OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	50-813
Submission Date	March 23, 2007
Brand Name	TBD
Generic Name	Amoxicillin Pulsatile Release Tablets (APC-111)
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Applicant	MiddleBrook Pharmaceuticals
Relevant IND(s)	62,576
Submission Type; Code	Original NDA
Formulation; Strength	Film-coated, modified-release tablet; 775 mg amoxicillin (anhydrous)
Indication(s)	Treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes* in adolescents and adults

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

MiddleBrook Pharmaceuticals (formerly Advancis Pharmaceuticals) submitted a New Drug Application (NDA) under 505(b)(2) for APC-111, a once-daily modified-release multiparticulate tablet formulation of amoxicillin, 775 mg. The Sponsor is proposing a dosing regimen of 775 mg once daily x 10 days for the treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes* in adolescents and adults. Amoxicillin has been approved in the U.S. since 1974. Available marketed products of amoxicillin for oral administration include various strengths of immediate-release capsules, tablets, oral solutions and oral suspensions. Oral amoxicillin is approved for use in adult and pediatric patients for the treatment of ear, nose and throat infections due to Streptococcus spp., *S. pneumoniae*, Staphylcoccus spp. or *H. influenzae*, lower respiratory tract infections, skin/skin structure infections, genitourinary tract infections and acute uncomplicated gonorrhea. The recommended adult dose of immediate-release amoxicillin for ear, nose and throat infections is 250 mg q8h or 500 mg q12h for mild/moderate infections and 500 mg q8h or 875 mg q12h for severe infections. APC-111 represents a change in formulation (modified-release vs. immediate-release), dosing regimen (once daily vs. twice or three times daily), and indication (limited to tonsillitis and/or pharyngitis due to *S. pyogenes* only).

Several pilot PK studies were conducted using different modified-release prototypes under IND 62,576 in support of the development of the final formulation. The final formulation, APC-111, 775 mg tablet, is comprised of 45% immediate-release amoxicillin (Pulse 1), 30% of one delayed-release pellet (Pulse 2) and 25% of a second delayed-release pellet (Pulse 3). The Sponsor submitted the results of five clinical pharmacology studies in support of the NDA, including a bioavailability (BA) study comparing APC-111 to amoxicillin oral suspension (111.109), a drug interaction study evaluating the effect of a proton pump inhibitor on the BA of APC-111 (111.110), a food effect study (111.111), a comparative BA study comparing four different modified-release formulations (111.112), and a relative bioequivalence (BE) study comparing APC-111 manufactured at two different manufacturing sites (111.115). All of the studies were reviewed, except for Study 111.112, as the findings were not found to contribute any additional information.

Two Phase III clinical studies, 111.301 and 111.302, were conducted in support of the NDA. Study 111.301 failed to demonstrate non-inferiority of APC-111, 775 mg once daily x 7 days, to oral penicillin VK, 250 mg four times daily (QID) x 10 days, for the treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes*. The Sponsor identified the difference in treatment duration between the two groups as the cause of the non-inferiority finding. Subsequently, the Sponsor conducted a second Phase III study, 111.302, to evaluate APC-111, 775 mg once daily x 10 days, rather than 7 days, versus penicillin VK, 250 mg QID x 10 days. Study 111.302 demonstrated non-inferiority of APC-111 to penicillin VK for the treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes* in adults and adolescents. In addition to the difference in treatment durations, Study 111.301 and 111.302 also differed in the administration of APC-111 with regard to food. In 111.301 APC-111 was administred without regard to food, while in 111.302 patients were instructed to take the test treatment with food (within 1 hour of completing a meal).

1.1. Recommendation

The Clinical Pharmacology and Biopharmaceutics information provided by the Applicant is acceptable.

Changes to the Sponsor's proposed label (Appendix 4.1) should be forwarded to the Sponsor.

