estimates for acetylsalicylic acid (ASA) were calculated using Phoenix® WinNonlin 6.3 with non-compartmental methods.

When calculating summary (descriptive) statistics, plasma concentrations below the LLOQ for acetylsalicylic acid (0.02 µg/mL) were treated as a zero value. The mean/median value at a time point with one or more concentrations below LLOQ (below quantifiable limit [BQL] value) was reported unless the resulting mean/median values was below the LLOQ, in which case the value was assigned as BQL. A high proportion of BQL values would affect the SD estimate; thus, if more than 30% of values were imputed, SD was not displayed.

For PK analysis, plasma concentrations below the LLOQ in individual profiles of each analyte were handled for PK analysis as follows. If the value occurred in a profile during the absorptive phase (i.e., before the maximum concentration in a profile was observed), it was assigned a value of zero. Any one BQL values that occurred between measurable concentrations, not in absorptive phase of a profile, was excluded from analysis. If two values below the LLOQ occurred in succession post peak time (or during the terminal phase), the profile was determined to have terminated at the last time point with measurable analyte concentration. Pharmacokinetic parameters were calculated for each analyte using the actual sampling times.

Within-Subject Variability and Analysis for Bioequivalence

The within-subject standard deviation (Swr) of acetylsalicylic acid PK parameters following replicate administration of the reference product (PA32540 [Formulation 1]) was estimated for AUCs and Cmax, respectively based on the procedures described in the Food and Drug Administration (FDA) Draft Guidance for Progesterone Bioequivalence Assessment, February 2011.

- If Swr was < 0.294, BE was to be determined using the conventional analysis of variance (ANOVA) on the natural logarithmic (ln)- transformed PK parameters,AUC0-t, AUC0-inf and Cmax, followed by two one-sided t-tests to assess the relative bioavailability of acetylsalicylic acid between treatments. The ANOVA model included sequence, period and treatment as fixed effects, and subject within sequence as a random effect.
  The geometric least-squares means ratios between treatments and the associated 90% CIs for AUCs and Cmax were to be calculated.
  Treatment A was considered to be bioequivalent to Treatment B when 90% CI was within 0.8-1.25.
- If Swr ≥ 0.294 for ASA PK parameters, the reference-scaled average BE procedure (FDA Draft Guidance for Progesterone Bioequivalence Assessment, 2011) was to be used to determine bioequivalence of AUCs and Cmax between the test and reference treatment.
  The adjusted point estimates (the point estimate of treatment difference adjusted for the within-subject variability of the Treatment B) and the upper bound of the 95% confidence interval for the adjusted point estimate were calculated.

  Two conditions were to be met for Treatment A to be considered bioequivalent to Treatment B in a highly variable drug product:
  a) The geometric least-squares mean ratio of Treatment A vs. Treatment B was to be within the limits of 80 to 125%.
  b) The upper bound of 95% confidence interval for the adjusted point estimate was to be ≤ 0

Sample Size:

From a previous bioequivalence (BE) study for PA32540 (PA32540-115), the intra-subject variability (CV%wr) in PK parameter AUCs and Cmax for acetylsalicylic acid was 37% and 41%, respectively.

With the assumption of CV%wr and assuming expected geometric mean ratio of 0.90 for AUCs and Cmax, a sample size of 37 completed subjects was estimated to provide at least 80% power to demonstrate BE of two PA32540 Formulations using the reference-replicated 3- way design and the reference- scaled average bioequivalence approach (Tothfalusi 2011, Karalis 2011). Considering a non-evaluable rate of 23%, a total of 48 subjects were randomized in this study.

Bioanalytical Method:

- Concentrations of acetylsalicylic acid in human plasma were analyzed according to (b) (4) Method P1353.01, entitled "Quantitation of Omeprazole, Salicylic Acid, and Acetylsalicylic Acid in Human Plasma via UPLC® with MS/MS Detection," which was validated under Project Code "AIEY2." (b) (4) (b) (4)
- Plasma samples were stored frozen at -70°C until analysis.
- The standard curve for acetylsalicylic acid with 8 concentration levels range from 0.02 to 10 µg/mL with a lower limit of quantitation (LLOQ) of 0.02 µg/mL, and was calculated using a linear (1/concentration squared weighted) least-squares regression algorithm. The average R^2 was 09969.
- Quality Control (QC) samples at 5 different concentrations (0.05, 0.12, 0.450, 1.50, and 7.50 µg/mL) of acetylsalicylic acid were prepared.
- The inter-assay coefficients of variation (CV) of the QCs for the acetylsalicylic acid runs ranged from 6.04% to 8.83%, with mean percent differences from theoretical ranging from -1.59% to 4.97%.
- The differences of back-calculated calibration curve values from nominal values for acetylsalicylic acid ranged from -3.80% to 7.71%.
- At least 10% of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.
- Plasma samples, stored at approximately -70°C, were analyzed within the time period for which the long-term plasma stability of acetylsalicylic acid has been established.
  - Plasma samples were collected between 1/27/2016 through 2/13/2016.
    - Plasma samples were analyzed between 02/22/2016 through 03/07/2016.
    - The maximum storage period from collection through analysis was 50 days.
    - The long term storage stability of salicylic acid and acetylsalicylic acid in human plasma at -70 °C was established for at least for 330 days. .

Method Validation (Project code: AIEY2, Addendum 1 and addendum 2):

- The standard curves were validated to the quantitation of acetylsalicylic acid nominal range of 0.0200 to 10.0 µg/mL. The correlation coefficient from five standard curves was > 0.9974 for each analytes.

Stability of acetylsalicylic acid in human plasma

Freeze-thaw	Room temperature	Ice	at 2°C-8°C	At -20°C	At –70°C
5	1 hr	2 hours	20.26 hr	13 days	330 days

- There were no significant matrix suppression effects indicated that could compromise the sensitivity or accuracy of the assay.
- Selectivity: No significant interfering peaks noted in blank human plasma samples
- Hemolysis: No effect from hemolysis on the quantitation of acetylsalicylic acid
- Lipemia: No effect from lipemia on the quantitation of acetylsalicylic acid
- There is no effect on the quantitation of acetylsalicylic acid in human plasma fortified with 50.0 µg/mL acetaminophen, 50 ng/mL Chlorpheniramine, 100 µg/mL naproxen, 50.0 µg/mL ibuprofen,

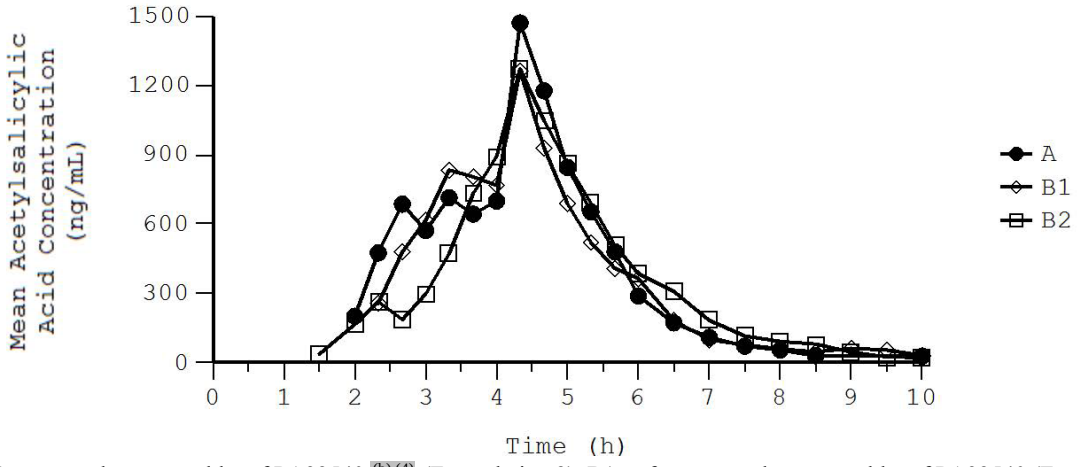
and 20.0 µg/mL caffeine, 500 pg/mL Ethinyl Estradiol, 25.0 ng/mL Norgestrel, and 100 ng/mL Norethindrone.

RESULTS:

Pharmacokinetics:

One subject (subject 1044) had only one value above the limit of quantification (BLQ) (at 10 hr post-dose) in the first dosing period (Treatment A) and it was not possible to evaluate PK parameters for this period. Thus, plasma samples for PK evaluations were available from 47 subjects who received PA32540-(b) (4) and from 48 subjects who received both the first dose and second dose of PA32540.
Five (5) subjects (subjects 1007, 1022, 1023, 1032 and 1044), whose t½ and AUC0-inf were not possible to estimate in one dosing period, were excluded from the PK analysis for AUC0-inf. Thus 43 subjects formed the $AUC_{0\text{-}inf}$ evaluable population.

Figure 1: Mean Plasma Acetylsalicylic Acid Concentration vs. Time Curves (Treatments A, B1 and B2)



A=test product: one tablet of PA32540-(b) (4) (Formulation 2). B1=reference product: one tablet of PA32540 (Formulation 1) the first occurrence. B2=reference product: one tablet of PA32540 (Formulation 1) the second occurrence.

Figure 2: Mean Plasma Acetylsalicylic Acid Concentration vs. Time Curves (Treatment A and Average of Treatments B1 and B2)

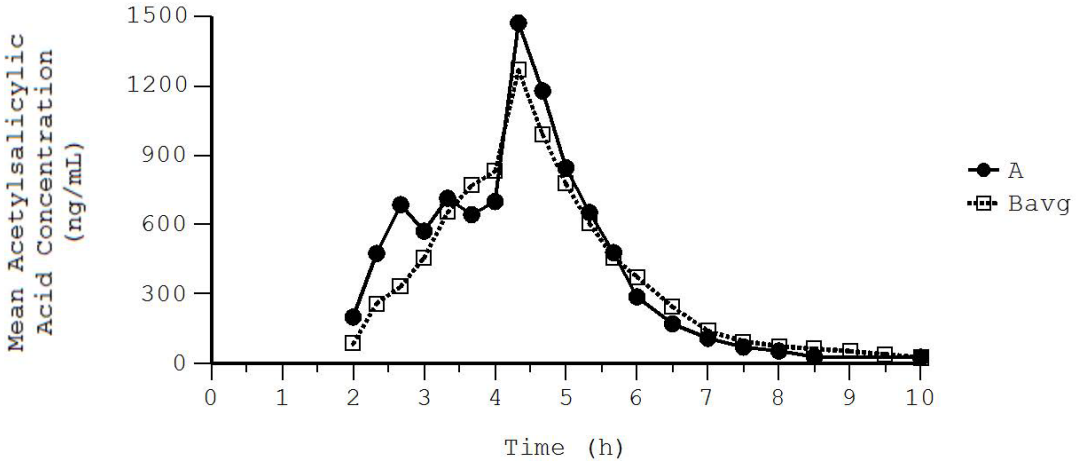


Table 2: Summary of Acetylsalicylic Acid PK Parameters

Treatment	Statistics	C_{max} (ng/mL)	t_{max}* (hr)	t_{lag}* (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	$t_{½}$ (hr)
	n	47	47	47	47	46	46
A	Mean*	3034.09	4.33	2.67	3323.83	3380.04	0.40
PA32540 (b) (4)	%CV	54	32	29	44	43	24
	GeoMean	2446.94	4.22	2.48	2945.69	3011.98	0.39
	Min	227	2.00	1.50	467.07	497.72	0.29
	Max	6540	9.50	4.33	7529.72	7542.91	0.88
	n	48	48	48	48	46	46
B1	Mean*	2645.63	4.33	2.52	2973.79	3059.22	0.46
PA32540	%CV	60	35	44	48	45	54
First Dose	GeoMean	1991.25	4.35	ND	2433.41	2633.54	0.42
	Min	121	2.33	0.00	88.05	378.15	0.28
	Max	5780	10.00	8.00	5697.51	5709.12	1.80
	n	48	48	48	48	47	47
B2	Mean*	2631.44	4.40	2.68	3078.07	3122.77	0.44
PA32540	%CV	50	33	35	45	45	34
Second Dose	GeoMean	2237.64	4.53	2.55	2688.55	2732.46	0.42
	Min	548	2.00	0.75	596.88	607.34	0.27
	Max	5760	10.05	4.33	6089.81	6107.11	1.22
	n	48	48	48	48	45	45
Average of	Mean*	2479.22	4.46	2.66	2903.62	3019.53	0.43
B1 and B2	%CV	51	26	35	45	42	28
	GeoMean	2110.85	4.44	ND	2557.80	2729.01	0.42
	Min	438.62	2.33	0.00	353.94	736.59	0.28
	Max	5125	7.32	5.66	5708.72	5722.88	0.87

GeoMean = geometric mean. *: Median for t_{max} and t_{lag}, na = not applicable.

The Swr values for Cmax and AUC0-t of acetylsalicylic acid for the reference treatment (Treatment B) were determined using the 47 subjects who had adequate plasma concentrations to assess the PK parameters for acetylsalicylic acid for both Cmax and AUC0-t values for all three periods (RSABE1 evaluable population). The Swr value for AUC0-inf of acetylsalicylic acid for the reference treatment (Treatment B) was determined in 43 subjects who had adequate plasma concentrations to assess the PK parameters for acetylsalicylic acid for AUC0-inf values for all three periods (RSABE2 evaluable population).

Intrasubject standard deviation (Swr) values for C_{max}, AUC_{0-t} and AUC_{0-inf} of acetylsalicylic acid for the Reference treatment (Treatment B) were greater than 0.294, indicating that EC-Aspirin PK parameters qualify for the reference-scaled average BE procedure to establish bioequivalence of AUCs and Cmax between two furmulations (please see the Section for Within-Subject Variability and Analysis for Bioequivalence).

Table 3: Summary of Statistical Analysis Results of Acetylsalicylic Acid PK Parameters:

	Referenced Scaled Average Bioequivalence (RSABE)		
	S_{wr} [>=0.294]	Point Estimate [0.80, 1.25]	Critical Bound [<=0]
C_{max} (N=47)	0.677	1.1760	-0.2055
AUC_{0-t} (N=47)	0.588	1.1669	-0.1386
AUC_{0-inf} (N=43)	0.475	1.1675	-0.0785

Swr: within-subject standard deviation of the PK parameter from the Reference product.

SAFETY:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory test (haemotology, clinical chemistry, urinalysis,) pregnancy test for female subjects, 12-lead electrocardiogram (ECG), and adverse event (AE) and serious adverse event monitoring.

According to the sponsor, there were no deaths, or serious adverse event (SAE) during the study and no subject was withdrawn from the study due to AE.

An overview of adverse events is displayed in Table 9. One subject (2%) reported AEs with administration of PA32540 (b) (4) and 8 subjects (17%) with PA32540. All AEs were mild in severity except two AEs, which were moderate in severity. One subject in the PA32540 (b) (4) group (2%) and 4 subjects in the PA32540 group (8%) had AEs that were considered by the Investigator to be related to treatment.

The AEs considered related to treatment by the Investigator were 1 each of nausea, vomiting, and abdominal distension for PA32540 (b) (4) and 1 report each of nausea, vomiting, abdominal discomfort, abdominal distension, epistaxis, and nasal congestion for PA32540. In addition, no clinically significant findings were noted in the clinical laboratory or vital sign data.

***Reviewer's Comment*:**

- *The within-subject standard deviation of acetylsalicylic acid pharmacokinetic parameters from the reference product PA32540 was estimated to be 0.677 for C_{max} and 0.588 for AUCt and 0.475 for AUC_{0-inf}, which are all greater than 0.294, confirming that EC-aspirin formulations are considered to be highly variable drug products and EC-Aspirin PK parameters qualify for the reference-scaled average BE procedure to establish bioequivalence of AUCs and Cmax between two formulations.*
- *The reference-scaled average bioequivalence assessment showed that the point estimates of the geometric least squares mean ratios, PA32540 (b) (4) vs. PA32540, for all bioavailability parameters of acetylsalicylic acid were within the interval of 0.80-1.25. In addition, the upper bound (critical bound) of the 95% confidence interval for the difference between PA32540 (b) (4) and PA32540 treatments (adjusted for the estimated intrasubject variability of PA32540) was less than zero.*
- *PA32540 (b) (4) is bioequivalent to PA32540 in terms of Cmax, AUC0-t and AUC0-inf of acetylsalicylic acid based on the reference-scaled average bioequivalence approach for highly variable drug products.*
- *Sampling time for 10 hours and washout period of 4 days were adequate as the half-lives of acetylsalicylic acid was approximately 0.4 hour.*

3.1.2 Study PA8140-104

TITLE: **Single-Dose Randomized Crossover Study to Assess the Intrasubject Variability of Acetylsalicylic Acid from Administration of Three Tablets (Dosed Concurrently) of PA8140 and to Evaluate the Relative Bioavailability of Three Tablets (Dosed Concurrently) of Two Formulations of PA8140 with the Partial Reference-Replicated 3-Way Design and the Reference-Scaled Average Bioequivalence Approach**

STUDY SITE:

Sponsor:	POZEN Inc. Chapel Hill, NC
Clinical Site:	PPD, Phase I Clinic, Austin, Texas 78744
Analytical Site:	(b) (4)
Study Data:	11/18/2015-12/17/2015

PHASE OF STUDY: Phase 1 study

OBJECTIVE:

Primary:

- To assess the intrasubject variability of acetylsalicylic acid following repeated single-dose administration of three tablets (dosed concurrently) of PA8140 as Formulation 1.
- To evaluate the relative bioavailability/bioequivalence of three tablets (dosed concurrently) of two PA8140 formulations (Formulation 1 and Formulation 2) with the partial reference replicated 3-way design and the reference-scaled average bioequivalence approach.

Secondary**:** To evaluate the safety of each of the treatments.

Background:

The current study was performed to determine the relative bioavailability of ASA from two formulations of PA32540. The formulations differed (b) (4)

STUDY DESIGN:

- **Treatment A (Test product)**: Three (3) tablets (dosed concurrently) of PA8140 (b) (4) (Formulation 2)
- **Treatment B (Reference Product)**: Three (3) tablets (dosed concurrently) of PA8140 (Formulation 1)

This study was an open-label, randomized, single-center, single-dose, 3-way crossover study in 36 healthy adult subjects (12/treatment sequence) evaluating two PA8140 formulations. There was at least a 4-day of washout period between the treatments. Each subject was to receive the reference product (Treatment B), 3 tablets of PA8140 (dosed concurrently) as Formulation 1, twice, and the test product (Treatment A), three tablets (dose concurrently) of PA8140 (b) (4) as Formulation 2, once in a randomized crossover fashion over 3 treatment periods based on the treatment sequence of BBA, BAB, or ABB.

Treatment Sequences

Sequence	Number of Subjects	Treatment Period 1	Treatment Period 2	Treatment Period 3

I	12	A	B	B
II	12	B	A	B
III	12	B	B	A

The study drug(s) was administered with 240 mL of water in the morning following an overnight fasting of at least 10 hours prior to dosing. Subject consumed a standardized breakfast at approximately one hour after dosing. The tablets were not to be broken, crushed or chewed. Subjects received standardized meals at appropriate times during the study, which were scheduled at the same time in each treatment period of the study. Pharmacokinetic (PK) blood samples were collected for up to 8.5 hours in each treatment period to determine the plasma concentrations of acetylsalicylic acid.

Study Population: The study included healthy males and non-pregnant, non-lactating female ages between 18-55 with good health with a BMI between 19-29 kg/m^2. This study had 36 healthy volunteers enrolled and all of them completed the study as planned by completing all three treatments periods.

Key exclusion criteria:

- Ingestion of any PPIs, H2-receptor antagonists, anticholinergics, over-the-counter anti-ulcer medications, gastric-altering compounds, ASA or salicylate-containing products, or selective serotonin reuptake inhibitors within 14 days prior to the first dose in Treatment Period 1 until after the last blood draw in the last Treatment Period.
- Significant history of acid-related GI symptoms, including peptic ulcer disease.
- Known allergy, hypersensitivity or intolerance to omeprazole or other PPIs (e.g., lansoprazole).
- Any GI disease, abnormality or gastric surgery that may have interfered with gastric emptying, motility, or drug absorption.
- Known allergic reaction, hypersensitivity or intolerance to ASA, and any subject in whom ASA or non-aspirin NSAIDs induce the symptoms of asthma, rhinitis and nasal polyps.
- Ingestion of grapefruit or grapefruit juice within the 10 days of dosing or during the study.

Concomitant Therapy:

The following medications were not permitted within 14 days prior the treatment and throughout the study: antibiotics, Pepto Bismol or any other aspirin-containing products, PPIs or gastroprotective agents, (including H2-receptor antagonists, misoprostol-containing preparations, sucralfate, and antacids), ASA or non-aspirin NSAIDs (including cyclooxygenase-2 selective and non-selective agents), bisphosphonates, steroids, anticoagulants, anticholinergic agents, and selective serotonin reuptake inhibitors.

Pharmacokinetic:

PK Blood Samples:

PK blood samples (2mL) were collected in each treatment period at pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.5, 7, 7.5, 8, and 8.5 hours post dose to determine the plasma concentration of only acetylsalicylic acid.

PK Analysis:

Pharmacokinetic parameter estimates for acetylsalicylic acid (ASA) were calculated using Phoenix® WinNonlin 6.3 with non-compartmental methods.

For PK analysis, plasma concentrations below the LLOQ in individual profiles of each analyte were handled for PK analysis as follows. If the value occurred in a profile during the absorptive phase (i.e., before the maximum concentration in a profile was observed), it was assigned a value of zero. Any one BQL values that occurred between measurable concentrations, not in absorptive phase of a profile, was excluded from analysis. If two values below the LLOQ occurred in succession post peak time (or during the terminal phase), the profile was determined to have terminated at the last time point with measurable analyte concentration. Pharmacokinetic parameters were calculated using the actual sampling times.

Within-Subject Variability and Analysis for Bioequivalence:
The within-subject standard deviation (Swr) of acetylsalicylic acid PK parameters following replicate administration of the reference product (PA8140 [Formulation 1], Treatment B) was estimated for AUCs and Cmax, respectively based on the procedures described in the Food and Drug Administration (FDA) Draft Guidance for Progesterone Bioequivalence Assessment, February 2011.

- If Swr was < 0.294, separately for AUC0-t, AUC0-∞ and Cmax, BE was to be determined using the conventional analysis of variance (ANOVA) on the natural logarithmic (ln)- transformed PK parameters,AUC0-t, AUC0-inf and Cmax, followed by two one-sided t-tests to assess the relative bioavailability of acetylsalicylic acid between treatments. The ANOVA model included sequence, period and treatment as fixed effects, and subject within sequence as a random effect.
  The geometric least-squares means ratios between treatments and the associated 90% CIs for AUCs and Cmax were to be calculated.
  Treatment A was considered to be bioequivalent to Treatment B when 90% CI was within 0.8-1.25.
- If Swr ≥ 0.294 for ASA PK parameters, the reference-scaled average BE (RSABE) procedure (FDA Draft Guidance for Progesterone Bioequivalence Assessment, 2011) was to be used to determine bioequivalence of AUCs and Cmax between the test and reference treatment.

  Two conditions were to be met for Treatment A to be considered bioequivalent to Treatment B in a highly variable drug product:
  a) The geometric least-squares mean ratio of Treatment A vs. Treatment B was to be within the limits of 80 to 125%.
  b) The upper bound of 95% confidence interval for the adjusted point estimate was to be ≤ 0

Sample Size:
From a previous bioequivalence (BE) study for PA8140, the intra-subject variability (CV%wr) in PK parameter AUCs and Cmax for acetylsalicylic acid was 33% and 60%, respectively. With the assumption of CV%wr and assuming expected geometric mean ratio of 1.05 for AUCs, a sample size of 33 completed subjects was estimated to provide at least 85% power to demonstrate BE of two PA8140 Formulations using the reference-replicated 3- way design and the reference- scaled average bioequivalence approach (Tothfalusi 2011, Karalis 2011). Considering a non-evaluable rate of 10%, a total of 36 subjects were randomized in this study.

Bioanalytical Method:

- Project samples were analyzed according to Concentrations of acetylsalicylic acid in human plasma were analyzed according (b) (4) Method P1353.00, entitled "Quantitation of Omeprazole, Salicylic Acid, and Acetylsalicylic Acid in Human Plasma via UPLC® with MS/MS Detection," which was validated under Project Code "AIEY2." which was validated under Project Code "AIEY2." (b) (4) (b) (4)

- Plasma samples were stored frozen at -70°C until analysis.
- The standard curve for acetylsalicylic acid with 8 concentration levels range from 0.02 to 10 µg/mL with a lower limit of quantitation (LLOQ) of 0.02 µg/mL, and was calculated using a linear (1/concentration squared weighted) least-squares regression algorithm. The average R^2 was 09977.
- Quality Control (QC) samples at 5 different concentrations (0.05, 0.12, 0.450, 1.50, and 7.50 µg/mL) of acetylsalicylic acid were prepared.
- The inter-assay coefficients of variation (CV) of the QCs for the acetylsalicylic acid runs ranged from 3.28% to 11.1%,with mean percent differences from theoretical ranging from 0.463% to 7.27%.
- The differences of back-calculated calibration curve values from nominal values for acetylsalicylic acid ranged from -4.88% to 3.56%.
- At least 10% of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.
- Plasma samples, stored at approximately -70°C, were analyzed within the time period for which the long-term plasma stability of acetylsalicylic acid has been established.
  - Plasma samples were collected between 11/18/2015 through 12/17/2015.
    - Plasma samples were analyzed between 01/07/2016 through 01/17/2016.
    - The maximum storage period from collection through analysis was 60 days.
    - The long term storage stability of acetylsalicylic acid in human plasma at -70 °C was established for at least for 330 days. .

Method Validation (Project code: AIEY2, Addendum 1 and addendum 2):

- The standard curves were validated to the quantitation of acetylsalicylic acid nominal range of 0.0200 to 10.0 µg/mL. The correlation coefficient from five standard curves was > 0.9974 for each analytes.

Stability of acetylsalicylic acid in human plasma

Freeze-thaw	Room temperature	Ice	at 2°C-8°C	At -20°C	At –70°C
5	1 hr	2 hours	20.26 hr	13 days	330 days

- There were no significant matrix suppression effects indicated that could compromise the sensitivity or accuracy of the assay.
- Selectivity: No significant interfering peaks noted in blank human plasma samples
- Hemolysis: No effect from hemolysis on the quantitation of acetylsalicylic acid
- Lipemia: No effect from lipemia on the quantitation of acetylsalicylic acid
- There is no effect on the quantitation of acetylsalicylic acid in human plasma fortified with 50.0 µg/mL acetaminophen, 50 ng/mL Chlorpheniramine, 100 µg/mL naproxen, 50.0 µg/mL ibuprofen, and 20.0 µg/mL caffeine, 500 pg/mL Ethinyl Estradiol, 25.0 ng/mL Norgestrel, and 100 ng/mL Norethindrone.

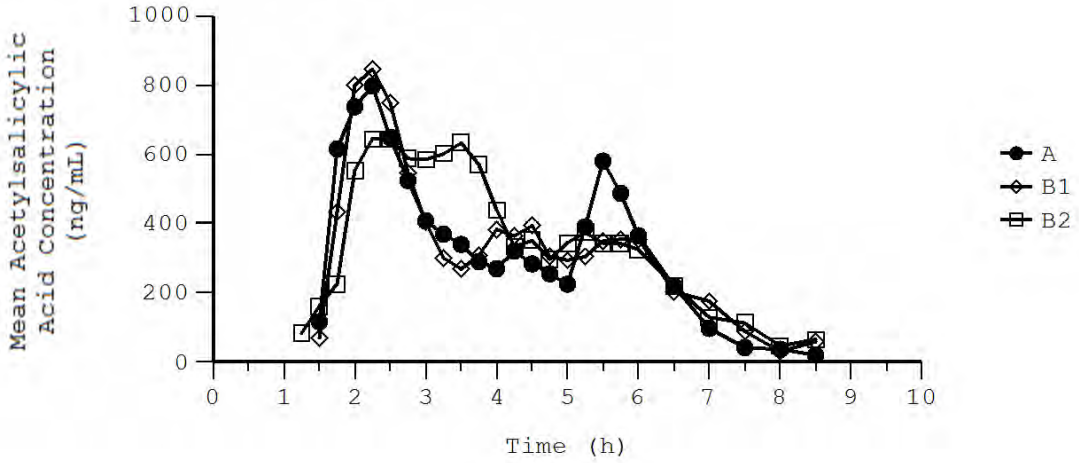
RESULTS:

Pharmacokinetics:

One subject (No. 1024) had values below the limit of quantification (BLQ) at all the time points in all three periods. This subject was excluded from the PK parameter calculation. Thirty-five subjects had PK parameters measurable in at least one period. These 35 subject formed the PK evaluable population and the BE evaluable population. Twenty eight subjects had PK parameters measurable in all three periods. These 28 subjects formed the RSABE evaluable population.

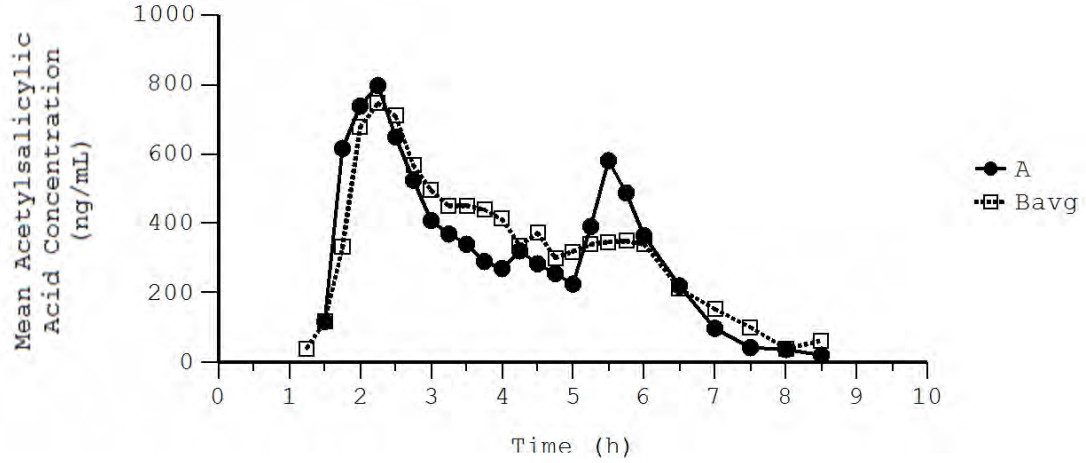
- In 3 subjects (No. 1010, 1018, and 1028), acetylsalicylic acid concentrations were not measurable, all below LLOQ (20.0 ng/mL), in all samples collected throughout the sampling period after Treatment A (PA8140 (b) (4)). In 1 subject (No. 1023), acetylsalicylic acid concentrations were measurable, above LLOQ (20.0 ng/mL), in only two samples after Treatment A (PA8140 (b) (4)), so there was insufficient data to estimate PK parameters.
- In 4 subjects, acetylsalicylic acid concentrations were not measurable, all below LLOQ (20.0 ng/mL), in all samples collected throughout the sampling period after Treatment B (PA8140), with 3 subjects (No. 1006, 1013, and 1007) after the first dose of PA8140 and 1 subject (No. 1010) after the second dose of PA8140. Subjects with values BLQ during one of their three treatment cycles were balanced between Treatment A and Treatment B.
- In 1 subject (No. 1025), acetylsalicylic acid concentrations were measureable, above LLOQ (20.0 ng/mL), in only four samples after Treatment B (PA8140), in both the first dose and the second dose of PA8140, so there was insufficient data to estimate all of the PK parameters.

Figure 1: Mean Plasma Acetylsalicylic Acid Concentration vs. Time Curves (Treatments A, B1 and B2)



A=test product: three tablets (dosed concurrently) of PA8140 (b) (4) (Formulation 2). B1=reference product: three tablets (dosed concurrently) of PA8140 (Formulation 1) the first occurrence. B2=reference product: three tablets (dosed concurrently) of PA8140 (Formulation 1) the second occurrence.

Figure 2: Mean Plasma Acetylsalicylic Acid Concentration vs. Time Curves (Treatment A and Average of Treatments B1 and B2)



A=Test product: three tablets (dosed concurrently) of PA8140 (b) (4) (Formulation 2). B_{avg}=average concentration of

Treatment B1 (first occurrence) and Treatment B2 (second occurrence) for subjects who had completed both B1 and B2.

Table 2: Summary of Acetylsalicylic Acid PK Parameters

Treatment	Statistics	C_{max} (ng/mL)	t_{max}* (hr)	t_{lag}* (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL	t½ (hr)
	n	31	31	31	31	31	31
A	Mean*	2377.00	3.05	1.57	2551.22	2572.60	0.40
PA8140 (b) (4)	%CV	54	43	60	38	38	30
	GeoMean	2079.91	3.25	ND	2346.99	2373.37	0.38
	Min	647	1.75	0.00	592.14	615.69	0.27
	Max	5400	6.50	5.25	4777.49	4789.75	0.79
	n	32	32	32	32	30	30
B1	Mean*	2185.59	4.00	1.88	2491.13	2564.43	0.39
PA8140	%CV	41	43	57	36	36	15
First Dose	GeoMean	2023.50	3.55	2.37	2327.49	2399.79	0.38
	Min	929	1.75	1.25	735.44	747.74	0.29
	Max	4590	7.00	6.50	4963.52	4987.27	0.54
	n	34	34	34	34	33	33
B2	Mean*	2095.65	3.29	2.25	2488.95	2469.96	0.37
PA8140	%CV	42	44	56	33	32	15
Second Dose	GeoMean	1922.50	3.50	2.29	2335.90	2327.10	0.37
	Min	863	1.50	0.50	790.43	805.21	0.29
	Max	3990	7.53	6.50	4080.23	4095.16	0.55
	n	31	31	31	31	28	28
Average of	Mean*	2067.88	3.74	2.29	2450.29	2459.87	0.38
B1 and B2	%CV	36	38	50	33	30	11
	GeoMean	1955.02	3.47	2.28	2314.21	2342.37	0.37
	Min	1045.79	1.73	0.79	770.36	770.36	0.31
	Max	4148.80	7.26	6.50	4413.32	4413.32	0.46

GeoMean = geometric mean. *: Median for t_{max} and t_{lag}, na = not applicable.

Multiple absorption peaks were observed after treatment with either PA8140 or PA8140 (b) (4) in individual subjects most likely due to the multiple tablets administered. This observation of multiple peaks in this study was consistent with study PA8140-102 which also had administered three tablets of PA8140.

The Swr value for Cmax of acetylsalicylic acid for the reference treatment (Treatment B) was determined using the Referenced-Scaled Average Bioequivalence (RSABE) evaluable population (N=28), who had adequate blood sampling to assess the PK parameters for acetylsalicylic acid for both Cmax and AUC values for all three periods. The Swr value for Cmax was 0.384, indicating a "highly variable" drug product for this parameter. Therefore, reference-scaled average bioequivalence approach was used for comparison of acetylsalicylic acid Cmax.

The Swr values for AUC0-t and AUC0-inf of acetylsalicylic acid for the reference treatment (Treatment B) were determined in 31 subjects and 28 subjects, respectively, using the BE evaluable population and whose both periods of Treatment B were measurable. The Swr values for AUC0-t and AUC0-inf were below 0.294, (0.261 and 0.270, respectively). Therefore, average bioequivalence approach were used for comparison of AUC0-t and AUC0-inf of acetylsalicylic acid.

Table 3: Summary of Statistical Analysis Results of Acetylsalicylic Acid PK Parameters:

	Referenced Scaled Average Bioequivalence (RSABE)		
C_{max} (N=28)	**S_{WR} [>=0.294]**	**Point Estimate [0.80, 1.25]**	**Critical Bound [<=0]**
USE RSABE: Criteria Met	0.384	1.0292	-0.0650

	Average Bioequivalence (ABE)			
AUC_{0-t} (N=35)	**S_{WR} [<0.294]**	**Ratio (%)**	**90% CI Lower**	**90% CI Upper**
USE UNSCALED ABE: $S_{WR} < 0.294$	0.261	99.75	90.59	109.84

	Average Bioequivalence (ABE)			
AUC_{0-inf} (N=35)	**S_{WR} [<0.294]**	**Ratio (%)**	**90% CI Lower**	**90% CI Upper**
USE UNSCALED ABE: $S_{WR} < 0.294$	0.270	99.44	90.32	109.49

Swr: within-subject standard deviation of the PK parameter from the Reference product.

SAFETY:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory test (haemotology, clinical chemistry, urinalysis,) pregnancy test for female subjects, 12-lead electrocardiogram (ECG), and adverse event (AE) and serious adverse event monitoring.

According to the sponsor, there were no deaths, or serious adverse event (SAE) during the study and no subject was withdrawn from the study due to AE.

Two subjects (6%) reported AEs with administration of PA8140 (b) (4) (Treatment A), and 4 subjects (11%) with PA8140 (Treatment B). All AEs were mild in severity. One subject (3%) in the PA8140 group had an AE that was considered by the Investigator to be related to treatment.

Nasal congestion was the most commonly reported AE for Treatment B (6%);

1 AE of fatigue was reported for 1 subject (3%) in Treatment A. The AE considered related to treatment by the Investigator was 1 report of vessel puncture site hematoma in Treatment B (PA8140). In addition, no clinically significant findings were noted in the clinical laboratory, ECG or vital sign data.

Reviewer's Comment:

- *The within-subject standard deviation (*Swr*) of acetylsalicylic acid PK parameters from the reference product, PA8140, was estimated to be:*
  - *0.384 (38.4%) for Cmax, appropriate for reference-scaled average bioequivalence approach,*
  - *0.261 (26.1%) for AUC0-t and 0.270 (27.0%) for AUC0-inf, appropriate for average bioequivalence approach, not for* (RSABE).
- *Cmax: The reference-scaled average bioequivalence assessment showed that the point estimate of the geometric least squares mean ratios, PA8140 (b) (4) vs. PA8140, for Cmax of acetylsalicylic acid*

were within the interval of 0.80-1.25. In addition, the upper bound (critical bound) of the 95% confidence interval for the difference between PA8140 (b) (4) and PA8140 treatments, adjusted for the estimated intrasubject variability of the PA8140 treatment was less than zero, indicating that PA8140 (b) (4) is bioequivalent to PA8140 in terms of Cmax of acetylsalicylic acid

- *AUC: The average bioequivalence assessment showed that the 90% confidence interval for the geometric least squares mean ratios, PA8140 (b) (4) vs. PA8140, for AUC0-t and AUC0-inf of acetylsalicylic acid were within the bioequivalence interval of 80%-125% indicating that PA8140-(b) (4) is bioequivalent to PA8140 in terms of AUC of acetylsalicylic acid.*
- *PA8140 (b) (4) is bioequivalent to PA8140 in terms of Cmax, AUC0-t and AUC0-inf of acetylsalicylic acid.*
- *Sampling time for 8.5 hours and washout period of 4 days were adequate as the half-lives of acetylsalicylic acid was approximately 0.4 hour.*

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/s/

DILARA JAPPAR
08/12/2016

SUE CHIH H LEE
08/12/2016

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 205103	Submission Date(s): 06/30/2014
Submission Type; Code	Resubmission
Brand Name	Yosprala
Generic Name	Aspirin Delayed Release/Omeprazole Immediate Release
Reviewer	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Sponsor	POZEN, Inc
Formulation; Strength(s)	Tablet, 81 mg or 325 mg Aspirin/40 mg Omeprazole
Proposed Indication	Use in the secondary prevention of cardiovascular and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers
Proposed Dosing Regimen	Once Daily tablet
PDUFA Goal Date:	11/21/2014

Executive Summary

This is was 505(b)(2) application for Yosprala (Delayed Release Aspirin/Immediate Release omeprazole) tablets referencing Ecotrin® (EC-Aspirin) and Prilosec® (EC-Omeprazole). The proposed product is an oral fixed dose combination product containing 81 mg or 325 mg aspirin in the inner enteric coated core (delayed release) surrounded by 40 mg omeprazole in the immediate-release film coat to release the active ingredients in a sequential fashion.

The original application was submitted on 03/25/2013. A full clinical pharmacology review was conducted during the 1st review cycle and application was acceptable from clinical pharmacology perspective. Please see Clinical Pharmacology review dated 04/18/2014. However, this application was issued a Complete Response (CR) action letter on 04/25/2014 due to deficiencies in a manufacturing facility. There were no deficiencies from clinical pharmacology.

The sponsor submitted a response to Complete Response action letter (resubmission) on June 30, 2014 with a revised label. There was no new clinical pharmacology study in this submission. Therefore, this application is acceptable from the clinical pharmacology perspective provided that a mutual agreement is reached regarding the labeling.

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/s/

DILARA JAPPAR
11/24/2014

SUE CHIH H LEE
11/24/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 205103	Submission Date(s): 03/25/2013, 09/20/2013, 3/26/2014
Submission Type; Code	Original submission 505 (b)(2); Standard Review
Brand Name	Yosprala
Generic Name	Aspirin Delayed Release/Omeprazole Immediate Release
Reviewer	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Sponsor	POZEN, Inc
Formulation; Strength(s)	Tablet, 81 mg or 325 mg Aspirin/40 mg Omeprazole
Proposed Indication	Use in the secondary prevention of cardiovascular and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers
Proposed Dosing Regimen	Once Daily tablet
Original PDUFA Goal Date:	01/24/2014
Extended PDUFA Goal Date:	04/25/2014

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1 Executive Summary

This is a 505(b)(2) application for Yosprala (Delayed Release Aspirin/Immediate Release omeprazole) tablets referencing Ecotrin® (EC-Aspirin) and Prilosec® (EC-Omeprazole). The proposed product is an oral fixed dose combination product containing 81 mg or 325 mg aspirin in the inner enteric coated core (delayed release) surrounded by 40 mg omeprazole in the immediate-release film coat to release the active ingredients in a sequential fashion. The proposed Yosprala products are also designated as PA8140 (81 mg EC-aspirin/40 mg IR-omeprazole) and PA32540 (325 mg EC-aspirin/40 mg IR-omeprazole) tablets. The proposed indication is use in the secondary prevention of cardiovascular and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers.

The clinical efficacy of Yosprala for secondary prevention of cardiovascular and cerebrovascular events was not demonstrated through clinical trials. Rather, bioavailability/bioequivalence of the aspirin component of Yosprala as compared to Ecotrin (81 mg & 325 mg) was used as evidence of efficacy in this regard.

The clinical efficacy of PA32540 for the risk reduction of developing aspirin-induced gastric ulcers was established in two phase III studies. However, the Phase III program did not evaluate the risk reduction potential of developing aspirin-induced gastric ulcers for PA8140 tablet. In order to extrapolate the clinical efficacy of PA32540 to PA8140 regarding the risk reduction of developing aspirin-induced gastric ulcers, the FDA requested the sponsor to conduct a relative bioavailability (BA) study comparing the omeprazole exposure between PA8140 and PA32540 in the December 6, 2013 teleconference. Due to this new requested relative BA study, the PDUFA date for this NDA application was extended by 3 month to April 25th, 2014. The sponsor conducted the requested relative BA study (Study PA8140-103) and submitted the study report on March 26th, 2014.

In support of this NDA application, the sponsor had conducted 17 clinical studies, including 6 PK/BA/BE studies, 1 PK/PD study, 5 PD (mucosal damage) studies, 2 inhibition of platelet aggregations studies, 2 phase III efficacy and safety studies, and one long term (12-monht) phase III safety study. Pharmacokinetics of PA8140 and PA32540 were only characterized in healthy subjects during the phase I studies, but not in patient population.

Internal Note Only:
The draft clinical pharmacology review for this NDA 205103 was completed in Mid-October of 2013. Due to the fact that the newly requested relative BA study (study PA8140-103) report was submitted on 03/26/2014, the clinical pharmacology review could not be finalized until 04/18/2014.

OSI Inspection:
OSI inspection for studies PA32540-115 and PA8140-102 for clinical and analytical sites were requested on 06/07/2013. The inspection report was completed on Nov 8, 2013 and found that there were no significant findings at both clinical and bioanalytical sites for these two studies. Therefore, the inspection report recommended that data for clinical and analytical portions of studies PA32540-115 and PA8140-102 are acceptable for further agency review.

OSI inspection for the newly submitted study PA8140-103 was not requested since the sponsor had used the same clinical site and the same bioanalytical site for this study as the studies PA32540-115 and PA8140-102 for which recent inspection was satisfactory.

1.1 Recommendation

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

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Dose Selection Rationale:

Aspirin:
The doses of aspirin in PA Tablets (81 mg and 325 mg) were selected based on the dose range covered by the OTC monograph for the reference drug, Ecotrin®, for vascular indications. Two bioequivalence bridging studies have been conducted with proposed products (PA8140 and PA32540) with the respective strengths of Ecotrin to support the efficacy of the proposed products for the cardiovascular and cerebrovascular indications.

According to the Division of Cardiovascular and Renal Products (DCRP), there is a lack of a dose-related increase in aspirin efficacy (no incremental benefit in chronic administration of doses of ASA above 100 mg,) while there is an aspirin dose-related increase in bleeding – particularly gastrointestinal bleeding, DCRP recommended that DGIEP approve only the proposed product containing 81 mg of ASA (i.e., PA8140). Please see the consult review by Dr. Preston Dunnmon (Medical reviewer in Division of Cardiovascular and Renal Products) dated 10/21/2013 for further detail. However, DGIEP will also consider PA32540 until DCRP has taken a final action on all aspirin products in this regard.

Omeprazole:
The sponsor compared 20 mg and 40 mg of IR-omeprazole for prevention of upper gastrointestinal (UGI) damage induced by EC-aspirin 325 mg. This was not done to evaluate UGI damage induced by EC-aspirin 81 mg. Based on omeprazole systemic exposure, gastric pH control and gastroduodenal mucosal protection data, sponsor selected 40 mg IR-omeprazole for their proposed product as explained below.

1. IR-omeprazole 40 mg results in approximately half the plasma omeprazole exposure observed with EC-omeprazole 40 mg following both single and multiple dosing.
2. Following 7 days of multiple dosing, 40 mg IR-omeprazole provides 24-hour pH control comparable to the pH control achieved with the currently marketed EC-omeprazole 20 mg.
3. PK/PD data from literature suggested that 20 mg IR-omeprazole would be sub-optimal for gastric mucosal protection relative to marketed EC products.
4. In Phase 1 studies, 40 mg IR-omeprazole provides a greater gastroduodenal mucosal protection compared 20 mg IR-omeprazole for aspirin 325 mg dose level.

Bioavailability/Bioequivalence and the efficacy or safety implications:

Acetylsalicylic Acid (Study PA8140-102 and Study PA32540-115):
The bioequivalence findings with respect to aspirin between the proposed products (PA32540 and PA8140) and the reference products (Ecotrin® 81 mg and 325 mg) were established using acetylsalicylic acid as the primary analyte as the cardio-protective activity of aspirin products is attributed to aspirin (acetylsalicylic acid), and not salicylic acid. The sponsor used a reference-scaled average BE approach as acetylsalicylic acid is a highly variable drug.

PA8140 tablet was bioequivalent to the reference product Ecotrin® 81 mg tablet in terms of acetylsalicylic acid exposure (Study PA8140-102). However, PA32540 tablet was not bioequivalent to the reference product Ecotrin® 325 mg tablet, and the bioavailability of acetylsalicylic acid from PA32540 was 10-15% less than that of Ecotrin® 325 mg dose (PA32540-115). Nonetheless, according to the consult review by Dr. Preston Dunnmon (Medical reviewer in Division of Cardiovascular and Renal Products) and Dr. Sudharshan Hariharan (Clinical Pharmacology Reviewer in DCP1) dated 10/21/2013, the 10-15% lower exposure to aspirin for PA32540 tablets compared to Ecotrin® 325 mg is not clinically meaningful as this change in aspirin plasma exposures at 325 mg does not affect platelet inhibition, and the only generally accepted and well-understood mechanism by which aspirin reduces the risk of adverse cardiovascular events is through inhibition of platelet aggregation via irreversible acetylation of the cyclooxygenase-1 (COX-1) enzyme. Therefore, this lack of bioequivalence between PA32540 and Ecotrin ® 325 mg for acetylsalicylic acid exposure does not impact the approvability of PA32540. As such, these BA/BE studies established the efficacy of the aspirin component in both PA8140 and PA32540.

Bioavailability of Omeprazole (Study PA32540-112, PA32540-113, and PA8140-103):
Following single and multiple dosing, the relative bioavailability (AUC) of omeprazole from PA32540 is about 51%-58% that of EC formulation of Prilosec® 40mg. Following 7 days of once daily dosing, PA8140 has approximately a 27% higher omeprazole exposure compared to that of PA32540. Therefore, the efficacy of omeprazole for PA8140 is established as no less than that for PA32540. Since the omeprazole systemic exposure for PA32540 is only approximately half of that from Prilosec 40 mg, this higher omeprazole exposure for PS8140 is not of a safety concern.

Single-Dose PK:
Single dose PK in healthy subjects was evaluated in several studies for PA32540 tablet and in one study for PA8140. The mean PK parameters of acetylsalicylic acid were fairly consistent across studies. Since omeprazole is a substrate of CYP2C19, an isozyme that exhibits polymorphism, the variability in omeprazole PK parameters across studies is greater as expected. The sponsor did not genotype the subjects for CYP2C19 enzyme in those studies.

Acetylsalicylic Acid PK (%CV):

Studies:	**C_{max} (µg/ml)**	**t_{max} (hr)**	**AUC_{0-t} (hr*µg/ml)**	**AUC_{0-inf} (hr*µg/ml)**	**$t_{½}$ (hr)**
PA32540-105	2.51 (81%)	3.25 (81%)	3.07 (52%)	3.13 (52%)	0.5 (39%)
PA32540-112	2.36 (56%)	3.0 (N/A)	3.25 (36%)	3.36 (34%)	0.450 (23%)
PA32540-113	2.26 (71%)	4.5 (n/a)	2.73 (64%)	2.99 (57%)	0.432 (96%)
PA32540-115	2.51 (69%)	4.42 (32%)	2.9 (62%)	2.94 (62%)	0.361 (33%)

Omeprazole PK (%CV):

Studies:	**C_{max} (ng/ml)**	**t_{max} (hr)**	**AUC_{0-t} (hr*ng/ml**	**AUC_{0-inf} (hr*ng/ml)**	**$t_{½}$ (hr)**
PA32540-104	774.9 (99%)	0.51 (36%)	1082.9 (136%)	1086.1 (135%)	1.05 (35%)
PA32540-105	856 (81%)	0.5 (48%)	1384 (108%)	1393 (108%)	1.15 (33%)
PA32540-112	617 (63%)	0.50 (N/A)	880 (109%)	881 (109%)	1.00 (40%)
PA32540-113	822 (86%)	0.5 (n/a)	1177 (96%)	1198 (99%)	1.12 (43%)
PA32540-115	Not Measured				
PA325-106*	738 (77%)	0.57 (62%)	903 (99%)	905 (99%)	1.04 (36%)

Study PA325-106* was conducted with Phase 1 formulation whereas the rest of the PK studies were conducted with Phase 3 and BE formulation.

Multiple-Dose PK (Study PA32540-112, PA8140-103):
Following once daily oral dosing of PA32540 tablet or EC Aspirin (Ecotrin®) 325 mg + EC omeprazole (Prilosec®) 40 mg for 7 days, there was an approximately 2-fold higher exposure for omeprazole (regardless of IR or EC formulation) and no accumulation for acetylsalicylic acid and salicylic acid.

PD Characteristic (Study PA32540-112):
Treatment with PA32540 resulted in a lower % time intragastric pH >4 compared with EC-ASA 325 mg (Ecotrin) + EC omeprazole 40 mg (Prilosec) (51% vs. 58%, respectively). This is consistent with the lower systemic exposure of omeprazole from PA32540 (IR formulation) compared to Prilosec 40 mg (EC omeprazole).

Food Effect (Study PA32540-105):
The effect of food on Yosprala were evaluated when PA32540 was administered 60 minutes prior to breakfast and within 5 minutes of breakfast compared to the fasted state. Overall, salicylic acid and omeprazole have more comparable plasma exposures and PK profiles when PA32540 was administered 60 minutes before breakfast (15-20% reduction in systemic exposure) than when PA32540 was administered within 5 minutes of breakfast compared to fasted state. In the Phase III clinical trials, PA32540 was administered about one hour before breakfast or the first meal of the day, which is aligned with the result of the food effect study. Therefore, the label will specify that the proposed product be taken at least 60 minutes before a meal. Although the effect of food on aspirin component of Yosprala was assessed based on salicylic acid exposure, not acetylsalicylic acid exposure, no further studies were requested as the current monograph does not impose any food restriction on OTC aspirin products.

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

Drug-Drug Interaction between aspirin and omeprazole (Study PA32540-104 and Study PA32540-113):
Co-administration of aspirin and omeprazole does not appear to affect each other's PK profiles suggesting the absence of PK drug-drug interaction between aspirin and omeprazole components of PA32540. Although the effect of omeprazole on aspirin PK was assessed based on salicylic acid exposure, not acetylsalicylic acid exposure, no further studies are requested since the efficacy of the aspirin component in both PA32540 and PA8140 as established through BA/BE studies are deemed acceptable as described above.

Drug-Drug Interaction between omeprazole and clopidogrel (Inhibition of Platelet Aggregation studies (Study PA32540-110 and PA32540-111):

The two studies that evaluated the pharmacodynamic (PD) interaction potential between omeprazole component of PA32540 and clopidogrel were consulted to the Division of Cardiovascular and Renal Products (please note that PK was not evaluated in these studies). The consult review indicated that it is not possible to rule out an interaction between the omeprazole component of PA32540 and clopidogrel 75 mg either administered concomitantly or when separated by 10 h. Please see the consult review by Dr. Preston Dunnmon (Medical reviewer in Division of Cardiovascular and Renal Products) and Dr. Sudharshan Hariharan (Clinical Pharmacology Reviewer in DCP1) dated 10/21/2013 for further detail.

Pediatric Studies:
The sponsor has sought a full waiver because studies are impossible or highly impractical and because the product would be ineffective and/or unsafe in pediatric patients.
As the use of aspirin for the proposed indication in the pediatric population is rare, the incidence of aspirin associated gastric ulcers would also expected to be rare, and Yosprala would be unsafe in all pediatric age groups due to the aspirin component, the DGIEP Division concurred with the sponsor's proposed rationale for requesting a waiver from the requirement to conducting studies with Yosprala in pediatric patients from birth to 18 years of age. During the PeRC meeting dated Sept 25, 2013, the PeRC agreed with the Division to grant a full waiver in pediatric patients because studies are impossible or highly impractical.

2 Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

Table 1: A partial list of Clinical Pharmacology Studies

Study ID	Center	Start- End Date	Objective	Primary Endpoints	Design[1)]	Treatment Duration	Test Articles	N[2)]
PA8140-102	1	9/29/12-10/15/12	Bioavailability and pharmacokinetics	Plasma levels of acetylsalicylic acid	OL, R, Reference-Replicated, 3-way Crossover	3 single dose periods (3 tablets) of 8 hours duration	PA8140 EC-aspirin 81 mg EC-aspirin 81 mg	N = 27
PA8140-103	1	1/17/14-2/7/214	Bioavailability and pharmacokinetics	Plasma levels of Omeprazole	OL,R,2-way crossover	Two 7 Days Treatment	PA8140 PA32540	N= 30
PA32540-115	1	2/11/12-3/1/12	Bioavailability and pharmacokinetics	Plasma levels of acetylsalicylic acid	OL, R, Reference-Replicated, 3-way Crossover	3 single dose periods of 12 hours duration	PA32540 EC-aspirin 325 mg EC-aspirin 325 mg	N = 42
PA32540-104	1	01/18/08-02/29/08	Bioavailability and pharmacokinetics	Plasma levels of salicylic acid	OL, R, 3-way Crossover	3 single dose periods of 72 hours duration	PA32540 Aspirin component of PA32540 EC-aspirin 325 mg	N = 36

PA32540-113	1	06/11/11-07/18/11	PK and Relative Bioavailability	Plasma levels of omeprazole and salicylic acid	OL, R, AC, 4-way Crossover	Four single-dose treatments	PA32540 EC-aspirin 325 mg / EC omeprazole 40 mg EC-aspirin 325 mg alone EC omeprazole 40 mg alone	N = 36
PA32540-105	1	08/06/11-08/25/11	Food Effect	Plasma Levels	OL, R, 3-way Crossover, Food effect	3 single dose periods	PA32540 5 min after meal 60 Min prior to meal 4 hour fast	N = 24
PA32540-112	1	06/05/11-06/26/11	Pharmacodynamic Effect on intragastric pH	Intragastric pH percent time > 4	OL, R, AC, 2-way Crossover	Two 7 day treatments	PA32540 EC omeprazole 40 mg / EC-aspirin 325 mg	N = 26
PA32540-110	1	08/23/09-11/28/09	Inhibition of Platelet aggregation	% IPA using Chronolog ADP agonist	OL, R, AC, Crossover	Three 7-day treatments	Clopidogrel / EC 325 mg aspirin QD Clopidogrel / PA32540 PA32540 in the morning / Clopidogrel (10 hours apart)	N = 30
PA32540-111	1	11/24/10-02/16/11	Inhibition of Platelet aggregation	%IPA using Chronolog ADP agonist	OL, R, AC, Crossover	Two 7-day treatments	PA32540 + Clopidogrel (10 hours apart) EC-aspirin 81 mg QD, + EC omeprazole 40 mg + Clopidogrel	N = 30

In addition to the above PK/PD studies in healthy volunteers, the sponsor had also conducted 5 mucosal damage studies, two of which had PK data in healthy volunteers, one with bioanalytical report (PA325-106). Additionally, the sponsor had also conducted two identical phase III 6-month efficacy and safety clinical trials (PA32540-301 and PA32540-302) and one phase III 12-month long-term safety clinical trial (PA32540-303) in patient population, in which plasma levels of aspirin or omeprazole were not measured.

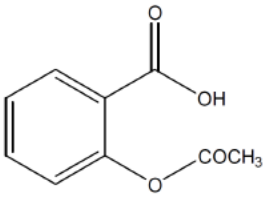
2.2 General Attributes

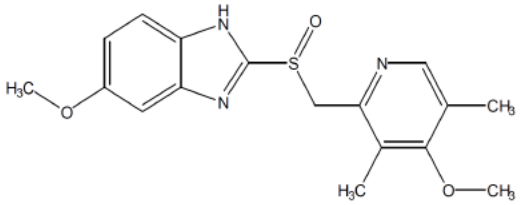
2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug products?

Drug Substance:

Name: Aspirin/Omeprazole

Chemical formula: $C_9H_8O_4$ / $C_{17}H_{19}N_3O_3S$
Molecular Weight (g/mol): 180.16/ 345.4
Structural formula:





Formulation:
The proposed products (PA8140 and PA32540) are an oral fixed dose combination products (tablets) containing 81 mg or 375 mg aspirin in the inner enteric coated core (delayed release) surrounded by 40 mg omeprazole in the immediate-release film coat to release active ingredients in a sequential fashion. PA8140 and PA32540 tablets are designed to release omeprazole immediately after ingestion and then expose the delayed release aspirin core (b) (4)

PA32540: Enteric-coated aspirin [EC-ASA] 325 mg + immediate-release [IR] omeprazole 40 mg
PA8140: Enteric-coated aspirin [EC-ASA] 81 mg + immediate-release [IR] omeprazole 40 mg

Both PA32540 and PA8140 Tablets consist of an aspirin core that is coated with (b) (4) film coats (b) (4)

(b) (4)

2.2.2 What is the proposed indication?

The proposed indication is for patients (b) (4)

2.2.3 What are the proposed mechanisms of actions?

This proposed formulation allows sequential release of omeprazole and aspirin, where the immediate release omeprazole in the outer layer gets released first in the stomach (b) (4)

(b) (4) followed by release of enteric coated aspirin in the interior core (b) (4)

Aspirin (acetylsalicylic acid) is an inhibitor of both prostaglandin synthesis and platelet aggregation.

Omeprazole is a proton pump inhibitor (PPI) that suppresses gastric acid secretion via specific inhibition of the H^+, K^+-ATPase enzyme (proton pump) located in the secretory membrane of the gastric parietal cell. Omeprazole does not exhibit anticholinergic or H_2 histamine antagonistic properties. In the acidic compartment of the parietal cell, omeprazole is protonated and converted into a pharmacologically active inhibitor that react with luminally accessible cysteines of H^+, K^+-ATPase to form a disulfide bond, thus irreversibly inhibiting H^+, K^+-ATPase activity. Since PPIs block the final common pathway of acid production in the stomach, they inhibit both basal and stimulated gastric acid secretion.

2.2.4 What are the proposed dosage and route of administration?

The proposed dosage is one 81 mg aspirin/40 mg omeprazole tablet or one 325 mg aspirin/40 mg omeprazole tablet to be administered orally once daily at least 60 minutes before meals. The tablets are to be swallowed whole with liquid and not to be split, chewed, crushed or dissolved. Use the lowest effective dose.

2.2.5 What is the regulatory background?

This is a 505(b)(2) application with the following two reference-listed product:

Name Reference listed drug(s)	Strength
Ecotrin® (Aspirin)	81mg & 325 mg
Prilosec® (Omeprazole)	40 mg

Currently, Ecotrin® (aspirin delayed-release tablets) is available as enteric coated tablets containing 325 mg or 81 mg of aspirin for oral administration.

Prilosec® (omeprazole magnesium) is available as delayed-release capsules and delayed-released oral suspension. The Prilosec® formulation used for comparison in this NDA submission is 40 mg delayed-release capsules formulation. The proposed formulation of omeprazole in this application is immediate release formulation. The current Prilosec label does not have indication for risk reduction of NSAID-associated gastric ulcer.

The clinical efficacy of Yosprala for use in secondary prevention of cardiovascular and cerebrovascular events were established in part through the demonstration of bioequivalence of aspirin component of Yosprala to Ecotrin (81 mg & 325 mg) in two separate scaled – bioequivalence studies (PA8140-102 and PA32540-115). The sponsor had also compared relative bioavailability of omeprazole component of PA32540 to Prilosec® 40 mg. The clinical efficacy of PA32540 regarding the risk reduction of developing aspirin-induced gastric ulcers was established in two phase III studies. However, the Phase III program did not evaluate the risk reduction potential of developing aspirin-induced gastric ulcers for PA8140 tablet. In order to extrapolate the clinical efficacy of PA32540 to PA8140 regarding the risk reduction of developing aspirin-induced gastric ulcers, the sponsor was requested to conduct a relative BA study comparing the omeprazole exposure from PA8140 to that of PA32540 during December 6,

2013 teleconference. Due to this new requested relative BA study, the PDUFA date was extended by 3 month to April 25th, 2014. The sponsor conducted the requested relative BA study (Study PA8140-103) during the review cycle and submitted the study report on March 26th, 2014.

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The Yosprala clinical development program is consisted of 16 clinical studies: 5 phase 1 PK studies, 1 PK/PD study, 5 mucosal damage studies, 2 inhibition of platelet aggregations studies, 2 phase III efficacy and safety studies, and one phase 3 long term safety study.

Phase I PK/PD studies:

- Study PA8140-102 was an open-label, randomized, single-center, single-dose, 3-way crossover study in 27 healthy adult subjects under fasting condition to evaluate the relative bioavailability/bioequivalence of acetylsalicylic acid from administration of three tablets of PA8140 and three tablets Ecotrin® 81 mg using the partial reference replicated 3-way design and the reference-scaled average bioequivalence approach.

- Study PA8140-103 was open-label, randomized, single-center, multiple-dose, 2-way crossover study in 30 healthy adult subjects under fasting condition with 7 days treatment to evaluate the relative bioavailability of omeprazole from PA8140 to that of PA32540.

- Study PA32540-115 was an open-label, randomized, single-center, single-dose, 3-way crossover study in 42 healthy adult subjects under fasting condition to evaluate the relative bioavailability/bioequivalence of acetylsalicylic acid from administration of PA32540 and Ecotrin® 325 mg using the partial reference replicated 3-way design and the reference-scaled average bioequivalence approach.

- Study PA32540-105 was an open-label, randomized, single-center, single-dose, 3-way crossover PK study in 24 healthy subjects to evaluate the effect of food administered at different times on bioavailability of salicylic acid and omeprazole from PA32540 tablet. However, this study was not designed to assess the effects of food on the bioavailability of acetylsalicylic acid.

- Study PA32540-112 was an open-label, randomized, single-center, multiple-dose, 2-way crossover PK and PD study in 26 healthy subjects with 7-day treatment period to evaluate the pharmacodynamic effect of PA32540 vs. Ecotrin® 325 mg + Prilosec® 40 mg, as measured by intragastric pH (percent time pH >4.0) on Day 7 and to assess the pharmacokinetics (PK) of omeprazole and salicylic acid after the first dose and at steady-state of each treatment.

- Study PA32540-104 was an open-label, randomized, single-center, single-dose, 3-way crossover study in 36 healthy subjects under fasting condition to evaluate the pharmacokinetics and relative bioavailability of aspirin from a single oral dose of 325 mg aspirin administered as PA32540, as the aspirin component of PA32540, or as Ecotrin®.

- Study PA32540-113 was an open-label, randomized, single-center, single-dose, 4-way crossover PK study in 36 healthy subjects under fasting condition to evaluate the PK and relative BA of salicylic acid and omeprazole following single-dose oral administration of PA32540, Ecotrin® 325 mg co-administered with Prilosec® 40 mg, Ecotrin® 325 mg alone and Prilosec® 40 mg

alone to assess the potential drug-drug interaction between omeprazole and salicylic acid from aspirin. However, this study was not designed to assess the PK and relative bioavailability of acetylsalicylic acid.

Mucosal Damage Studies: These studies were reviewed by Medical Officer of DGIEP. This reviewer focused on study results only.

- Study PA8140-101 was a Phase 1, randomized, open-label, single-blind, parallel-group, single-center study in 90 healthy volunteers aged 50 or older to compare the Day 14 incidences of gastroduodenal mucosal damage using Grade 3 or 4 scores for PA8140 plus celecoxib (200 mg), EC-aspirin 81 mg plus celecoxib (200 mg) and PA08140 administered once a day for 13 days.

- Study PA325-101 was Phase 1, randomized, open-label, investigator-blinded, parallel group, single center study in 80 healthy volunteers with 27 days of dosing to compare the gastroprotective effects of a once-daily dose of PA32520 tablet (combining 325 mg pH-sensitive coated aspirin and 20 mg immediate release omeprazole) versus a once-daily dose of 325 mg enteric coated aspirin (Bayer® EC aspirin 325 mg tablet) utilizing Lanza scores from endoscopy. This study also evaluated the PK of salicylic acid and omeprazole after the first dose and at steady state on Day 13 in subset of population. However, these PK studies did not contain bioanalytical report. Additionally, gastric pH was measured at baseline, Day 14 and Day 28. Since PA32520 is not being sought in this application, and there is no PK comparison of PA32520 vs. PA32540 in this study report, the PK and PD component of this study was not reviewed in detail in this NDA review.

- Study PA325-102 was a Phase I, stratified, randomized, open-label, investigator-blinded, parallel group, single-center study in 80 healthy volunteers with 27 days of dosing to compare the gastroduodenal effects of a once daily dose of PA32520 tablet (Delayed release aspirin 325 mg/ immediate release omeprazole 20 mg Tablet) versus a once-daily dose of 81 mg EC aspirin (Bayer® EC aspirin 81 mg tablets) utilizing Lanza scores from endoscopy findings. Gastric pH was monitored at baseline, Day 14 and Day 28.

- Study PA325-106 was a Phase I, randomized, open-label, investigator-blinded, parallel group, single center study in 80 healthy volunteers with 27 days of dosing to compare the incidence of Grade 3 and 4 Lanza damage in the stomach and duodenum after treatment with once-daily PA32540 versus once-daily EC aspirin 325 mg. PK of acetylsalicylic acid, salicylic acid and omeprazole were also evaluated on Day 1 and Day 13.

- Study PA32540-109 was a Phase 1, open-label, single-blind, randomized, three-arm, parallel-group study in 90 healthy volunteers aged 50 or older with 13 days of dosing to compare the gastroduodenal mucosal damage as determined by Lanza grade 3 or 4 scores at Day 14 after treatment with PA32540, PA32540 + celecoxib 200 mg, and EC aspirin 325 mg + celecoxib 200 mg.

Platelet Aggregation Inhibition Studies (drug interaction between omeprazole and clopidogrel):
The following two studies were consulted to the Division of Cardiovascular and Renal Products. Please see the consult review by Dr. Preston Dunnmon (Medical reviewer in Division of Cardiovascular and Renal Products) and Dr. Sudharshan Hariharan (Clinical Pharmacology Reviewer in DCP1) dated 10/21/2013 for further detail.

- Study PA32540-110 was a randomized, open-label, single-center, cross-over study in 30 healthy volunteers aged 40 years or older with 7 days of treatment to evaluate platelet aggregation

following administration of clopidogrel + aspirin and clopidogrel + PA32540. Additionally, platelet aggregation was evaluated following administration of clopidogrel taken at least 10 hours after PA32540.

- Study PA32540-111 an open-label, single-center, randomized, 2-way crossover study in 30 healthy subjects aged 40 years or older with 7 days of treatment to evaluate adenosine diphosphate (ADP)-induced platelet aggregation following administration of clopidogrel, EC-ASA 81 mg, and EC omeprazole 40 mg, all dosed concomitantly, and PA32540 and clopidogrel dosed 10 hours apart.

Phase III studies:

- Study PA32540-301 and PA32540-302 were randomized, double-blind, parallel-group, multicenter, 6-month safety and efficacy study in 500 patients to demonstrate that PA32540 caused fewer gastric ulcers in subjects at risk for developing aspirin-associated gastric ulcers compared to EC-aspirin 325 mg.

- Study PA32540-301 was an open-label, multi-center clinical study to evaluate the 12- month long-term safety of PA32540 in subjects at risk for developing ASA-associated gastric ulcers.

2.3.2 What was the clinical endpoint in the Phase 3 trials?

Primary efficacy endpoint was the cumulative incidence of gastric ulcers, defined as a mucosal break of at least 3 mm in diameter with depth, throughout the 6 months of treatment.
The secondary endpoints included the following: (1) the cumulative incidence of gastric and/or duodenal ulcers, (2) the proportion of subjects with "Treatment Success" defined as those without gastric ulcers and without pre-specified UGI adverse events leading to discontinuation, (3) the proportion of subjects discontinuing the study due to pre-specified UGI adverse events at any time throughout 6 months of treatment, and (4) the proportion of subjects with heartburn resolution, defined as the answer "None" on a post-baseline heartburn assessment.

2.3.3 What is sponsor's dose selection rationale?

Aspirin:
The doses of aspirin in Yosprala Tablets (81 mg and 325 mg) were selected based on the dose range established in the aspirin professional labeling (21 CFR 343.80) for vascular indications. Two bioequivalence bridging studies have been conducted with proposed products (PA8140 and PA32540) with the respective strengths of Ecotrin to support for the efficacy of proposed products for the cardiovascular and cerebrovascular indications.

Given the lack of a dose-related increase in efficacy (no incremental benefit in chronic administration of doses of ASA above 100 mg,) and a dose-related increase in bleeding – particularly gastrointestinal bleeding, Division of Cardiovascular and Renal Products recommend the DGIEP to approve only the dose of 81 mg of ASA. Please see the consult review by Dr. Preston Dunnmon (Medical reviewer in Division of Cardiovascular and Renal Products) dated 10/21/2013 for further detail.

IR-Omeprazole:
The sponsor had compared 20 mg and 40 mg of IR-omeprazole for prevention of UGI damage inducted by EC-aspirin 325 mg. However, the sponsor did not conduct any dose-ranging study comparing 20 mg and 40 mg IR-omeprazole for prevention of UGI damage inducted by EC-aspirin 81 mg. Plasma exposure, pH control and gastroduodenal mucosal protection data were

the basis for selection of 40 mg IR-omeprazole as the lowest effective dose. While EC-omeprazole (PRILOSEC®) does not have the indication for risk reduction of NSAID-associated gastric ulcer, the single isomer, esomeprazole (NEXIUM®), is approved for that indication at doses of 20 mg or 40 mg once daily for up to 6 months.

- *Plasma Exposure*: Plasma exposure to omeprazole from the IR-omeprazole formulation 40 mg in PA32540 was 51-58% of that seen for EC-omeprazole 40 mg (Prilosec®) following both single dose and multiple dose administration in healthy subjects (Study PA325-112 and Study PA325-113), which is in the range of that was reported for EC-omeprazole 20 mg (Andersson 2001; Stedman 2000). Exposure of 20 mg IR-omeprazole from PA32520 tablet from study PA325-101 appears to be 2-3-fold lower than the omeprazole exposure from PA32540 tablet based on cross-study comparison (Study PA325-101).

- *pH Control*: Following multiple dosing for 7 days, IR-omeprazole 40 mg from PA32540 Tablets appears to produce comparable pH control, expressed as % time over 24 hours that the pH >4 , (51%) as EC omeprazole 20 mg.
  Further, literature PK/PD data indicate that IR-omeprazole 20 mg from PA32520 tablet would be sub-optimal for gastric mucosal protection relative to marketed EC products. Based on the plasma omeprazole exposure and the PK/PD relationship, a mean percent time gastric pH >4 is predicted to be 33.9%, very similar to the reported 33% for EC-omeprazole 10 mg (Burget 1990), a strength that has been shown to be insufficient to reduce the risk of gastric and duodenal damage.

  Table 2: Summary of POZEN and Published Data on 24-hour Gastric pH Control in Healthy Subjects

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

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

- *Gastroduodenal Mucosal Protection*: Study PA8140-101, PA325-101, PA325-102, PA325-106 and PA32540-109 had evaluated the gastroduodenal mucosal damage of PA8140, PA32520 and PA32540 tablets comparing gastroduodenal mucosal protection ability of 20 mg and 40 mg omeprazole, where the gastroduodenal mucosal damage was assessed using Lanza scores. Grade 0 Lanza represents a normal gastroduodenal mucosa, the ideal intended therapeutic goal for the PA products. Lanza scores 3 or 4 represents ≥ 11 erosions or hemorrhages or any ulcer.

  Of 5 mucosal damage studies, only the study PA32540-109 was conducted with Phase 3 and BE Formulation (Please refer to section 2.5.1 for detailed information regarding formulation comparison). Study PA325-106, which had PK data available, was conducted with Phase 1 Formulation. Based on the cross-study PK comparison, the PK of acetylsalicylic acid, salicylic acid and omeprazole from Phase 1 formulation used in Study PA32540-106 were similar to that of Phase 3 and BE formulation used in Study PA32540-104, PA32540-105, PA32540-112 and PA32540-113 (please see section 2.4.6 for detailed PK comparison). Therefore, the results of

mucosal damage study PA325-106 that used Phase 1 formulation can reasonably be extrapolated to Phase 3 and BE formulation. However, studies PA8140-101, PA325-101, and PA325-102 had used early phase formulations that were not properly linked to the TBM formulation. Therefore, results of these studies should be interpreted with reservation.

Although both PA32520 and PA32540 Tablets cause significantly less gastroduodenal injury compared to EC-aspirin treatment, PA32540 had lower percentage of subjects exhibiting UGI damage compared PA32520 where the incidence of gastroduodenal injury showed a dose-dependent trend.

Table 3: UGI Protection Provided by PA325 Products – H. pylori Negative Subjects Day 14

Lanza Scores	PA32540	PA32520	EC-aspirin 325 mg	p-value[1]		
	N=69	N=60	N=68	PA32540 vs. EC-aspirin 325 mg	PA32520 vs. EC-aspirin 325 mg	PA32540 vs. PA32520
Grade 0 Lanza	53 (76.8)	25 (41.7)	15 (22.1)	<0.001	0.022	<0.001
Grade 3or4 Lanza	3 (4.3)	4 (6.7)	22 (32.4)	<0.001	<0.001	0.704

Source Data: Cross-study analysis using data from PA325-101, PA325-102, PA325-106, PA32540-109
[1]Fisher's exact test

Table 4: UGI Protection Provided by PA325 Products – H. pylori Negative Subjects Day 28

Lanza Scores	PA32540	PA32520	EC-Aspirin 325 mg	p-value[1]		
	N=40	N=60	N=68	PA32540 vs. EC-Aspirin 325 mg	PA32520 vs. EC-Aspirin 325 mg	PA32540 vs. PA32520
Grade 0 Lanza	30 (75.0)	25 (41.7)	10 (14.7)	<0.001	<0.001	0.001
Grade 3or4 Lanza	1 (2.5)	3 (5.0)	24 (35.3)	<0.001	<0.001	0.648

Source Data: Cross-study analysis using data from PA325-101, PA325-102, PA325-106
[1]Fisher's exact test

As demonstrated in below table-5, a cross-study comparison appeared to show that 40 mg IR-omeprazole in PA8140 may also provide significant protection against UGI damage from 81 mg aspirin. However, the sponsor did not evaluate the UGI protection potential of 20 mg IR omeprazole for UGI damage from 81 mg aspirin.

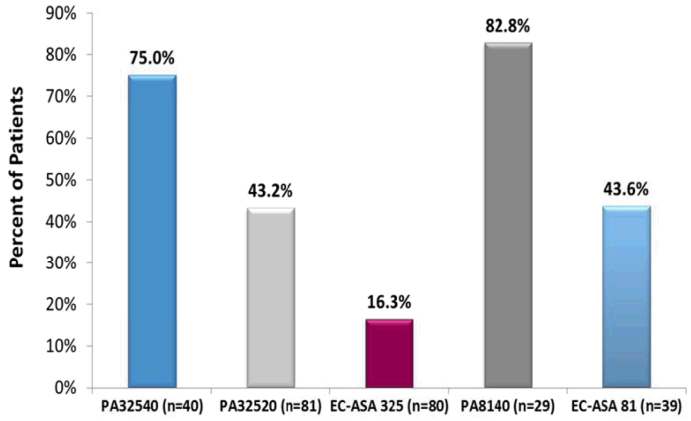
Table 5: UGI Protection Provided by PA8140 - H. pylori Negative Subjects Day 14

Lanza Scores	PA8140	EC-Aspirin 81 mg	p-value[1]
	N=29	N=29	PA8140 vs. EC-Aspirin 81 mg
Grade 0 Lanza	24 (82.8)	10 (34.5)	<0.001
Grade 3 or 4 Lanza	0 (0)	8 (27.6)	0.004

Source Data: Cross-study analysis using data from PA325-102 Table 14.2.1.2H, PA08140-101 Table 14.2.1
[1]Fisher's exact test

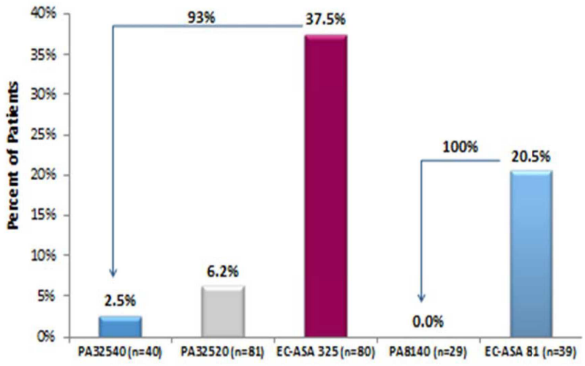
When UGI damage is compared across the studies, the same pattern of UGI protection seen with *H. pylori* negative subjects is also seen in the total population both with respect to Grade 0 and Grade 3 or 4 Lanza scores.

*Figure 1: Percent of Subjects with Gastroduodenal Grande 0 Lanza Scores from a Pooled Analysis of Phase 1 Data-all Subjects**



Source Data: PA325-101, PA325-102, PA325-106, PA08140-101
* PA325 and EC-aspirin 325 mg data Day 28; PA8140 and EC-aspirin 81 mg data Day 14

*Figure 2: Percent of Subjects with Gastroduodenal Grande 3 or 4 Lanza Scores from a Pooled Analysis of Phase 1 Data-all Subjects**



Source Data: PA325-101, PA325-102, PA325-106, PA08140-101
* PA325 and EC-aspirin 325 mg data Day 28; PA8140 and EC-aspirin 81 mg data Day 14

2.3.4 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the sponsor had used HPLC-MS/MS analytical method to measure the plasma concentration of acetylsalicylic acid, salicylic acid, and omeprazole with 0.02 µg/mL, 0.10 µg/mL and 1.0 ng/mL detection limits, respectively. Please refer to 2.6, Analytical Section for more detail.

2.4 PK Characteristics

2.4.1 Is aspirin (acetylsalicylic acid) component of Yosprala bioequivalent to the reference product Ecotrin at proposed dosages?

The bioequivalence between the proposed products (PA32540 and PA8140) and the reference products (Ecotrin 81 mg and 325 mg) were established based on exposure of acetylsalicylic acid as the primary analyte as the cardioprotective activity of aspirin products is attributed to aspirin (acetylsalicylic acid), not salicylic acid. The sponsor had conducted 2 separate BE studies comparing aspirin (acetylsalicylic acid) component of PA8140 and PA32540 to corresponding strength of reference product Ecotrin 81 mg and Ecotrin 325 mg. Both of the BE studies (PA8140-102 and PA32540-115) had used partial reference-replicate3-way design with a reference-scaled average BE approach as acetylsalicylic acid is considered to be a highly variable drug. Theses BE studies had shown that aspirin component of PA8140 was bioequivalent to that of reference product Ecotrin 81 mg (study PA8140-102). However at 325 mg strength, PA 32540 tablet was not bioequivalent to the reference product Ecotrin® 325 mg tablet, and the bioavailability of aspirin from PA32540 was 15% less than that of Ecotrin 325 mg dose (PA32540-115). Nonetheless, according to the consult review by Dr. Preston Dunnmon (Medical reviewer in Division of Cardiovascular and Renal Products) and Dr. Sudharshan Hariharan, (Clinical Pharmacology Reviewer in DCP1) dated 10/21/2013, the 10-15% lower exposure to aspirin for PA32540 tablets compared to Ecotrin® 325 mg is not clinically meaningful as this change in aspirin plasma exposures at 325 mg does not affect platelet inhibition and the only generally accepted and well-understood mechanism by which aspirin reduces the risk of adverse cardiovascular events is through inhibition of platelet aggregation via irreversible acetylation of the cyclooxygenase-1 (COX-1) enzyme. Therefore, this lack of bioequivalence between PA32540 and Ecotrin ® 325 mg for acetylsalicylic acid exposure will not be a review issue.

Bioequivalence for the 81 mg Aspirin Strength:

Study PA8140-102 was an open-label, randomized, single-center, single-dose, 3-way crossover study in 27 healthy subjects under fasting condition to evaluate the relative bioavailability/bioequivalence of PA8140 and an enteric-coat (EC) formulation of aspirin (Ecotrin® 81 mg) using the partial reference replicated 3-way design. Each subject was to receive a single dose of 3 tablets of the reference product (B), Ecotrin® 81 mg, twice, and a single dose of 3 tablets of the test product (A), PA8140, once in a randomized crossover fashion over 3 treatment periods. Three (3) tablets of PA8140 or Ecotrin® 81 mg were administered simultaneously in order to ensure measurable plasma ASA concentrations after a single dose. The study drugs were administered following an overnight fasting of at least 10 hours prior to dosing. Subjects received a standardized breakfast an hour after the dosing. The study drug was to be swallowed as whole and was not to be broken, crushed, or chewed. There was at least a 7-day of washout period between the treatments. PK blood samples were collected for up to 8 hours in each treatment period to determine the plasma concentrations of acetylsalicylic acid.

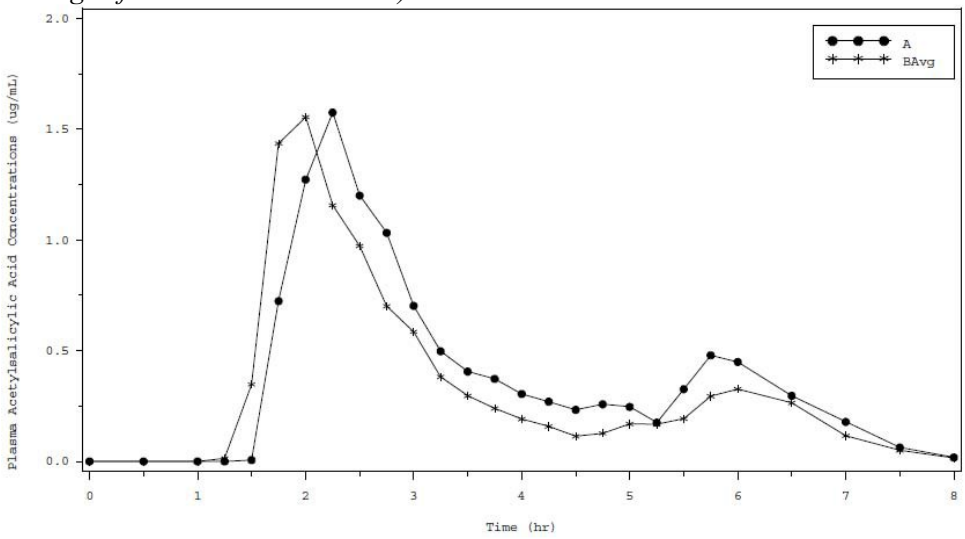
This study had 27 healthy volunteers enrolled and 26 of them completed the study as planned receiving all three treatment periods. One subject (Subject 1017) in sequence BBA was withdrawn following completion second treatment periods due to difficulty with blood draws (this subject received both doses of EC-ASA 81 mg, but did not receive the PA8140 treatment). In one subject (No 1009) after both doses of 3 tablets of Ecotrin® 81 mg and another subject (No. 1004) after the second dose of 3 tablets of Ecotrin® 81 mg did not have any measurable concentration of acetylsalicylic acid throughout the entire sampling period. These 3 profiles were

included in the summary statistics for the concentration data at each time point; however, PK parameters for the three profiles were not calculated. One subject (No. 1004) in sequence BAB during the first dosing period (Treatment B1) had quantifiable concentration of acetylsalicylic acid in the pre-dose sample (0.458 µg/mL) that was almost 40% of the peak concentration (1.15 µg/mL) in the same profile and thus was excluded from PK data summary and analysis. The sponsor stated it is unclear why this occurred without any non-compliance finding.

The within-subject standard deviation (Swr) of acetylsalicylic acid PK parameters following replicate administration of the reference product (Ecotrin® 81 mg) was estimated for AUCs and C_{max}, respectively based on the procedures described in the Food and Drug Administration (FDA) Draft Guidance for Progesterone Bioequivalence Assessment, February 2011. Intrasubject standard deviation (Swr) values for C_{max}, AUC_{0-t} and AUC_{0-inf} of acetylsalicylic acid for the Reference treatment in the 24 subjects who completed both periods of Treatment B were all are greater than 0.294, indicating that EC-Aspirin PK parameters qualify for the reference-scaled average BE procedure to establish bioequivalence of AUCs and C_{max} between PA8140 and Ecotrin® 81 mg.

Two conditions were to be met for Treatment A to be considered bioequivalent to Treatment B in a highly variable drug product:
a) The geometric least-squares mean (GLSM) ratio of Treatment A vs. Treatment B was to be within the limits of 80 to 125%.
b) The upper bound of 95% confidence interval for the adjusted point estimate was to be ≤ 0.

Figure 3: Mean Plasma Acetylsalicylic Acid Concentration vs. Time Curves (Treatment A and Average of Treatments B1 and B2)



Treatment A= PA8140 Treatment B= Ecotrin® 81 mg

Table 6: Summary of Acetylsalicylic Acid Pharmacokinetic Parameters

Treatment	Statistics	C_{max} (µg/mL)	t_{max}* (hr)	t_{lag}* (hr)	AUC_{0-t} (hr*µg/mL)	AUC_{0-inf} (hr*µg/mL	t½ (hr)
	n	26	26	26	26	26	26

A	Mean*	2.64	2.50	1.50	2.96	2.98	0.357
PA8140	%CV	41	na	na	28	28	17
	GeoMean	2.40	na	na	2.82	2.84	0.353
	Min –Max	0.676-4.80	1.75-7.0	1.25-6.0	0.799-4.62	0.827-4.64	0.257-0.508
	n	25	25	25	25	25	25
B1	Mean*	2.46	2.50	1.50	2.58	2.60	0.374
Ecotrin® 81 mg	%CV	57	na	na	39	38	23
First Dose	GeoMean	2.15	na	na	2.40	2.43	0.365
	Min –Max	0.732-6.18	1.75-7.0	1.0-6.0	0.943-4.94	1.01-4.95	0.282-0.627
	n	24	24	24	24	24	24
B2	Mean*	2.97	2.63	1.50	2.85	2.87	0.372
Ecotrin® 81 mg	%CV	71	na	na	34	34	17
Second Dose	GeoMean	2.39	na	na	2.67	2.69	0.368
	Min –Max	0.587-8.67	1.5-6.0	1.0-4.25	1.05-5.28	1.07-5.29	0.288-0.568
	n	24	24	24	24	24	24
Average of	Mean*	2.73	2.88	1.45	2.72	2.74	0.375
B1 and B2	%CV	52	na	na	30	30	18
	GeoMean	2.44	na	na	2.60	2.62	0.369
	Min –Max	1.04-7.02	1.63-6.25	1.0-4.0	1.37-4.50	1.39-4.51	0.290-0.563

Table 7: Summary of Statistical Analysis Results of Acetylsalicylic Acid Pharmacokinetic Parameters:

	Reference-Scaled Average Bioequivalence Assessment for Highly Variable Drug Products*		
Aspirin PK Parameter	**Swr**	**Geometric Least Squares Mean Treatment Ratio (A/B)**	**Upper Bound of the 95% Condiference Interval for the Adjusted Treatment Difference (A-B)**
AUC_{0-inf}	0.320	1.112	-0.021
AUC_{0-t}	0.328	1.116	-0.023
C_{max}	0.562	1.053	-0.149

*: Based on FDA Draft Guidance for Progesterone Bioequivalence Assessment, February 2011.
Swr: within-subject standard deviation of the PK parameter from the Reference product.

The point estimates of the GLSM ratios, PA8140 vs. Ecotrin® 81 mg, for all bioavailability parameters of acetylsalicylic acid were within the interval of 0.80-1.25. In addition, the upper bound of the 95% confidence interval for the difference between Test and Reference treatments, adjusted for the estimated intrasubject variability of the Reference treatment was less than zero, indicate that PA8140 is bioequivalent to Ecotrin® 81 mg in terms of C_{max}, AUC_{0-t} and AUC_{0-inf} of acetylsalicylic acid.

Reviewer's Comment:

- *The within-subject standard deviation of acetylsalicylic acid PK parameters from the reference product Ecotrin® 81 mg was estimated to be 0.562 for Cmax and 0.320 for AUC0-inf, which are all greater than 0.294, confirming that EC-aspirin formulations are considered to be highly variable drug products and EC-Aspirin PK parameters qualify for the reference-scaled average BE procedure to establish bioequivalence of AUCs and Cmax between PA8140 and Ecotrin® 81mg.*

- *BE analysis based on reference-scaled average bioequivalence approach demonstrated the bioequivalence between PA8140 and Ecotrin® 81 mg in terms of bioavailability parameters of acetylsalicylic acid.*

- *The mean PK plasma profiles, as well as most of the individual PK plasma profiles, for both PA8140 and Ecotrin® 81 mg had shown multiple absorption peaks (a large absorption peak occurring around 1.5-2.5 hr post-dose followed by a smaller secondary peak occurring around 5.5-6.5 hours post=dose). These observed multiple peaks could be due the multiple tablets administration. This kind of multiple peak was not observed when single tablet of 325 mg PA32540 or Ecotrin® 325 mg was administered in study PA32540-115.*

- *Bioequivalence between 3 tablets of PA8140 and 3 tablets of Ecotrin® also suggest that the lack of effect of IR-omeprazole 120 mg on the relative bioavailability of acetylsalicylic acid (243 mg) from an EC aspirin formulation.*

- *The drugs (PA8140 or Ecotrin® 81 mg) were administered one hour before breakfast following an overnight fasting in this study, which is consistent with recommendation regarding the food in phase 3 studies and proposed label.*

- *PK analysis, plots have been replicated and consistent with sponsor's analysis.*

- *Scaled BE analysis was repeated and the result was consistent with sponsor's analysis.*

Bioequivalence for the 325 mg Aspirin Strength (PA32540):

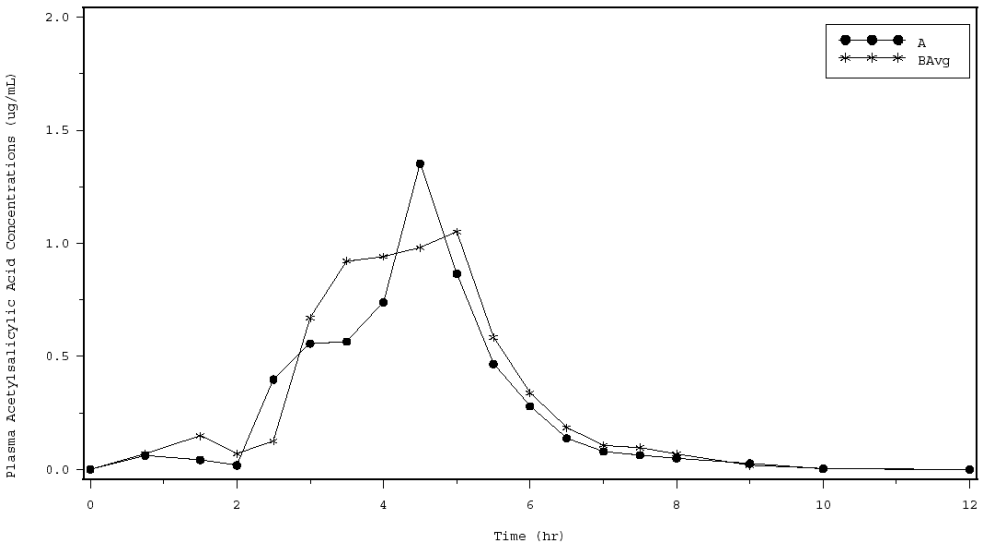
Study PA32540-115 was an open-label, randomized, single-center, single-dose, 3-way crossover study in 42 healthy subjects under fasting condition to evaluate the relative bioavailability/bioequivalence of PA32540 and an enteric-coat (EC) formulation of aspirin (Ecotrin® 325 mg) using the partial reference replicated 3-way design and the reference-scaled average bioequivalence approach. Each subject was to receive a single dose of the reference product (B), Ecotrin® 325 mg, twice, and a single dose of the test product (A), PA32540, once in a randomized crossover fashion over 3 treatment periods. The study drugs were administered following an overnight fasting of at least 10 hours prior to dosing and an additional 4 hours of fasting post-dose. The study drug was to be swallowed as whole and was not to be broken, crushed, or chewed. There was at least a 7-day of washout period between the treatments. PK blood samples were collected for up to 12 hours in each treatment period to determine the plasma concentrations of acetylsalicylic acid.

This study had 42 healthy volunteers enrolled and 39 of them completed the study as planned receiving all three treatment periods. Subject 1009 in Sequence BBA was withdrawn after the first treatment period due to a positive urine drug screen. This Subject 1009 also did not have any measurable concentrations of acetylsalicylic acid throughout the entire sampling period after the first dose of Ecotrin® (Treatment B1), and thus was not included in the descriptive statistics for PK parameters. Subject 1012 in Sequence BAB was lost to follow-up following the second treatment period and did not complete the 3rd treatment period. Subject 1027 in Sequence BAB discontinued after reporting flu-like symptoms and did not complete the 3rd treatment period. Additionally, $AUC_{0\text{-}inf}$ and $t_{1/2}$ could not be estimated in Subject 1036 in all three dose periods, since there were not sufficient time points to estimate terminal half-life in this subject.

The within-subject standard deviation (Swr) of acetylsalicylic acid PK parameters following replicate administration of the reference product (Ecotrin® 325 mg) was estimated for AUCs and C_{max}, respectively based on the procedures described in the Food and Drug Administration (FDA) Draft Guidance for Progesterone Bioequivalence Assessment, February 2011. Intrasubject standard deviation (Swr) values for C_{max}, AUC_{0-t} and AUC_{0-inf} of acetylsalicylic acid for the Reference treatment in the 39 subjects who completed both periods of Treatment B were all are greater than 0.294, indicating that EC-Aspirin PK parameters qualify for the reference-scaled average BE procedure to establish bioequivalence of AUCs and C_{max} between PA32540 and Ecotrin® 325 mg.

Two conditions were to be met for Treatment A to be considered bioequivalent to Treatment B in a highly variable drug product:
a) The geometric least-squares mean (GLSM) ratio of Treatment A vs. Treatment B was to be within the limits of 80 to 125%.
b) The upper bound of 95% confidence interval for the adjusted point estimate was to be ≤ 0.

Figure 4: Mean Plasma Acetylsalicylic Acid Concentration vs. Time Curves (Treatment A and Average of Treatments B1 and B2)



Treatment A= PA32540 Treatment B= Ecotrin® 81 mg

The sponsor had initially analyzed the PK data by excluding subject 1006 in Treatment A due to the fact that this subject had prolonged T_{lag} (5.0 hr) during treatment A and found PA32540 is bioequivalent to Ecotrin 325 mg in terms of acetylsalicylic acid bioavailability. However, FDA did not find the exclusion of subject 1006 justifiable especially when other subjects (subject IDs: 1005, 1028, 1036) who also had prolonged t_{lag} (4-4.5 hours) were included in the BE analysis. FDA's position on unacceptability of exclusion of subject 1006 in BE analysis was communicated the sponsor via an Advice letter dated 06/15/2012 prior to the NDA submission. Therefore, the sponsor had reanalyzed their data including subject 1006, as presented below:

Table 8: Summary of Acetylsalicylic Acid Pharmacokinetic Parameters (Including Subject 1006)

Treatment	Statistics	C_{max}	t_{max}*	t_{lag}*	AUC_{0-t}	AUC_{0-inf}	t½

		(µg/mL)	(hr)	(hr)	(hr*µg/mL)	(hr*µg/mL)	(hr)
	n	41	41	41	41	40	40
A	Mean*	2.51	4.42	2.73	2.90	2.94	0.361
PA32540	%CV	69	32	38	62	62	33
	GeoMean	2.01	na	na	2.41	2.44	0.348
	Min – Max	0.556-7.99	0.75-9.0	0.0-5.0	0.516-7.99	0.555-8.00	0.242-0.902
	n	41	41	41	41	40	40
B1	Mean*	2.90	4.50	3.00	3.23	3.29	0.388
EC-ASA	%CV	56	31	40	48	47	29
First Dose	GeoMean	2.26	na	na	2.69	2.75	0.374
	Min – Max	0.176-7.25	0.75-8.0	0.0-4.5	0.283-6.43	0.301-6.46	0.248-0.685
	n	39	39	39	39	38	38
B2	Mean*	3.09	4.00	2.00	3.46	3.52	0.381
EC-ASA	%CV	59	30	44	45	44	36
Second Dose	GeoMean	2.50	na	na	3.00	3.06	0.367
	Min – Max	0.316-8.21	0.75-7.5	0.0-4.5	0.322-5.91	0.334-5.92	0.262-1.06
	n	39	39	39	39	38	38
Average of	Mean*	3.01	4.25	2.52	3.35	3.41	0.383
B1 and B2	%CV	52	24	32	42	41	28
	GeoMean	2.46	na	na	2.93	3.00	0.372
	Min – Max	0.246-6.17	0.75-7.5	0.0-4.5	0.339-5.62	0.362-5.63	0.264-0.821

GeoMean = geometric mean. *: Median for t_{max}.and t_{lag} , na = not applicable.

Table 9: Summary of Statistical Analysis Results of Acetylsalicylic Acid Pharmacokinetic Parameters (including subject 10060):

	Reference-Scaled Average Bioequivalence Assessment for Highly Variable Drug Products*		
PK Parameter	**Swr**	**Geometric Least Squares Mean Treatment Ratio (A/B)**	**Upper Bound of the Aspirin 95% Confidence Interval for the Adjusted Treatment Difference (A-B)**
AUC_{0-inf}	0.361	0.840	0.037
AUC_{0-t}	0.359	0.848	0.030
C_{max}	0.385	0.860	0.030

*: Based on FDA Draft Guidance for Progesterone Bioequivalence Assessment, February 2011.
Swr: within-subject standard deviation of the PK parameter from the Reference product

Although the point estimates of the GLSM ratios, PA32540 vs. Ecotrin®, for all bioavailability parameters of acetylsalicylic acid were within the interval of 0.80-1.25, the upper bound of the 95% confidence interval for the difference between Test and Reference treatments, adjusted for the estimated intrasubject variability of the Reference treatment was not less than zero. Therefore, based on this analysis, bioequivalence between PA32540 and Ecotrin® 325 mg has not been demonstrated.

Reviewer's Comment:

- *The within-subject standard deviation of acetylsalicylic acid pharmacokinetic parameters from the reference product Ecotrin® (EC-Aspirin 325 mg) was estimated to be 0.385 for Cmax and 0.361 for AUC0-inf, which are all greater than 0.294, confirming that EC-aspirin formulations are considered to be highly variable drug products and EC-Aspirin PK parameters qualify for the reference-scaled average BE procedure to establish bioequivalence of AUCs and Cmax between PA32540 and Ecotrin®.*

- *BE analysis based on reference-scaled average bioequivalence approach did not show bioequivalence between PA32540 and Ecotrin® 325 mg in terms of bioavailability parameters of acetylsalicylic acid. The point estimate for acetylsalicylic acid exposure (AUC and Cmax) was about 15% lower for PA32540 Tablets compared to Ecotrin 325 mg. Nonetheless, according to the review by Dr. Preston Dunnmon and Dr. Sudharshan Hariharan dated 10/21/2013, because antithrombotic effect of aspirin saturates at 81 mg, this observed small difference in acetylsalicylic acid exposure is not clinically meaningful, Please see consult review from Division of Cardiovascular and Renal Products dated 10/21/2013 for further detail.*

- *PK analysis, plots have been replicated and consistent with sponsor's analysis.*

- *Scaled BE analysis was repeated, and results are consistent with sponsor's analysis.*

2.4.2 Was aspirin component from PA32540 bioequivalent to reference product Ecotrin ® 325 mg in terms of salicylic acid exposure?

Bioequivalence in terms of salicylic acid as the secondary analyte was evaluated in 3 separated studies (PA32540-104, PA32540-112 and PA32540-113) at 325 mg aspirin dose level. All of these studies had demonstrated that aspirin component of PA32540 was bioequivalent to reference product Ecotrin® 325 mg in terms of salicylic acid exposure. However, the sponsor has not evaluated the bioequivalence of salicylic acid at 81mg aspirin level comparing PA8140 vs. Ecotrin 81 mg.

Study 32540-104 (DDI study)

Table 10: Statistical Analysis of Salicylic Acid PK Parameters between Treatments

PK Parameters	Geometric LSM PA32540	Geometric LSM Ecotrin® 325 mg	**PA32540/ Ecotrin® 325 mg** Geom. LSM Ratio (90% CI)
$AUC_{0\text{-}inf}$ (hr*µg/ml)	104.4	95.4	1.095 (0.967, 1.239)
$AUC_{0\text{-}t}$ (hr*µg/ml)	103.1	93.8	1.100 (0.970, 1.247)
C_{max} (µg/ml)	17.4	16.1	1.077 (0.959, 1.209)

Please see section 2.4.4 for detailed PK parameters.

Study PA32540-112 (single and multiple doses PK/PD study)

Table 11: Statistical Analysis of Salicylic Acid PK Parameters between Treatments

PK Parameter	**PA32540 / EC-ASA 325 mg + EC omeprazole 40 mg** Geometric LSM Ratio (90% Confidence Interval)	
	Salicylic Acid	
	Day 1	Day 7

AUC_{0-24} (hr*µg/mL)	0.978 (0.937-1.021)	0.905 (0.820-0.999)
C_{max} (µg/mL)	1.010 (0.907-1.125)	0.964 (0.867-1.072)

PA32540 is bioequivalent to Ecotrin® in terms of in terms of salicylic acid AUC and C_{max} of following single- or multiple-dose administration.
Please see section 2.4.7 for detailed PK parameters.

Study PA32540-113 (DDI study)

Table 12: Statistical Analysis of Salicylic Acid PK Parameters between Treatments:

	Ratio of Geometric Least-Squares Means (90% CIs)		
Salicylic Acid PK Parameter	**PA32540/ EC-ASA + EC-Omeprazole**	**PA32540/ EC-ASA**	**EC-ASA + EC-Omeprazole/ EC-ASA**
AUC_{0-inf}	0.962 (0.933 – 0.992)	0.999 (0.969 – 1.030)	1.038 (1.007 – 1.070)
AUC_{0-t}	0.959 (0.929 – 0.991)	0.996 (0.965 – 1.028)	1.038 (1.005 – 1.072)
C_{max}	0.979 (0.912 – 1.050)	0.972 (0.906 – 1.044)	0.994 (0.926 – 1.066)

PA32540 was bioequivalent to EC-ASA 325 mg (Ecotrin®) whether EC-ASA-325 mg was administered alone or with EC-Omeprazole 40 mg concomitantly in terms of salicylic acid C_{max}, AUC_{0-inf} and AUC_{0-t}
Please see section 2.4.4 for detailed PK parameters.

2.4.3 What is the relative bioavailability of omeprazole in PA32540 compared to reference product Prilosec?

The relative bioavailability of IR omeprazole 40 mg from PA32540 compared to the reference product Prilosec® 40 mg (EC omeprazole) was evaluated in two separate studies (PA32540-112 and PA32540-113). The relative bioavailability (AUC) of omeprazole following IR formulation from PA32540 is about 5%1-58% that of EC formulation from Prilosec for the same dose amount of omeprazole (40 mg) following both single and multiple dosing.

Study PA32540-112:

Table 13: Statistical Analysis of Omeprazole PK Parameters between Treatments following single dose (Day 1) and multiple doses (Day 5 and Day 7) administration

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

Please see section 2.4.7 for detailed PK parameters.

Study PA32540-113:

Table 14: Statistical Analysis Results of Omeprazole PK Parameters following single dose administration:

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

Please see section 2.4.4 for detailed PK parameters.

2.4.4 What is the relative bioavailability of omeprazole from PA8140 compared to PA32540?

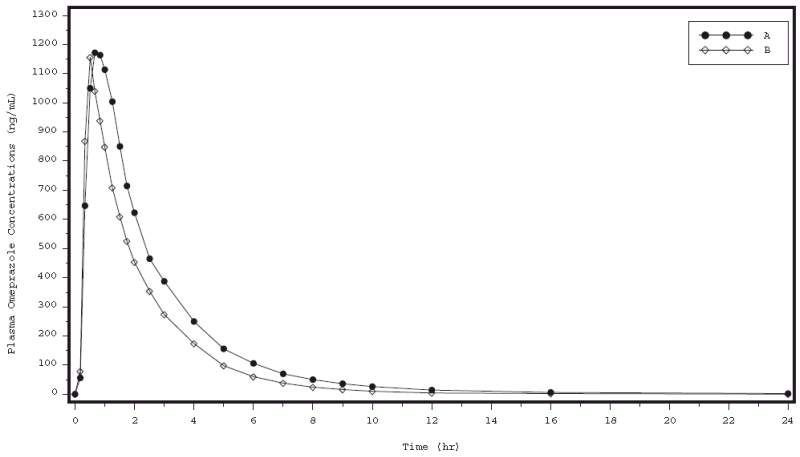
Initially, the relative bioavailability omeprazole following IR-omeprazole 40 mg from PA8140 administration compared to that of reference product Prilosec® 40 mg (EC formulation) or PA32540 was not evaluated in this NDA application. Upon a request from the agency during a teleconference dated December 6, 2013, the sponsor had conducted a relative BA study (Study PA8140-103) comparing the exposure of omeprazole from PA8140 to that of PA32540.

Study PA8140-103 was an open-label, randomized, single-center, multiple-dose, 2-way crossover PK study in 30 healthy subjects with 7-day treatment period to compare the relative bioavailability of omeprazole from PA8140 to that of PA32540. Standardized breakfasts were provided at least 60 minutes after study drug administration on Days 1-4. Standardized lunches (the first post dose meal) were provided at least 4 hours after study drug administration on Days 5-7. The study drug was to be swallowed as whole. There was at least a 7-day of washout period between the treatments. Pharmacokinetic (PK) blood samples were collected for up to 24 hours on Day 7 to determine the plasma concentrations of omeprazole.

- Treatment A (Study product): One tablet of PA8140 (delayed-release aspirin 81 mg + IR-omeprazole 40 mg) administered in the morning once daily for 7 consecutive days
- Treatment B (Reference Product): One tablet of PA32540 (delayed-release aspirin 325 mg + IR-omeprazole 40 mg) administered in the morning once daily for 7 consecutive days

This study had 30 healthy volunteers enrolled and all of them completed the study as planned receiving both treatments.

Figure 5: Mean Plasma Omeprazole Concentration vs. Time Curves on Day 7 Following Repeat Doses of Each Treatment



Treatment A: one tablet of PA8140 once daily for 7 days
Treatment B: one tablet of PA32540 once daily for 7 days.

Table 15: Summary of Omeprazole Pharmacokinetic Parameters for Each Treatment on Day 7:

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

Table 16: Summary of Statistical Analysis Results of Omeprazole Pharmacokinetic Parameters between Treatments on Day 7:

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

Reviewer's Comment:

- *Following 7 days of multiple dosing, omeprazole exposure (AUC) from PA8140 was slightly higher (27%) than that of PA32540 where the Cmax was very similar between PA8140 and PA32540.*
- *Multiples dose omeprazole PK of PA32540 following 7 days of dosing from this current study (PA8140-103) is consistent with the multiple dose omeprazole PK of PA32540 from study PA32540-112.*
- *PK analysis, Plots and BE analysis were re-analyzed and results are consistent with sponsor's analysis.*

2.4.5 Does coadministration of aspirin and omeprazole in PA32540 tablets affect each other's PK profile?

The sponsor had conducted two studies (PA32540-113 and PA32540-104) to assess the potential drug-drug interaction between aspirin and omeprazole. Both studies had demonstrated that co-

administration of aspirin and omeprazole does not appear to affect each other's PK profiles regardless of omeprazole formulation (IR or EC) suggesting the absence of PK drug-drug interaction between aspirin and omeprazole components of PA32540. Although the effect of omeprazole on aspirin PK was assessed based on salicylic acid exposure, not acetylsalicylic acid exposure, no further studies are requested since the efficacy of the aspirin component in both PA32540 and PA8140 as established through BA/BE studies are deemed acceptable. In addition, based on the metabolism and elimination pathways of omeprazole and aspirin, drug-drug interaction is not expected between aspirin and omeprazole.

Study PA32540-113

PA32540-113 was open-label, randomized, single-center, single-dose, 4-way crossover PK study in 36 healthy subjects to evaluate the PK and relative BA of salicylic acid and omeprazole with single dose administration of following treatments.

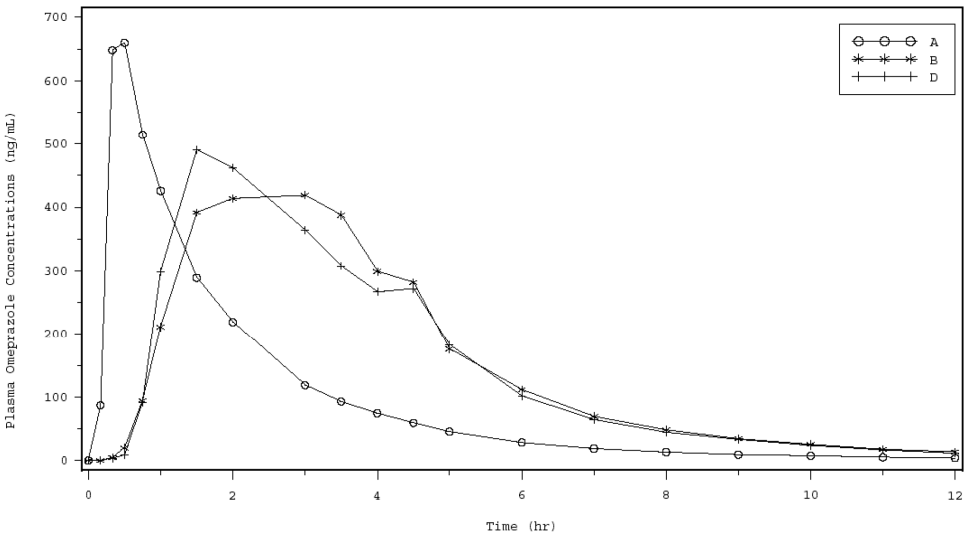
- Treatment A: One (1) tablet of PA32540 (EC-ASA 325 mg + IR-omeprazole 40 mg)
- Treatment B: One (1) tablet of EC-ASA (Ecotrin®) 325 mg coadministered with one (1) capsule of EC-omeprazole 40 mg (Prilosec®)
- Treatment C: One (1) tablet of EC-ASA (Ecotrin®) 325 mg alone
- Treatment D: One (1) capsule of EC-omeprazole (Prilosec®) 40 mg alone

However, this study was not designed to assess the effects of PK and relative bioavailability of acetylsalicylic acid. All subjects underwent an overnight fast of at least 10 hours prior to the morning and no food was allowed for at least 4 hours postdose. There was at least a 7-day of washout period between the treatments. The study drug(s) was to be swallowed as whole and was not to be broken, crushed, and chewed. PK blood samples were collected for up to 48 hours post-dose to determine the plasma concentrations of salicylic acid and acetylsalicylic acid and for 12 hours post dose to determine the plasma concentration of omeprazole.

This study had 36 healthy volunteers enrolled and 35 of them completed the study as planned receiving all 4 treatments. One subject (subject 1006) was withdrawn following completion of the first treatment period (PA32540 tablet) due to a concomitant medication requirement following a hand fracture.

Omeprazole Plasma Concentrations

Figure 6: Mean Plasma Omeprazole Concentration vs. Time Curves Following Single-Dose



Treatment A: PA32540
Treatment B: EC-ASA 325 mg + EC-Omeprazole 40 mg
Treatment D: EC-omeprazole 40 mg alone

Table 17: Summary of Omeprazole Pharmacokinetic Parameters:

Treatment	Statistics	C_{max} (ng/mL)	t_{max}* (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	t½ (hr)
A PA32540	Mean*	822	0.50*	1177	1198	1.12
	%CV	86	n/a	96	99	43
B EC-ASA + EC-Omeprazole	Mean*	767	2.0*	1856	1909	1.24
	%CV	63	n/a	98	104	41
D EC-Omeprazole Alone	Mean*	735	2.0*	1853	1901	1.29
	%CV	62	n/a	96	102	40

Table 18: Summary of Statistical Analysis Results of Omeprazole Pharmacokinetic Parameters:

	Ratio of Geometric Least-Squares Means (90% CIs)		
Omeprazole PK Parameter	**PA32540/ EC-ASA + EC-Omeprazole**	**PA32540/ EC-Omeprazole**	**EC-ASA + EC-Omeprazole/ EC-Omeprazole**
AUC_{0-inf}	0.548 (0.477 – 0.629)	0.564 (0.491 – 0.648)	1.029 (0.896 – 1.182)
AUC_{0-t}	0.548 (0.477 – 0.629)	0.563 (0.490 – 0.647)	1.028 (0.895 – 1.181)
C_{max}	0.877 (0.703 – 1.095)	0.930 (0.745 – 1.160)	1.060 (0.849 – 1.324)

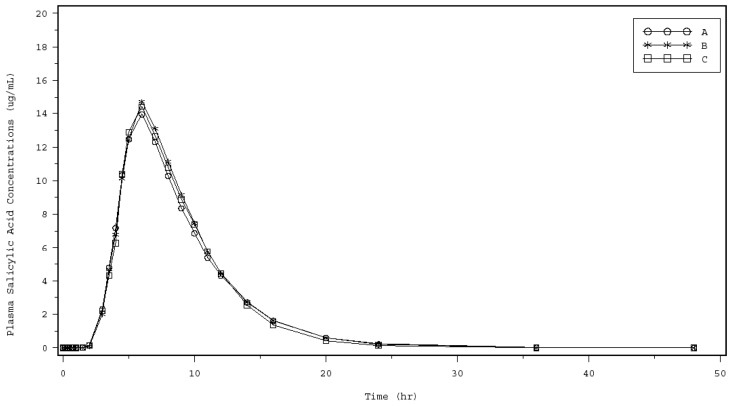
Reviewer's Comment:
Co-Administration of Ecotrin 325 mg with Prilosec (EC-omeprazole) 40 mg did not affect the plasma exposure of omeprazole from Prilosec 40 mg.

Salicylic Acid Plasma Concentrations

Three subjects had measurable salicylic acid concentrations in pre-dose samples: one subject prior to PA32540 (Period 3), and 2 subjects prior to EC-ASA alone (Period 2 or 3). The pre-dose

concentrations were all very low and less than 2% of C_{max} of the profile; therefore, they were included in the analysis.

Figure 7: Mean Plasma Salicylic Acid Concentration vs. Time Curves Following Single-Dose



Treatment A: PA32540
Treatment B: EC-ASA 325 mg + EC-Omeprazole 40 mg
Treatment C: EC-ASA 325 mg alone

Table 19: Summary of Salicylic Acid Pharmacokinetic Parameters:

Treatment	Statistics	C_{max} (ug/mL)	t_{max}* (hr)	AUC_{0-t} (hr*ug/mL)	AUC_{0-inf} (hr*ug/mL)	t½ (hr)
A PA32540	Mean *	16.6	6.0*	99.4	100	2.34
	%CV	26	n/a	29	29	23
B EC-ASA + EC-Omeprazole	Mean*	16.9	6.0*	104	105	2.27
	%CV	29	n/a	32	32	25
C EC-ASA Alone	Mean*	17.0	6.0*	99.6	100	2.22
	%CV	27	n/a	28	28	22

GeoMean = geometric mean. * Median for t_{max} and t_{lag}. n/a = not applicable.

Table 20: Summary of Statistical Analysis of Salicylic Acid Pharmacokinetic Parameters:

	Ratio of Geometric Least-Squares Means (90% CIs)		
Salicylic Acid PK Parameter	**PA32540/ EC-ASA + EC-Omeprazole**	**PA32540/ EC-ASA**	**EC-ASA + EC-Omeprazole/ EC-ASA**
AUC_{0-inf}	0.962 (0.933 – 0.992)	0.999 (0.969 – 1.030)	1.038 (1.007 – 1.070)
AUC_{0-t}	0.959 (0.929 – 0.991)	0.996 (0.965 – 1.028)	1.038 (1.005 – 1.072)
C_{max}	0.979 (0.912 – 1.050)	0.972 (0.906 – 1.044)	0.994 (0.926 – 1.066)

Reviewer's Comment:

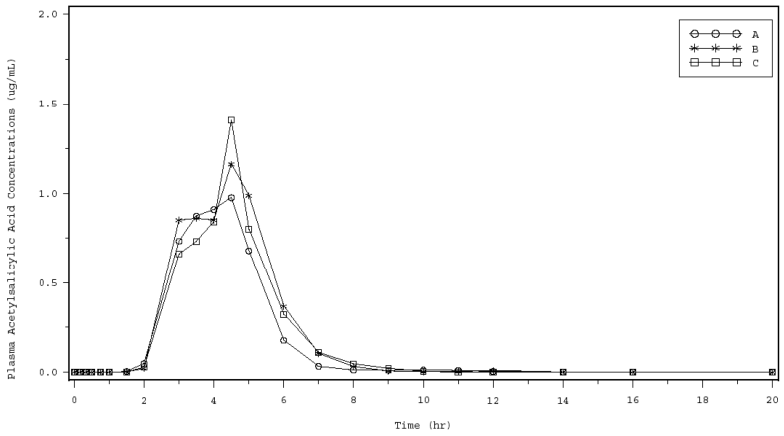
- *The mean plasma profiles of salicylic acid from single-dose administration of all 3 treatments were almost superimposable.*

- *The 90% CIs for the GLSM ratios for salicylic acid C_{max}, AUC0-inf and AUC0-t were all within the (0.80 – 1.25) limits for each treatment comparison indicating concomitant administration of omeprazole 40 mg (regardless of IR or EC formulation) with EC-ASA 325 mg did not affect the plasma exposure of salicylic acid.*

- *PA32540 was bioequivalent to EC-ASA 325 mg (Ecotrin®) whether EC-ASA-325 mg was administered alone or with EC-Omeprazole 40 mg concomitantly in terms of salicylic acid C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$.*

Acetylsalicylic Acid Plasma Concentrations

Figure 8: Mean Plasma Acetylsalicylic Acid Concentration vs. Time Curves



Treatment A: PA32540
Treatment B: EC-ASA 325 mg + EC-Omeprazole 40 mg
Treatment C: EC-ASA 325 mg alone

Table 21: Summary of Acetylsalicylic Acid Pharmacokinetic Parameters:

Treatment	Statistics	C_{max} (ug/mL)	t_{max}* (hr)	$AUC_{0\text{-}t}$ (hr*ug/mL)	$AUC_{0\text{–}inf}$ (hr*ug/mL)	t½ (hr)
A PA32540	Mean*	2.26	4.5 *	2.73	2.99	0.432
	%CV	71	n/a	64	57	96
B EC-Omeprazole + EC-ASA	Mean*	2.71	4.5 *	3.34	3.54	0.376
	%CV	71	n/a	55	50	25
C EC-ASA Alone	Mean*	2.47	4.5 *	3.09	3.17	0.381
	%CV	56	n/a	48	47	30

Table 22: Exploratory Statistical Analysis of Acetylsalicylic Acid Pharmacokinetic Parameters

	Ratios of Geometric Least-Squares Means (90% CIs)		
ASA PK Parameter	**PA32540/ EC-ASA + EC-Omeprazole**	**PA32540/ EC-ASA**	**EC-ASA + EC-Omeprazole/ EC-ASA**
$AUC_{0\text{–}inf}$	0.844 (0.689 – 1.034)	0.959 (0.785 – 1.172)	1.136 (0.932 – 1.385)
$AUC_{0\text{-}t}$	0.814 (0.650 – 1.018)	0.844 (0.675 – 1.056)	1.038 (0.829 – 1.300)
C_{max}	0.809 (0.621 – 1.055)	0.814 (0.624 – 1.061)	1.006 (0.770 – 1.313)

Reviewer's Comment:

- *The sponsor states that the pharmacokinetic parameters and associated statistical analysis results for acetylsalicylic acid are for information only. No interpretation or conclusions were made for acetylsalicylic pharmacokinetic data as the study was not designed to assess the PK and relative BA of acetylsalicylic acid.*

Study PA32540-104:
Study PA32540-104 was an open-label, randomized, single-center, single-dose, 3-way crossover study in 36 healthy subjects to evaluate the pharmacokinetics and relative bioavailability of single oral dose of 325 mg aspirin administered in following 3 formulations:

- Treatment A: One (1) tablet of PA32540 (EC-ASA 325 mg + IR-omeprazole 40 mg)
- Treatment B: One (1) tablet of the aspirin component of PA32540 (PA32540 without the omeprazole)
- Treatment C: One (1) tablet of EC-ASA (Ecotrin®) 325 mg

All subjects underwent an overnight fast of at least 10 hours prior to the morning and no food was allowed for at least 4 hours post-dose. There was a 5-day of washout period between the treatments. The study drug(s) was administered with 240 mL of water and was to be swallowed as whole and was not to be broken, crushed, and chewed. PK blood samples were collected for up to 72 hours post-dose to determine the plasma concentrations of salicylic acid, acetylsalicylic acid, and omeprazole.
Of 36 enrolled subjects, 35 of them completed the study as planned receiving all 3 treatments. One subject (subject 1025) was discontinued after the first treatment period due to withdrawal of consent.

Salicylic Acid Plasma Concentrations

Figure 9: Mean Plasma Salicylic Acid Concentration vs. Time Curves

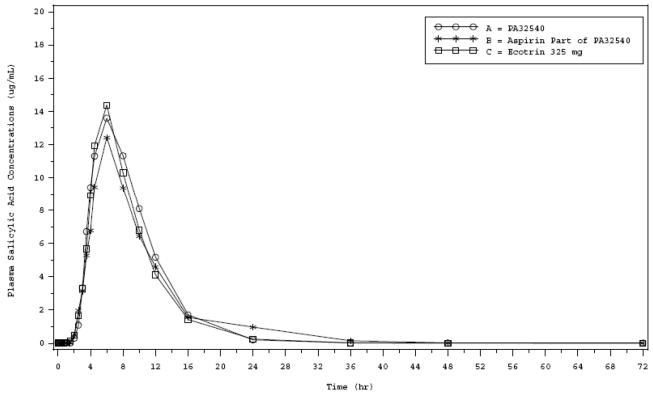


Table 23: Summary of Salicylic Acid Pharmacokinetic Parameters:

Treatment	Statistics	C_{max} (µg/ml)	t_{max} (hr)	AUC_{0-t} (hr*µg/ml)	AUC_{0-inf} (hr*µg/ml)	$t_{½}$ (hr)
A PA32540	Mean %CV	17.9 27	5.81 34	107.4 30	108.7 29	2.42 28
B Aspirin Component of PA32540	Mean %CV	17.0 29	6.96 69	99.9 38	100.9 39	2.38 29
C Ecotrin® 325 mg	Mean %CV	16.8 29	5.73 27	100.2 35	101.7 34	2.42 32

Table 24: Summary of Statistical Analysis of Salicylic Acid PK Parameters Between Treatments

PK Parameter	Geometric LSM			Treatment Comparison	
	A	B	C	A/C Geom. LSM Ratio (90% CI)	B/C Geom. LSM Ratio (90% CI)
$AUC_{0\text{-}inf}$ (hr*µg/ml)	104.4	91.7	95.4	1.095 (0.967, 1.239)	0.962 (0.850, 1.089)
$AUC_{0\text{-}t}$ (hr*µg/ml)	103.1	90.9	93.8	1.100 (0.970, 1.247)	0.969 (0.855, 1.099)
C_{max} (µg/ml)	17.4	15.9	16.1	1.077 (0.959, 1.209)	0.987 (0.880, 1.108)

Reviewer's Comment:

- *The 90% CIs for the GLSM ratios for salicylic acid C_{max}, AUC0-inf and AUC0-t were all within the (0.80 – 1.25) limits for each treatment comparison indicating concomitant administration of omeprazole 40 mg with EC-ASA 325 mg did not affect the plasma exposure of salicylic acid.*

- *The aspirin component of PA32540 is bioequivalent to Ecotrin® 325 mg in terms of salicylic acid AUC0-inf and C_{max}..*

Acetylsalicylic Acid Plasma Concentrations

Figure 10: Mean Plasma Acetylsalicylic Acid Concentration vs. Time Curves

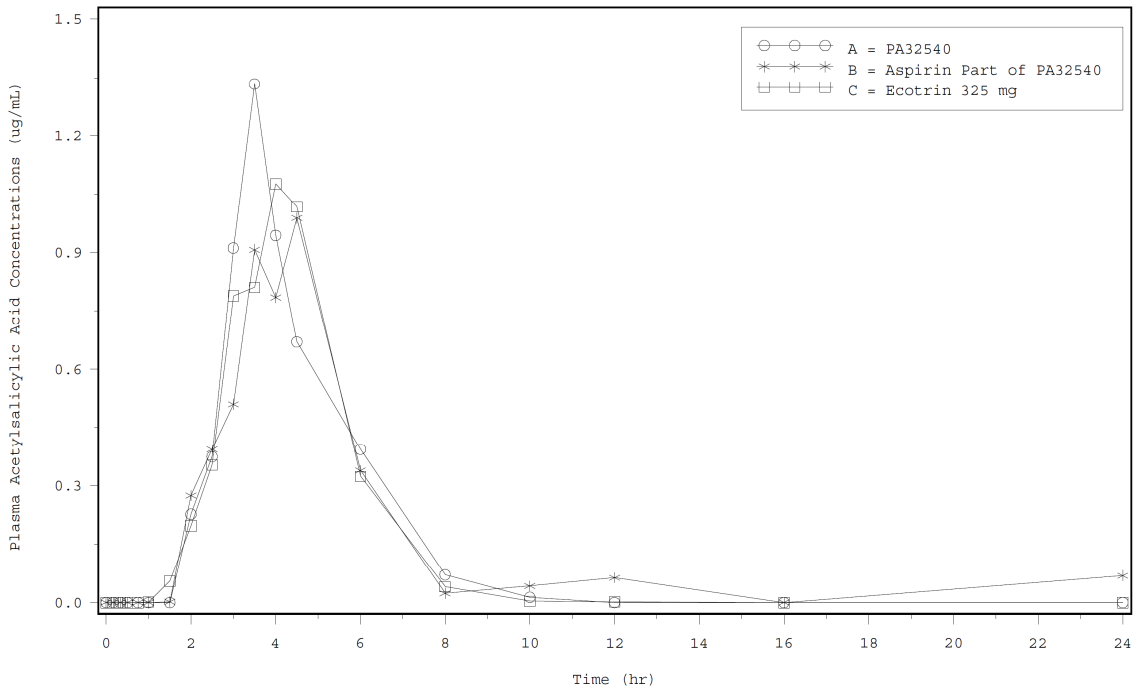


Table 25: Summary of Statistical Analysis of Acetylsalicylic Acid PK Parameters Between Treatments

PK Parameter	Geom. LSMean A	Geom. LSMean B	Geom. LSMean C	Comparison	Ratio	90% CI Lower	90% CI Upper
AUCinf (hr*ug/mL)	3.67	3.47	3.40	A vs C	1.078	0.804	1.445
				B vs C	1.019	0.732	1.419
AUC0-t (hr*ug/mL)	2.40	2.71	2.51	A vs C	0.954	0.658	1.382
				B vs C	1.079	0.736	1.580
Cmax (ug/mL)	1.85	2.06	1.87	A vs C	0.988	0.719	1.358
				B vs C	1.101	0.800	1.515

Reviewer's Comment:

- *Plasma acetylsalicylic acid concentrations were very low or below LLOQ at sampling times before 2 hours and after 6 hours in the majority of subjects receiving Treatments A, B or C. The sponsor states that this narrow window of measurable acetylsalicylic acid concentrations combined with an unpredictable t_{max} and low sampling frequency between 2 and 6 hours precluded any meaningful assessment of acetylsalicylic acid PK parameters. Therefore, the pharmacokinetic parameters and associated statistical analysis results for acetylsalicylic acid are for information only. No interpretation or conclusions were made for acetylsalicylic pharmacokinetic data.*

2.4.6 How does the pharmacodynamics effect of proposed product PA32540 compared to the reference product Prilosec?

Treatment with PA32540 resulted in lower percent time intragastric pH >4 compared with EC-ASA 325 mg (Ecotrin) + EC omeprazole 40 mg (Prilosec) (51% vs. 58%, respectively; P=0.004). This is consistent with lower systemic exposure of omeprazole from PA32540 (IR formulation) compared to Prilosec (EC omeprazole).

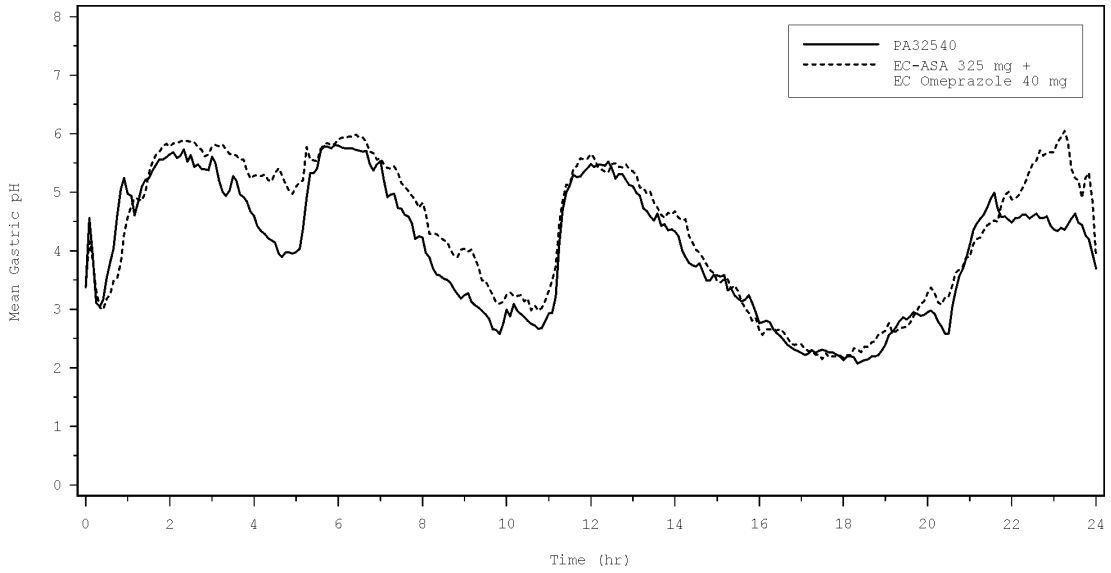
Study PA32540-112 was an open-label, randomized, single-center, multiple-dose, 2-way crossover PK and PD study in 26 healthy subjects with 7-day treatment period to evaluate the pharmacodynamic effect of PA32540 vs. EC Aspirin (Ecotrin®) 325 mg + EC omeprazole (Prilosec®) 40 mg, as measured by 24-hour intragastric pH (percent time intragastric pH >4.0) on Day 7, after seven once-daily doses of each treatment. The study drug(s) was administered after an overnight of fasting and a standard breakfast was served to the subjects at least 60 minutes after the study drug administration. The study drugs was to be swallowed as whole and was not to be broken, crushed, chewed, or opened. There was at least a 7-day of washout period between the treatments. To assess the pharmacodynamics (PD) effect (intragastric pH for a period of 24 hours), a pH probe was placed on Day 7 following an overnight fasting and prior to receiving the Day 7 dose of study drug.
This study had 26 healthy volunteers enrolled and all of them completed the study as planned receiving both treatments. Two subjects were not included in the PD population. One subject due to invalid recording of pH data in Treatment Period 2 (subject vomited, thus ending the pH monitoring) and one subject due to a corrupt data file with unreliable time stamping in Treatment Period 1.

Table 26: Summary of Percent Time Gastric pH >4 on Day 7 (Per-protocol Population)

	PA32540 (n=24)	EC-ASA 325 mg + EC omeprazole 40 mg (n=24)
Mean (SD)	50.49 (18.51)	57.49 (16.01)

Median	44.95	55.71
CV	37	28
Range	27.61-99.79	21.05-97.18

Figure 11: Mean Gastric pH Data over 24 Hours on Day 7 (Per-Protocol Population)



Reviewer's Comment:

- *Treatment with PA32540 resulted in lower percent time intragastric pH >4 compared with EC-ASA 325 mg + EC omeprazole 40 mg. This is consistent with lower (about 50%) systemic exposure of omeprazole from PA32540 (IR formulation) compared to Prilosec (EC omeprazole).*

2.4.7 What are the single dose PK parameters of parent drug and relevant metabolites in healthy adults?

PA32540 tablet:

The single dose PK in healthy subjects was evaluated in several studies for PA32540 tablet and in one study for PA8140. For PA32540, the mean PK parameters of acetylsalicylic acid, salicylic acid and omeprazole appears to be consistent across different studies.

Table 29: Acetylsalicylic Acid PK of PA32540 (% CV)

Studies:	**C_{max} (µg/ml)**	**t_{max} (hr)**	**AUC_{0-t} (hr*µg/ml)**	**AUC_{0-inf} (hr*µg/ml)**	**$t_{½}$ (hr)**
PA32540-105	2.51 (81%)	3.25 (81%)	3.07 (52%)	3.13 (52%)	0.5 (39%)
PA32540-112	2.36 (56%)	3.0 (N/A)	3.25 (36%)	3.36 (34%)	0.450 (23%)
PA32540-113	2.26 (71%)	4.5 (n/a)	2.73 (64%)	2.99 (57%)	0.432 (96%)
PA32540-115	2.51 (69%)	4.42 (32%)	2.9 (62%)	2.94 (62%)	0.361 (33%)

Table 30: Salicylic Acid PK of PA32540 (%CV)

Studies:	**C_{max}**	**t_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**	**$t_{½}$**

	(µg/ml)	(hr)	(hr*µg/ml)	(hr*µg/ml)	(hr)
PA32540-104	17.9 (27%)	5.81 (34%)	107.4 (30%)	108.7 (29%)	2.42 (28%)
PA32540-105	14.5 (37%)	5.0 (72%)	89.4 (36%)	92.7 (35%)	2.29 (17%)
PA32540-112	15.5 (28%)	4.50 (N/A)	94.6 (43%)	96.4 (45%)	2.40 (34%)
PA32540-113	16.6 (26%)	6.0 (n/a)	99.4 (29%)	100 (29%)	2.34 (23%)
PA32540-115	Not Measured				
PA325-106*	18.2 (29%)	4.89 (83%)	102.1 (37%)	103.6 (36%)	2.32 (20%)

Table 31: Omeprazole PK of PA32540 (%CV)

Studies:	C_{max} (ng/ml)	t_{max} (hr)	AUC_{0-t} (hr*ng/ml	AUC_{0-inf} (hr*ng/ml)	$t_{½}$ (hr)
PA32540-104	774.9 (99%)	0.51 (36%)	1082.9 (136%)	1086.1 (135%)	1.05 (35%)
PA32540-105	856 (81%)	0.5 (48%)	1384 (108%)	1393 (108%)	1.15 (33%)
PA32540-112	617 (63%)	0.50 (N/A)	880 (109%)	881 (109%)	1.00 (40%)
PA32540-113	822 (86%)	0.5 (n/a)	1177 (96%)	1198 (99%)	1.12 (43%)
PA32540-115	Not Measured				
PA325-106*	738 (77%)	0.57 (62%)	903 (99%)	905 (99%)	1.04 (36%)

Study PA325-106* was conducted with Phase 1 formulation whereas the rest of the PK studies were conducted with Phase 3 and BE formulation.

PA8140:

The single dose PK of PA8140 was evaluated in study PA8140-102, where the sponsor only measured the concentration of acetylsalicylic acid, but not salicylic acid or omeprazole. Please see section 2.4.1 for detail PK parameters

Table 32: Acetylsalicylic Acid PK of PA8140 (%CV):

Studies:	C_{max} (µg/ml)	t_{max} (hr)	AUC_{0-t} (hr*µg/ml)	AUC_{0-inf} (hr*µg/ml)	$t_{½}$ (hr)
PA8140-102	2.64 (41%)	2.50 (n/a)	2.96 (28%)	2.98 (28%)	0.357 (17%)

2.4.8 What are the multiple dose PK parameters of parent drug and metabolites in healthy adults?

The multiple dose PK of PA32540 was evaluated in Study PA32540-112.

Following 7 days of multiple-dosing of PA32540 tablet or EC Aspirin (Ecotrin®) 325 mg + EC omeprazole (Prilosec®) 40 mg, there were approximately 2-fold accumulations for omeprazole (regardless of IR or EC formulation) and no accumulation for acetylsalicylic acid and salicylic acid.

The sponsor had conducted one multiple dose PK study (Study PA32540-112) was an open-label, randomized, single-center, multiple-dose, 2-way crossover PK and PD study in 26 healthy subjects with 7-day treatment period to assess the PK of omeprazole and salicylic acid after the first dose and at steady-state of PA32540 vs. EC Aspirin (Ecotrin®) 325 mg + EC omeprazole (Prilosec®) 40 mg, The study drug(s) was administered after an overnight of fasting that began no later than midnight. A standard breakfast was served to the subjects at least 60 minutes after the study drug administration. The study drug (tablet or capsule) was to be swallowed as whole and was not to be broken, crushed, chewed, or opened. There was at least a 7-day of washout period between the treatments. Pharmacokinetic (PK) blood samples were collected for up to 24 hours on Day 1 and Day 7 to determine the plasma concentrations of omeprazole, salicylic acid,

and acetylsalicylic acid. In addition, PK blood samples were also collected for 12 hours on Day 5 to determine the plasma concentration of omeprazole.

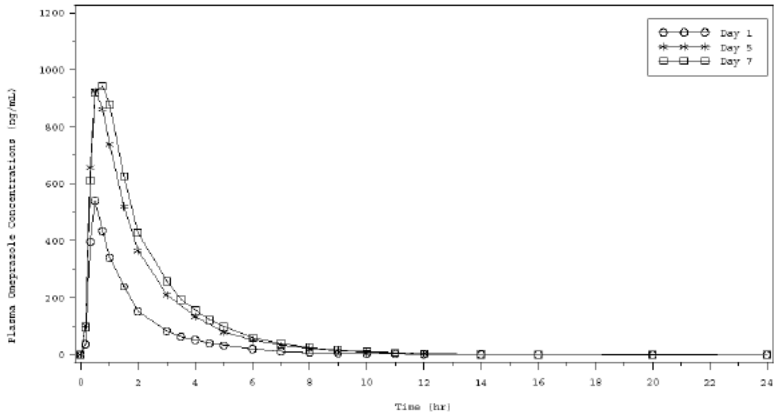
- Treatment A (Study product): One tablet of PA32540 (Enteric-coated aspirin [EC-ASA] 325 mg and immediate-release [IR] omeprazole 40 mg) administered 60 minutes prior to breakfast in the morning once daily for 7 consecutive days
- Treatment B (Reference Product): One tablet of EC-ASA (Ecotrin®) 325 mg + one capsule of EC omeprazole (Prilosec®) 40 mg administered 60 minutes prior to breakfast in the morning once daily for 7 consecutive days

This study had 26 healthy volunteers enrolled and all of them completed the study as planned receiving both treatments

Omeprazole Plasma Concentrations

Figure 12: Mean Plasma Omeprazole Concentration vs. Time Curves Following Single or Repeat Doses of Each Treatment

Treatment A: One tablet of PA32540 (EC-ASA 325 mg and IR omeprazole 40 mg) administered 60 minutes prior to breakfast once daily for 7 days



Treatment B: One tablet of EC-ASA (Ecotrin®) 325 mg + one capsule of EC omeprazole (Prilosec®) 40 mg administered 60 minutes prior to breakfast once daily for 7 days

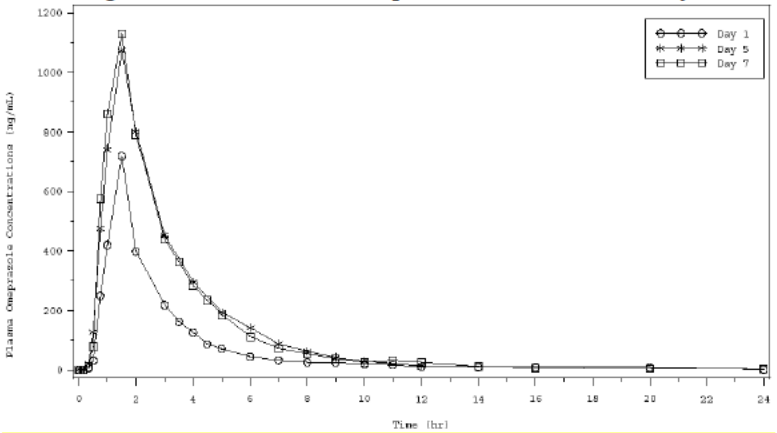


Table 33: Summary of Omeprazole PK Parameters for Each Treatment by Study Day

Study Day	Treatment	Statistics	C_{max} (ng/mL)	t_{max}* (hr)	AUC_{0-12} (hr*ng/mL)	AUC_{0-24} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	$t_{½}$ (hr)
1	A	Mean %CV	617 63	0.50 N/A	874 107	880 109	881 109	1.00 40
1	B	Mean %CV	869 65	1.50 N/A	1458 92	1549 89	1552 89	1.04 43
5	A	Mean %CV	1040 61	0.50 N/A	1911 92	1922 93	N/A	1.09 37
5	B	Mean %CV	1288 34	1.50 N/A	2892 53	2929 55	N/A	1.26 36
7	A	Mean %CV	1196 71	0.50 N/A	2174 88	2187 88	N/A	1.09 35
7	B	Mean %CV	1345 44	1.25 N/A	2890 58	2985 59	N/A	1.19 36

Treatment A: PA32540
Treatment B: EC-ASA 325 mg + EC Omeprazole 40 mg

Table 34: Summary of Statistical Analysis Results of Omeprazole PK Parameters between Study Days

	GLSM Ratio (90% Confidence Interval)					
Omeprazole	Treatment A (PA32540)			Treatment B (EC-ASA 325 mg + EC omeprazole 40 mg)		
PK parameter	Day 5/Day 1	Day 7/Day 1	Day 7/Day 5	Day 5/Day 1	Day 7/Day 1	Day 7/Day 5
AUC_{0-24} (hr*ng/mL)	2.101 (1.685-2.621)	2.371 (1.901-2.957)	1.128 (0.905-1.407)	2.127 (1.923-2.353)	2.146 (1.940-2.374)	1.009 (0.912-1.116)
AUC_{0-12} (hr*ng/mL)	2.101 (1.685-2.620)	2.370 (1.901-2.955)	1.128 (0.904-1.406)	2.275 (1.980-2.613)	2.255 (1.963-2.590)	0.991 (0.863-1.139)
C_{max} (ng/mL)	1.796 (1.351-2.387)	1.939 (1.458-2.578)	1.080 (0.812-1.435)	1.673 (1.385-2.020)	1.679 (1.390-2.027)	1.004 (0.831-1.212)

Reviewer's Comment:

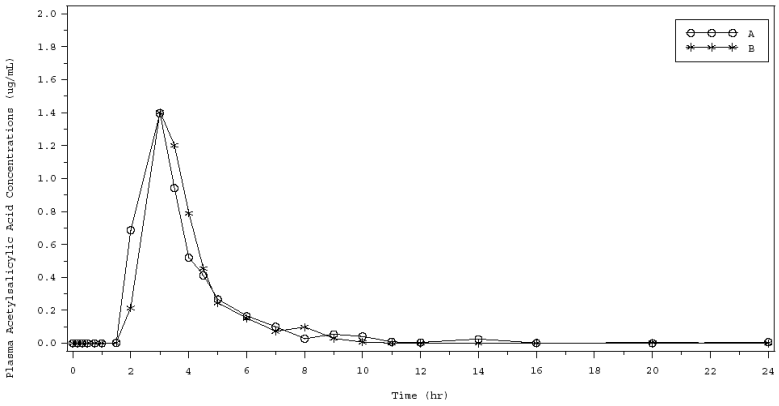
- *There appears to be approximately two-fold higher exposure of omeprazole following multiples dosing of PA32540 and EC omeprazole compared to single-dose. The steady-state appears to have reached by Day 5.*

Acetylsalicylic Acid Plasma Concentrations

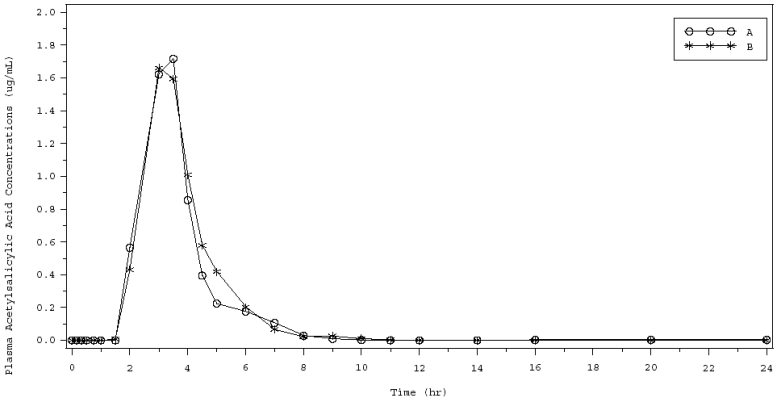
Two subjects receiving Treatment B did not have measurable plasma concentrations of acetylsalicylic acid throughout the 24-hour sampling period on Day 1 or on Day 7, and thus were excluded from summary statistics.

Figure 13: Mean Plasma Acetylsalicylic Acid Concentration vs. Time Curves Following Single or Repeat Doses of Each Treatment

Day 1



Day 7



Treatment A: PA32540
Treatment B: EC-ASA 325 mg + EC Omeprazole 40 mg

Table 35: Summary of Acetylsalicylic Acid PK Parameters for Each Treatment by Study Day

Study Day	Treatment	Statistics	C_{max} (µg/mL)	t_{max}* (hr)	AUC_{0-t} (hr*µg/mL)	AUC_{0-24} (hr*µg/mL)	$AUC_{0-\infty}$ (hr*µg/mL)	t½ (hr)
1	A	Mean %CV	2.36 56	3.0 N/A	3.25 36	3.36 34	3.36 34	0.450 23
1	B	Mean %CV	2.21 55	3.5 N/A	3.08 44	3.15 43	3.15 43	0.427 21
7	A	Mean %CV	2.91 54	3.5 N/A	3.88 37	3.91 37	N/A	0.388 14
7	B	Mean %CV	2.87 42	3.5 N/A	3.78 40	3.80 40	N/A	0.385 15

Treatment A: PA32540
Treatment B: EC-ASA 325 mg + EC Omeprazole 40 mg

Table 36: Results of Statistical Analysis of Salicylic Acid and Acetylsalicylic Acid PK Parameters between Treatments

PK Parameter	PA32540 vs. EC-ASA 325 mg + EC omeprazole 40 mg Geometric LSM Ratio (90% Confidence Interval)			
	Salicylic Acid		Acetylsalicylic Acid	
	Day 1	Day 7	Day 1	Day 7
AUC_{0-24} (hr*µg/mL)	0.978 (0.937-1.021)	0.905 (0.820-0.999)	1.121 (0.877-1.434)	1.019 (0.887-1.172)
C_{max} (µg/mL)	1.010 (0.907-1.125)	0.964 (0.867-1.072)	1.117 (0.756-1.652)	0.820 (0.575-1.169)

Reviewer's Comment:

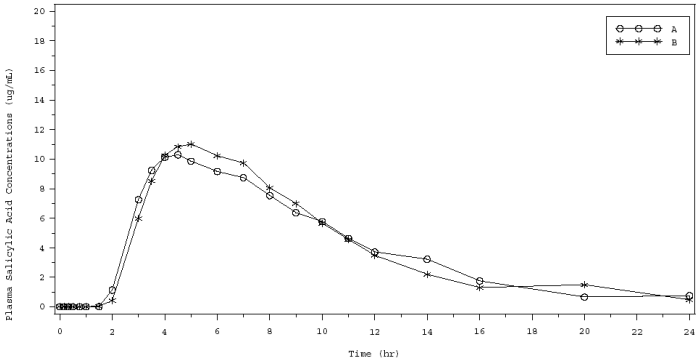
- *There is no significant accumulation in exposure of acetysalicylic acid following multiple dosing, as the exposure of acetylsalicylic acid following multiple doses was very similar to that of single dose for both PA32540 and Ecotrin®, and the ratio of AUC and Cmax from Day 7 to Day 1 were very close to 1.0 for both treatments.*
- *The mean PK profiles and plasma exposures of acetylsalicylic acid from PA32540 and Ecotrin® were similar on both Day 1 and Day 7.*

Salicylic Acid Plasma Concentrations

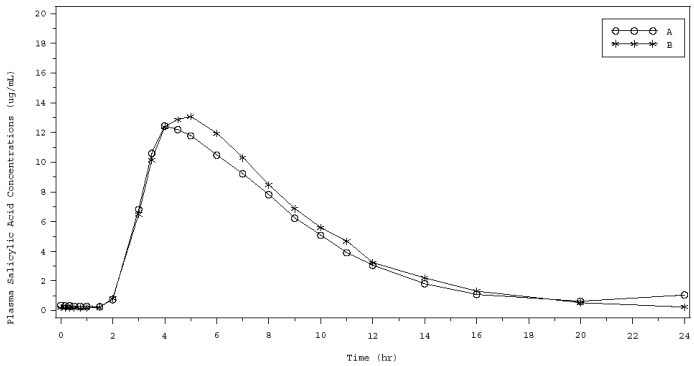
One subject receiving Treatment B did not have measurable plasma concentrations of salicylic acid throughout the 24- hour sampling period on Day 7, and thus was excluded from summary statistics.

Figure 14: Mean Plasma Salicylic Acid Concentration vs. Time Curves Following Single or Repeat Doses of Each Treatment

Day 1



Day 7



Treatment A: PA32540
Treatment B: EC-ASA 325 mg + EC Omeprazole 40 mg

Table 37: Summary of Salicylic Acid PK Parameters for Each Treatment by Study Day

Study Day	Treatment	Statistics	C_{max} (µg/mL)	t_{max}* (hr)	AUC_{0-t} (hr*µg/mL)	AUC_{0-24} (hr*µg/mL)	$AUC_{0-\infty}$ (hr*µg/mL)	$t_{½}$ (hr)
1	A	Mean %CV	15.5 28	4.50 N/A	94.6 43	94.8 43	96.4 45	2.40 34
1	B	Mean %CV	15.3 27	4.50 N/A	96.2 44	96.5 43	97.9 46	2.42 32
7	A	Mean %CV	16.2 29	4.50 N/A	91.0 55	91.3 55	N/A	2.26 34
7	B	Mean %CV	16.6 26	4.00 N/A	97.1 44	97.4 44	N/A	2.34 35

*Values for t_{max} are median and range.
Treatment A: PA32540
Treatment B: EC-ASA 325 mg + EC Omeprazole 40 mg

Table 38: Summary of Statistical Analysis of Salicylic Acid PK Parameters between Days for Each Treatment

	GLSM Ratio (90% Confidence Interval)					
Treatment	Goem.LS Mean				90% CI	
	Day 1	Day 7	Comparison	Ratio	Lower	Upper
AUC_{0-24} (hr*ng/mL)						
A	87.7	82.5	Day 7 vs. 1	0.941	0.849	1.043
B	88.4	90.8	Day 7 vs. 1	1.027	0.982	1.075
C_{max} (ng/mL)						
A	14.9	15.6	Day 7 vs. 1	1.042	0.950	1.143
B	14.8	16.1	Day 7 vs. 1	1.086	0.978	1.205

Treatment A: PA32540
Treatment B: EC-ASA 325 mg + EC Omeprazole 40 mg

Table 39: Results of Statistical Analysis of Salicylic Acid PK Parameters between Treatments

PK Parameter	PA32540 vs. EC-ASA 325 mg + EC omeprazole 40 mg Geometric LSM Ratio (90% Confidence Interval)

	Salicylic Acid	
	Day 1	Day 7
AUC_{0-24} (hr*µg/mL)	0.978 (0.937-1.021)	0.905 (0.820-0.999)
C_{max} (µg/mL)	1.010 (0.907-1.125)	0.964 (0.867-1.072)

Reviewer's Comment:

- *There is no accumulation in exposure of salicylic acid following multiple dosing, as the exposure of salicylic acid following multiple doses was very similar to that of single dose for both PA32540 and Ecotrin®, and the ratio of AUC and Cmax from Day 7 to Day 1 were very close to 1.0 for both treatments.*
- *PK profiles and plasma exposure of salicylic acid from PA32540 and Ecotrin® were similar on both Day 1 and Day 7.*
- *BE analysis showed that the 90% CIs for the geometric least squares mean (GLSM) ratios (PA32540 vs. Ecotrin®) for salicylic acid Cmax and AUC0-24 were all within the 0.80 to 1.25 limits on Day 1 and Day 7, indicating that PA32540 is bioequivalent to Ecotrin® in terms of AUC and Cmax of salicylic acid following single- or repeat-dose administration.*

2.4.9 How does the PK of the drug and its metabolites in healthy adults compare to that in patients with the target disease?

Sponsor had only measured the PK of aspirin (acetylsalicylic acid), salicylic acid, omeprazole from Yosprala and from reference products Ecotrin and Prilosec in healthy subjects in phase 1 studies, but not in target patient population in phase3 studies.

2.4.10 What are the characteristics of drug metabolism?

The sponsor did not conduct any metabolism study in this submission.

- Omeprazole is extensively metabolized by CYP2C19 and CYP3A4.

- Aspirin (acetylsalicylic acid) is rapidly hydrolyzed in the plasma to salicylic acid. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10 - 20 grams), the plasma half-life may be increased to over 20 hours.

2.5 General Biopharmaceutics

2.5.1 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

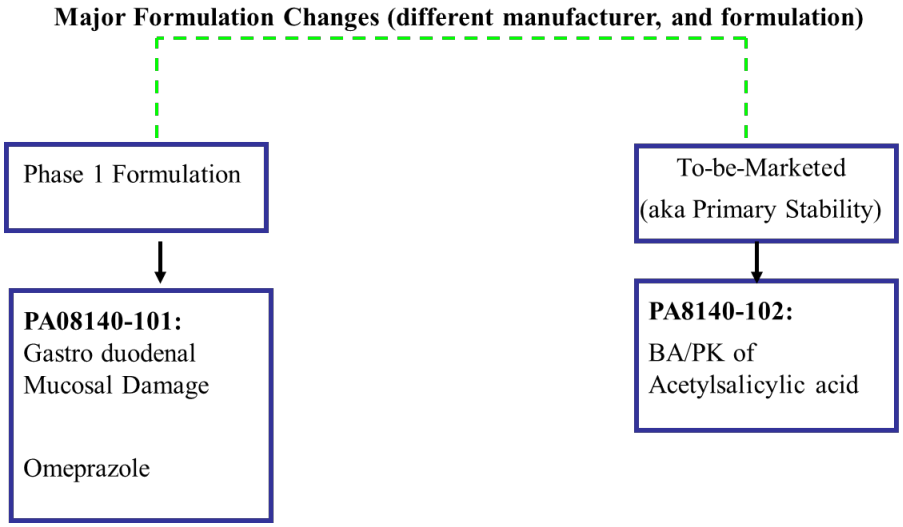
There have been one formulation change with PA8140 tablet and 3 formulation changes with PA32540 tablets during the development process. These formulation changes do not impact the approvability of current NDA application:

- For PA8140, The pivotal bioequivalence study (PA8140-102) comparing PA8140 tablet to the reference product Ecotrin® 81 mg was conducted with the to-be-marketed (TBM) formulation (aka primary stability formulation).

- For PA32540, all phase 1 clinical pharmacology studies and phase 3 studies were conducted with Phase 3 and BE formulation. Although there were minor formulation changes from the Phase 3 and BE Formulation to the to-be-marketed (TBM) formulation (aka Primary stability formulation), according to the Biopharm reviewers (Dr. Banu Zolnik and Dr. Sandra Suarez Sharp), theses formulation changes were minor and do not require in in-vivo bioequivalence study.

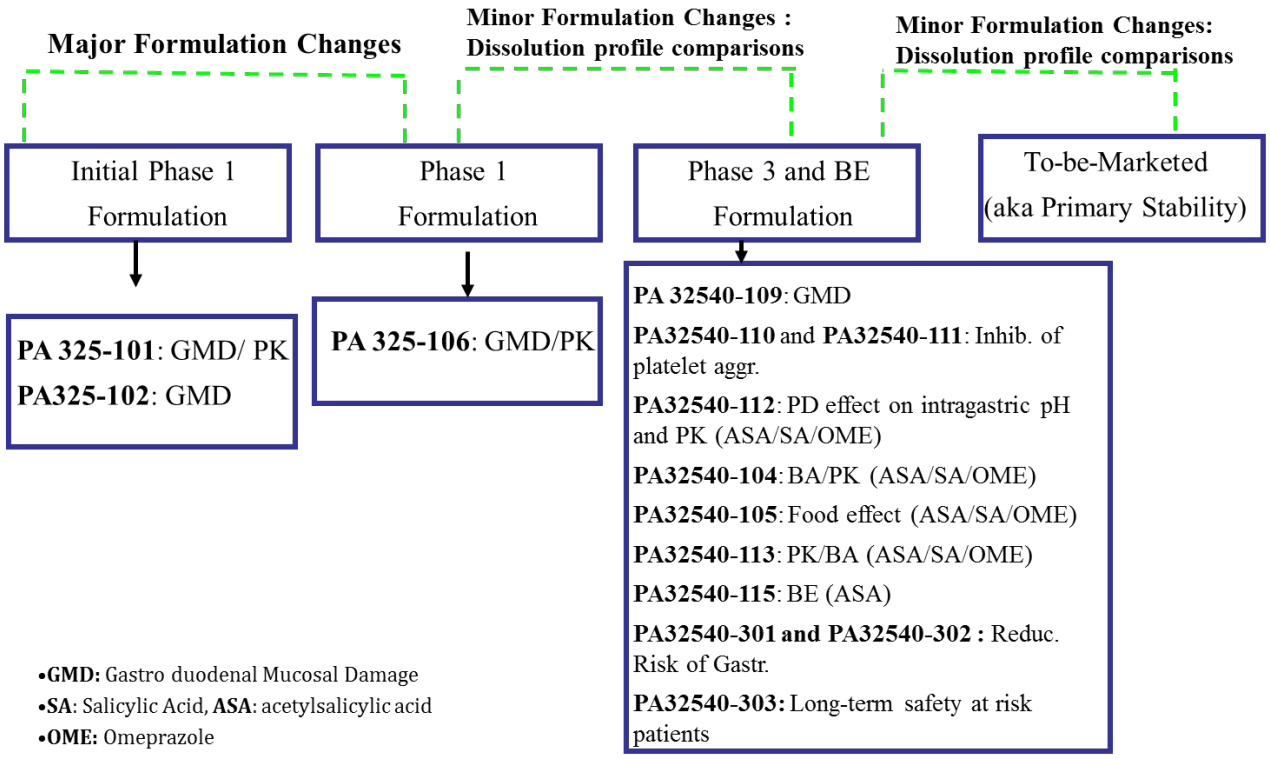
Please refer to Appendices 3.1 for detailed formulation information.

PA8140 tablet formulation development:



The pivotal bioequivalence study (PA8140-102) comparing PA8140 tablet to the reference product Ecotrin® 81 mg was conducted with the TBM formulation (aka primary stability formulation). However, the Phase 1 formulation that was used in mucosal damage study PA8140-101 was not linked to the TBM formulation via an *in-vivo* bioequivalence study.

PA32540 Tablet Formulation Development:



There were minor formulation changes from the Phase 3 and BE Formulation (that was used in phase 3 clinical trials and phase 1 clinical pharmacology studies) to the to-be-marketed formulation (aka Primary stability formulation). However, according to the Biopharm reviewers (Dr. Banu Zolnik and Dr. Sandra Suarez Sharp), theses formulation changes were minor and do not require in-vivo bioequivalence study.

Of 4 mucosal damage studies at 325 mg aspirin dose level, one of the study PA32540-109 was conducted with Phase 3 and BE Formulation. Another study PA325-106 was conducted with Phase 1 Formulation. Based on the cross-study PK comparison, the PK of acetylsalicylic acid, salicylic acid and omeprazole from Phase 1 formulation used in Study PA32540-106 were similar to that of Phase 3 and BE formulation used in Study PA32540-104, PA32540-105, PA32540-112 and PA32540-113 (please see section 2.4.6 for detailed PK comparison). Therefore, the results of mucosal damage study PA325-106 that used Phase 1 formulation can reasonably be extrapolated to Phase 3 and BE formulation. Two of the studies, PA325-101 and PA325-102, were conducted with Initial Phase 1 Formulation, which had used PA32520 tablet that contains 325 mg aspirin/20 omeprazole. (b) (4)

2.5.2 What is the effect of food on the bioavailability of the drug?

The effect food on Yosprala were evaluated when PA32540 was administered 60 minutes prior to breakfast and within 5 minutes of breakfast compared to the fasted state. Overall, salicylic acid and omeprazole have more comparable plasma exposures and PK profiles when PA32540 was administered 60 minutes before breakfast than when PA32540 was administered within 5 minutes

of breakfast compared to fasted state. In the Phase III pivotal trials, PA32540 was administered about one hour before breakfast or the first meal of the day, which is aligned with the result of the food effect study. Therefore, the label will specify that the proposed product be taken at least 60 minutes before a meal.

> Note: Although the effect of food on aspirin component of Yosprala was assessed based on salicylic acid exposure, not acetylsalicylic acid exposure, no further studies are needed as the current monograph does not impose any food restriction on OTC aspirin product.

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

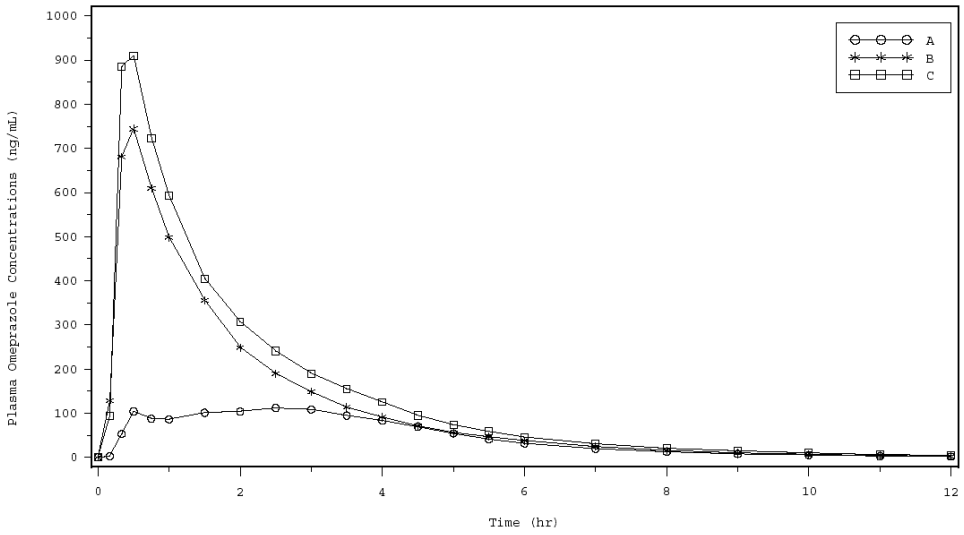
Study PA32540-105 was an open-label, randomized, single-center, single-dose, 3-way crossover PK study in 24 healthy subjects to evaluate the effect of food on exposure of salicylic acid and omeprazole. However, this study was not designed to assess the effects of food on the bioavailability of acetylsalicylic acid. All subjects underwent an overnight fast of at least 10 hours prior to the morning of Day 1. Subjects received 3 separate single doses of PA32540 in a randomized, crossover fashion:

- Treatment A: One (1) tablet of PA32540 (EC-ASA 325 mg + IR omeprazole 40 mg) administered within 5 minutes after completion of a standardized high-fat, high-calorie breakfast
- Treatment B: One (1) tablet of PA32540 (EC-ASA 325 mg + IR omeprazole 40 mg) administered at 60 minutes prior to a standardized high-fat, high-calorie breakfast
- Treatment C: One (1) tablet of PA32540 (EC-ASA 325 mg + IR omeprazole 40 mg) followed by an additional 4-hour fast

There was at least a 7-day of washout period between the treatments. The study drug was to be swallowed as whole and was not to be broken, crushed, and chewed. PK blood samples were collected for up to 48 hours post-dose to determine the plasma concentrations of salicylic acid and acetylsalicylic acid and for 12 hours post dose to determine the plasma concentration of omeprazole.
This study had 24 healthy volunteers enrolled and 22 of them completed the study as planned receiving all three treatments. Two subjects were withdrawn prior to study drug administration in Period 3 due to positive urine drug screens. Two subjects (subject 1002 and 1023) had measurable salicylic acid concentrations in the pre-dose samples in Treatments A and C. These predose concentrations were all very low and less than 1.5% of the C_{max} values in that corresponding subject, and therefore, were included in the analysis. Six subjects in Treatment A and one subject in Treatment B had only two measurable salicylic acid concentrations throughout the entire sampling period. Therefore, salicylic acid AUC_{0-t}, AUC_{0-inf} and $t_{1/2}$ values could not be estimated for these subjects.

Omeprazole Plasma Concentrations

Figure 15: Mean Plasma Omeprazole Concentration vs. Time Curves



Treatment A: PA32540 with food
Treatment B: PA32540 60 minutes before food
Treatment C: PA32540 Fasting

Table 40: Summary of Omeprazole Pharmacokinetic Parameters:

Treatment	Statistics	C_{max} (ng/mL)	t_{max}* (hr)	t_{lag}* (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	t½ (hr)
A							
PA32540	Mean *	204	2.00	0.17	544	549	1.06
with food	%CV	127	57	108	99	99	34
B							
PA32540	Mean*	856	0.50	0.00	1384	1393	1.15
60 minutes	%CV	81	48	331	108	108	33
before Food							
C							
PA32540	Mean*	1035	0.50	0.00	1703	1720	1.18
Fasting	%CV	79	27	331	112	113	34

Table 41: Summary of Statistical Analysis Results of Omeprazole Pharmacokinetic Parameters:

	Ratio of Geometric Least-Squares Means (90% CIs)	
Omeprazole PK Parameter	**With High-Fat Meal/ Fasting Conditions**	**60 Min Prior to High-Fat Meal/ Fasting Conditions**
AUC_{0-inf}	0.329 (0.273 – 0.397)	0.834 (0.689 – 1.009)
AUC_{0-t}	0.328 (0.272 – 0.396)	0.835 (0.689 – 1.011)
C_{max}	0.163 (0.128 – 0.209)	0.856 (0.667 – 1.099)

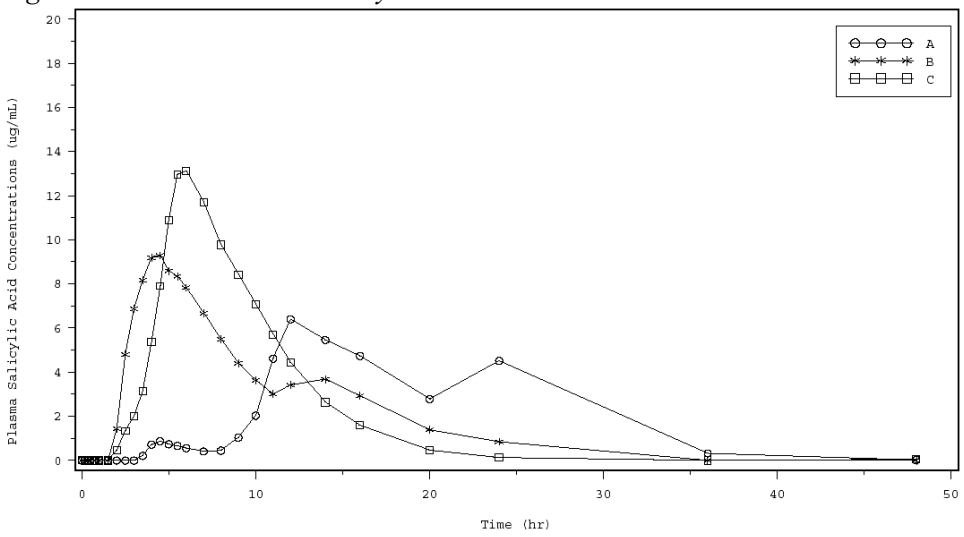
Reviewer's Comment:

- *In comparison to PA32540 administered under fasting conditions:*

- *Administration of PA32540 sixty minutes prior to breakfast did not significantly affect the absorption characteristics of omeprazole (similar plasma omeprazole profiles between Treatment B and C, with unchanged median t_{max}), but resulted in slightly reduced omeprazole plasma concentrations (14-16% reduction in AUCs and Cmax) compared with fasting conditions.*
- *Administration of PA32540 with the high-fat breakfast resulted in a slight delay in the absorption of omeprazole (median t_{max} was prolonged by about 1.5 hrs) and a substantial reduction in omeprazole plasma exposure (about 67% and 84%, reduction in AUC and Cmax, respectively) compared with fasting conditions.*
- *The 90% CIs of the GLSM ratios for omeprazole AUCs and Cmax for both treatment comparisons were outside the (0.80 – 1.25) limit. None of the 90% CIs for the Treatment A/C ratio (high-fat meal/fasting conditions) contained 1.0, indicating a significant food effect when PA32540 was administered immediately following a meal relative to fasting conditions*.

Salicylic Acid Plasma Concentrations

Figure 16: Mean Plasma Salicylic Acid Concentration vs. Time Curves



Treatment A: PA32540 with food
Treatment B: PA32540 60 minutes before food
Treatment C: PA32540 Fasting

Table 42: Summary of Salicylic Acid Pharmacokinetic Parameters:

Treatment	Statistics	C_{max} (ug/mL)	t_{max}* (hr)	t_{lag}* (hr)	AUC_{0-t} (hr*ug/mL)	AUC_{0-inf} (hr*ug/mL)	t½ (hr)
A							
PA32540 with food	Mean*	14.6	15.0	10.0	95.3	101	2.36
	%CV	34	42	51	36	34	23
B							
PA32540 60 minutes before Food	Mean*	14.5	5.00	1.52	89.4	92.7	2.29
	%CV	37	72	114	36	35	17
C							
PA32540 Fasting	Mean*	15.7	5.50	2.50	93.8	94.6	2.21
	%CV	28	33	47	27	27	23

GeoMean = geometric mean. * Median for t_{max} and t_{lag}. n/a = not applicable for median value.

Table 43: Summary of Statistical Analysis of Salicylic Acid Pharmacokinetic Parameters:

	Ratio of Geometric Least-Squares Means (90% CIs)	
Salicylic Acid PK Parameter	**With High-Fat Meal/ Fasting Conditions**	**60 Min Prior to High-Fat Meal/ Fasting Conditions**
AUC_{0-inf}	1.027 (0.950 – 1.110)	0.949 (0.884 – 1.018)
AUC_{0-t}	0.955 (0.853 – 1.070)	0.931 (0.838 – 1.035)
C_{max}	0.909 (0.770 – 1.073)	0.912 (0.771 – 1.080)

Reviewer's Comment:

In comparison to PA32540 administered under fasting conditions:

- *The median t_{max} for salicylic acid was slightly shortened by about 0.5 hour when PA32540 was administered 60 minutes before a high-fat meal, but was significantly prolonged by about 10 hrs when PA32540 was administered within 5 minutes after a high-fat meal compared to fasting state.*

- *The extent of bioavailability (AUCs) of salicylic acid was unchanged, and Cmax was only slightly reduced by about 9% when PA32540 was administered with food (with immediately after or 60 minutes before food) compared to fasting condition.*

- *The 90% CIs of the GLSM ratios for salicylic acid AUCs fell within the (0.80 – 1.25) limit for each treatment comparison, indicating that administration of PA32540 sixty minutes before or immediately after a high-fat meal did not affect overall plasma exposure to salicylic acid or the extent of bioavailability relative to fasting conditions.*

- *The 90% CI of the GLSM ratios for salicylic acid Cmax for each treatment comparison fell outside the (0.80 – 1.25) limit, but contained 1.0. Based on the point estimates, there was an approximate 9% of reduction in salicylic acid Cmax when PA32540 was administered 60 minutes before or immediately after a high-fat meal compared with fasting conditions.*

Acetylsalicylic Acid Plasma Concentrations

Plasma acetylsalicylic acid concentrations were very low and sporadically measurable especially when PA32540 was administered with a high-fat meal.
Two subjects, one receiving Treatment A and the other receiving Treatment B did not have any measurable acetylsalicylic acid concentrations throughout the entire sampling period and, thus, were excluded from the summary statistics.
Seven subjects receiving Treatment A and 1 subject receiving Treatment B had only one measurable acetylsalicylic acid concentration in plasma throughout the 48-hour sampling period.
In addition, 7 subjects receiving Treatment A and 3 subjects receiving Treatment B had only two quantifiable acetylsalicylic acid concentration in plasma throughout the 48-hour sampling period.
Only 8 subjects having sufficient data to estimate acetylsalicylic acid AUC0-t, AUC0-inf and t1/2 values; thus, the true mean/median values for the AUC values in Treatment A could be overestimated based on only limited subject data. Therefore, summary statistics for acetylsalicylic acid AUCs in Treatment A are not presented.

Table 44: Summary of Acetylsalicylic Acid Pharmacokinetic Parameters:

Treatment	Statistics	C_{max} (ug/mL)	t_{max}* (hr)	t_{lag}* (hr)	AUC_{0-t} (hr*ug/mL)	AUC_{0-inf} (hr*ug/mL)	t½ (hr)
A							
PA32540	Mean *	2.40	14.0	12.0	n/p	n/p	0.40
with food	%CV	88	42	39	n/p	n/p	17
B							
PA32540	Mean*	2.51	3.25	1.50	3.07	3.13	0.50
60 minutes	%CV	81	81	106	52	52	39
before Food							
C							
PA32540	Mean*	2.65	4.50	2.50	3.23	3.41	0.42
Fasting	%CV	56	30	40	44	41	47

Table 45: Statistical Analysis of Acetylsalicylic Acid Pharmacokinetic Parameters

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

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

Reviewer's Comment:
The comparison of acetylsalicylic acid pharmacokinetic parameters between Treatment B and Treatment C was performed using an ANOVA. However, no comparison of acetylsalicylic acid pharmacokinetic parameters between Treatment A and Treatment C were calculated due to the very small number of subjects (only 8) with estimable parameters of acetylsalicylic acid following Treatment A. However, the sponsor states that the pharmacokinetic parameters and associated statistical analysis results for acetylsalicylic acid are for information only. No interpretation or conclusions were made for acetylsalicylic pharmacokinetic data as this study was not designed to assess effect of food on the pharmacokinetics and relative bioavailability of acetylsalicylic acid.

2.5.3 How the drug was administered in relation to meal in phase 3 studies?

In all Phase III studies, patients were instructed to take the study medication in the morning, approximately 1 hour prior to the breakfast or the first meal of the day. However, the proposed label recommends the tablets to be taken at least 1 hour before meals, but does not specify breakfast or first meal of the day.

2.6 Analytical Section

2.6.1 What bioanalytical methods were used to assess the concentration?

The sponsor had used validated HPLC-MS/MS analytical methods developed [redacted] (b) (4) development to measure the plasma concentration of acetylsalicylic acid, salicylic acid and omeprazole in all of the PK studies. The following information applies to all studies that contain PK data (Study PA8140-102, PA32540-104, PA32540-105, PA32540-112, PA32540-113, PA32540-115 and PA325-106).

Acetylsalicylic acid

- Plasma samples for acetylsalicylic acid and salicylic acid were stored frozen at -70°C until analysis.
- The lower limit of quantitation (LLOQ) for acetylsalicylic acid was 0.02 µg/mL.
- The standard curve for acetylsalicylic acid with 8 concentration levels ranged from 0.02 to 10 µg/mL and was calculated using a quadratic (1/concentration squared weighted) least-squares regression algorithm.
- Quality Control (QC) samples at 5 different concentrations (0.05, 0.125, 0.450, 1.50, and 7.50 µg/mL) of acetylsalicylic acid were prepared.
- Plasma samples, stored at approximately -70°C, were analyzed within the time period for which the long-term plasma stability of salicylic acid and acetylsalicylic acid has been established for 359 days.
- The inter-assay coefficients of variation of the QCs, the mean percent differences from theoretical, and the differences of back-calculated calibration curve values from nominal values for acetylsalicylic acid were all within the acceptable ranges.

Studies:	inter-assay coefficients of variation (CV) of the QCs	Mean % differences from theoretical	differences of back-calculated calibration curve values from nominal values
PA8140-102	6.83% to 10.6%	0.611% to 3.78%	-1.24% to 1.27%
PA32540-104	3.56% to 7.58%	-1.65% to 5.44%.	-1.24% to 1.51%
PA32540-105	4.20% to 9.78%	-1.25% to 4.11%	-1.65% to 1.10%
PA32540-112	4.7% to 9.0%	-3.3% to 1.3%	-1.6% to 1.0%
PA32540-113	6.18% to 10.6%	–2.57% to 2.48%	- 0.92% to 1.19%
PA32540-115	8.26% to 14.1%	-2.50% to 2.20%	-0.586% to 0.638%
PA325-106	6.06% to 7.00%	-5.82% to -3.43%	-1.29% to 2.02%

Salicylic acid

- Plasma samples for acetylsalicylic acid and salicylic acid were stored frozen at -70 °C until analysis.
- The lower limit of quantitation (LLOQ) for salicylic acid was 0.1 µg/mL.
- The standard curve for salicylic acid with 8 concentration levels ranged from 0.10 to 50 µg/mL and was calculated using a quadratic (1/concentration squared weighted) least-squares regression algorithm.
- QC samples at 5 different concentrations (0.250, 0.625, 2.25, 7.50, and 37.50 µg/mL) of salicylic acid were prepared.
- Plasma samples, stored at approximately -70°C, were analyzed within the time period for which the long-term plasma stability of salicylic acid and acetylsalicylic acid has been established for 359 days.
- The inter-assay coefficients of variation of the QCs, the mean percent differences from theoretical, and the differences of back-calculated calibration curve values from nominal values for salicylic acid were all within the acceptable ranges.

Studies:	inter-assay coefficients of variation (CV) of the QCs	Mean % differences from theoretical	differences of back-calculated calibration curve values from nominal values
PA32540-104	2.92% to 6.07%,	-5.92% to 4.35%.	-1.47% to 1.57%
PA32540-105	2.23% to 3.58%,	-0.99% to 1.20%.	-0.54% to 0.54%
PA32540-112	3.1% to 4.0%,	-1.8% to -1.0%.	-1.0% to 0.8%
PA32540-113	2.3% to 3.28%	–2.06% to 0.59%.	- 0.377% to 0.594%
PA325-106:	2.45% to 3.71%,	-4.53% to -2.32%.	0.623% to 0.781%

Omeprazole:

- Plasma samples for omeprazole were stored frozen at -20°C until analysis
- The lower limit of quantitation (LLOQ) for omeprazole was 1 ng/mL.
- Calibration standard curve consisted of 7 level ranged from 1 to 1000 ng/mL in human plasma and was calculated using a quadratic (1/concentration weighted) least-squares regression algorithm.
- QC samples at 5 different concentrations (2.6, 8.0, 30.0, 130, and 750 ng/mL) of omeprazole were prepared
- Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term plasma stability of omeprazole has been established for 449 days.
- The inter-assay coefficients of variation of the QCs, the mean percent differences from theoretical, and the differences of back-calculated calibration curve values from nominal values for omeprazole were all within the acceptable ranges.

Studies:	inter-assay coefficients of variation (CV) of the QCs	Mean % differences from theoretical	differences of back-calculated calibration curve values from nominal values
PA32540-104	1.39% to 2.81%	0.797% to 2.46%.	-2.44 to 2.11%.
PA32540-105	2.26% to 4.34%	-1.66% to 0.24%	-2.63 to 3.45%.
PA32540-112	2.5% to 10.2%	-0.1% to 1.4%.	-1.0% to 1.2%.
PA32540-113:	2.33% to 14.9%,	-2.27% to -0.05%.	-4.32 to 4.46%.
PA325-106	2.80% to 7.89%,	0.959% to 4.08%.	-1.05 to 0.737%.

2.6.2 Were the analytical assay methods adequately validated?

The bioanalytical methods (HPLC-MS/MS) for measurement of acetylsalicylic acid, salicylic acid and omeprazole used in all of studies with PK data were appropriated validate with adequate sensitivity, selectivity, stability, linearity. All of the bioanalytical work, including validation, was conducted (b) (4)

Acetylsalicylic Acid and Salicylic Acid:

- Calibration Curve:
  The standard curves were validated to the quantitation of acetylsalicylic acid nominal range of 0.0200 to 10.0 µg/mL and salicylic acid within a nominal range of 0.100 to 50.0 µg/mL. The average correlation coefficient from five standard curves was > 0.9978 for each analytes.

- Stability of Acetylsalicylic acid and of salicylic acid in human plasma:

Freeze-thaw	Room temperature	Ice	at 2°C-8°C	at -20°C	at -70°C

3	5 hour for Salicylc acid Negative bias for acetylsalicylic acid	5 hours	173hours	21 hours	359 days

Note: the supporting data for long term stability at -70 °C for 359 days was presented in the study report for Study PA32540-104, not in the validation reports.

- No apparent abnormalities associated with reinjection of sample extracts were observed.

- Selectivity:
  There were no significant matrix suppression effects that could compromise the sensitivity or accuracy of the assay.
  There is no effect on the quantitation of acetylsalicylic acid and salicylic acid in human plasma fortified with 50.0 µg/mL acetaminophen, 100 µg/mL naproxen, 50.0 µg/mL ibuprofen, and 20.0 µg/mL caffeine.

Omeprazole:

- Calibration Curve:
  The method is validated to the quantitation of omeprazole within a nominal range of 1.00 to 1000 ng/mL. The average correlation coefficient from four standard curves was > 0.9995.

- Stability of omeprazole in human plasma:

Freeze-thaw	Room temperature	at 4°C	At -20°C
6	26	126 hours	449 Days

- No apparent abnormalities associated with reinjection of sample extracts were observed.

- Selectivity:
  There is no effect on the quantitation of omeprazole in human plasma fortified to a concentration of approximately 50.0 µg/mL acetaminophen, 100 µg/mL naproxen, 50.0 µg/mL ibuprofen, 20.0 µg/mL caffeine, 10.0 µg/mL acetylsalicylic acid, and 50.0 µg/mL salicylic acid.

3 Appendix:

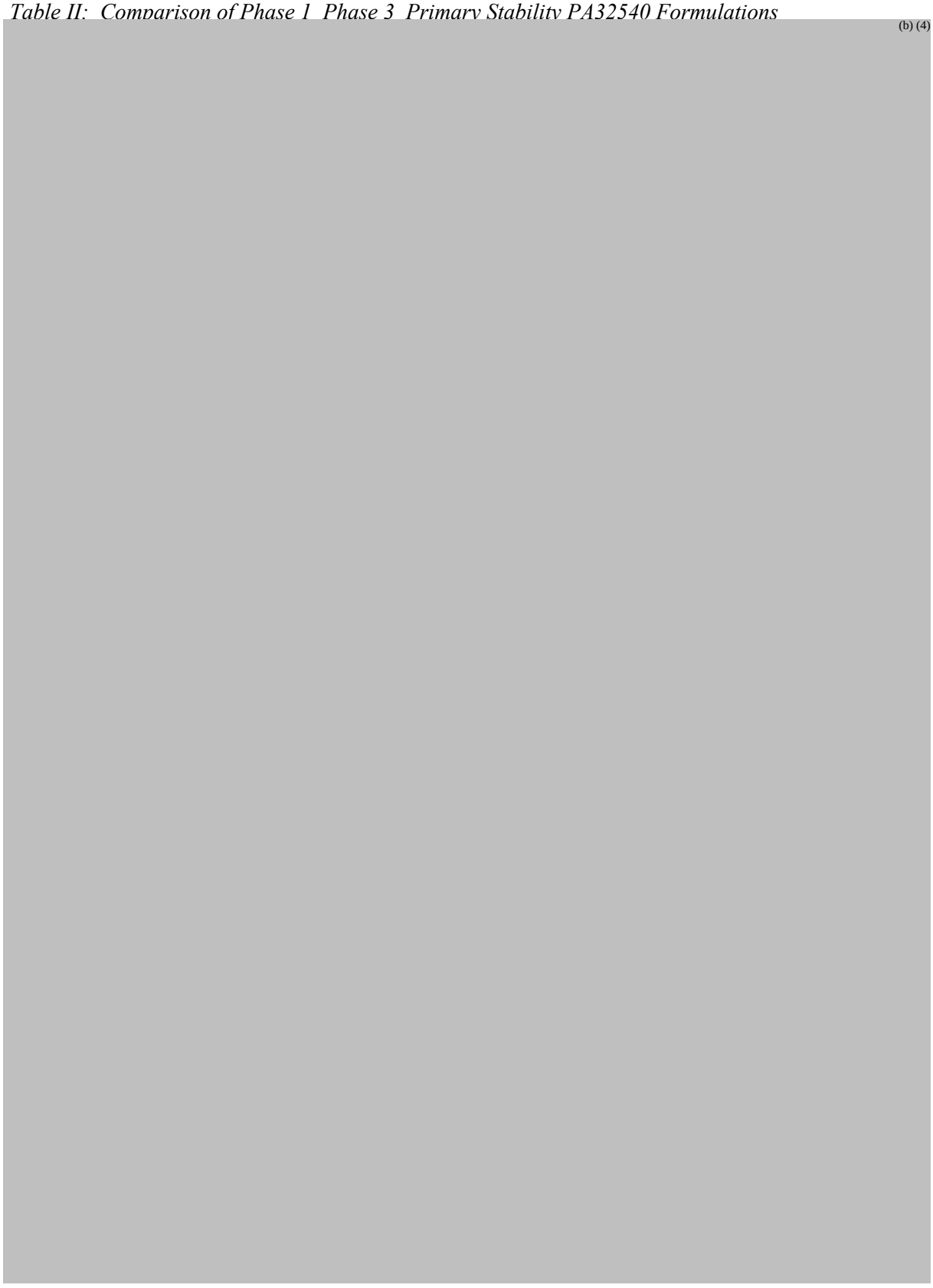
3.1 Formulation:

Table I: Comparison of Phase 1 and Primary Stability PA8140 Formulations

(b) (4)

Table II: Comparison of Phase 1, Phase 3, Primary Stability PA32540 Formulations

(b) (4)



3.2 OCP Filling Form:

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**205103**	**Brand Name**	
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**(aspirin/omeprazole) Tablets**
Medical Division	**DGIEP**	**Drug Class**	**NSAID/PPI**
OCP Reviewer	**Dilara Jappar**	**Indication(s)**	**secondary prevention of cardiovascular and cerebrovascular events in patients at risk for developing aspirin-associated gastric ulcers**
OCP Team Leader	**Sue-Chih Lee**	**Dosage Form**	**Delayed release Aspirin /Immediate release Omeprazole**
Pharmacometrics Reviewer		**Dosing Regimen**	**Once daily (QD)**
Date of Submission	**03-25-2013**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**12-26-2013**	**Sponsor**	**POZEN, Inc.**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**04/25/2014**	**Application Type**	**505 (b)(2)**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**3**	**3**	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Transporters characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**X**			
multiple dose:	**X**			
Patients- (non- C IBS)				
single dose:				
multiple dose:				
Other disease patients				
Dose proportionality – (Dose-Response)				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**2**		**Platelet aggregation studies**
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**	**1**	
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**	**1**	**Comparing omeprazole of PA32540 vs. PA8140**
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**2**	**2**	
replicate design; single / multi dose:	**X**	**2**	**2**	
Food-drug interaction studies	**X**	**1**	**1**	
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**12**	**10**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		There were minor formulation changes from the phase 3 clinical trials to the to-be-marketed products. However, according to the Biopharm reviewers (Dr. Banu Zolnik and Dr. Sandra Suarez Sharp), theses formulation changes were minor and do not required in human bioequivalence study.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted	X			

	bioavailability data satisfying the CFR requirements?				
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or		X		

	pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Requesting waiver for pediatric studies
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	X			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

The NDA is **Filelable** from clinical pharmacology perspective.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Dilara Jappar — May 06th, 2013
Reviewing Clinical Pharmacologist — Date

Sue-Chih Lee
Team Leader/Supervisor — Date

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

/s/

DILARA JAPPAR
04/18/2014

SUE CHIH H LEE
04/18/2014

Due to the submission dated 3/26/14, this review could not be completed according to the PDUFA V timeline.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**205103**	**Brand Name**	
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**(aspirin/omeprazole) Tablets**
Medical Division	**DGIEP**	**Drug Class**	**NSAID/PPI**
OCP Reviewer	**Dilara Jappar**	**Indication(s)**	**secondary prevention of cardiovascular and cerebrovascular events in patients at risk for developing aspirin-associated gastric ulcers**
OCP Team Leader	**Sue-Chih Lee**	**Dosage Form**	**Delayed release Aspirin /Immediate release Omeprazole**
Pharmacometrics Reviewer		**Dosing Regimen**	**Once daily (QD)**
Date of Submission	**03-25-2013**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**12-26-2013**	**Sponsor**	**POZEN, Inc.**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**01/24/2013**	**Application Type**	**505 (b)(2)**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Transporters characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**X**			
multiple dose:	**X**			
Patients- (non- C IBS)				
single dose:				
multiple dose:				
Other disease patients				
Dose proportionality – (Dose-Response)				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**2**		**Platelet aggregation studies**
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**2**		
replicate design; single / multi dose:	**X**	**2**		
Food-drug interaction studies	**X**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**8**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
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2	Has the applicant provided metabolism and drug-drug interaction information?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
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11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or		X		

	pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Requesting waiver for pediatric studies
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
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	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	X			

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Dilara Jappar — May 06th, 2013
Reviewing Clinical Pharmacologist — Date

Sue-Chih Lee
Team Leader/Supervisor — Date

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

/s/

DILARA JAPPAR
05/09/2013

SUE CHIH H LEE
05/10/2013