1.2. Phase IV Commitments

No Phase IV commitments are recommended

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

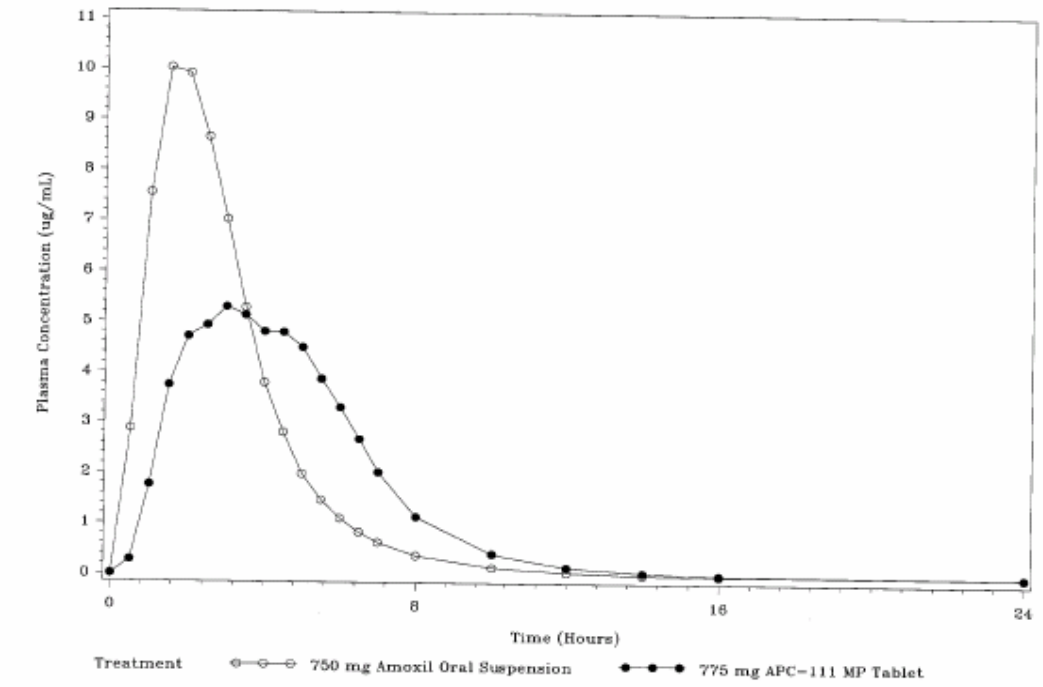
Amoxicillin PK parameters were compared following single oral doses of APC-111, 775 mg, and Amoxil® (amoxicillin) Suspension, 750 mg (Table 1.3-1). Both doses were administered with a low-calorie breakfast. The T_{max} following administration of APC-111 was significantly delayed compared to the suspension – 3.1 hours versus 1.8 hours. The dose-normalized Cmax was 40% lower for APC-111 versus amoxicillin suspension, while $AUC_{0-\infty}$ was 14% lower (90%CI 83.1 – 89.7). The elimination $T_{1/2}$ was 1.4 hours following APC-111 and 1.6 hours following amoxicillin suspension. The absolute time unbound amoxicillin concentrations remained above the target MIC of 0.06 µg/mL (T>MIC) was slightly longer for APC-111 than for amoxicillin suspension, 13.3 hours vs. 11.7 hours.

Table 1.3-1 Dose-Normalized PK Parameters Following Single Oral Doses of APC-111 (775 mg) and Amoxicillin Suspension (750 mg)

PK Parameter	APC-111 (A)	Amoxicillin Suspension (B)	Ratio (%) (A/B)	90% CI
T>MIC 0.06 µg/mL (total amoxicillin) (h)	13.6	12.1	112.3	107.0, 117.8
Dose-normalized $AUC_{0-\infty}$	0.038	0.044	86.33	83.1, 89.7
Dose-normalized AUC_{0-t}	0.037	0.044	85.9	82.8, 89.2
Dose-normalized Cmax	0.0084	0.014	60.5	57.1, 64.1

Note: AUC and C_{max} values were dose-normalized by dividing the geometric mean by the dose.

Figure 1.3-1 Mean Total Plasma Amoxicillin Concentration vs. Time Curves for Single Doses of 750 mg Amoxicillin Suspension and 775 mg APC-111.



The results of Study 111.109 demonstrated no accumulation of amoxicillin in healthy subjects following seven days of 775 mg APC-111 administration once daily with a low calorie breakfast. Mean PK parameter estimates were comparable between Day 1 and Day 7 of administration. Single and multiple-dose PK data are shown below in Table 1.3-2.

Table 1.3-2 Single and Multiple Dose PK of Amoxicillin Following 7 Days of APC-111, 775 mg Once Daily (Study 111.109)

	Total Amoxicillin				Unbound Amoxicillin[a]	
	AUC_{0-t} (µg•h/mL)	$T_{1/2}$ (hr)	Cmax (µg/mL)	Tmax (hr)	T>MIC[b] (hr)	T>MIC[b] (%)
Day 1 (Single-Dose)						
Mean	29.4	1.44	6.62	3.14	13.3	55.5
SD	5.28	0.25	1.05	1.38	2.71	11.3
Day 7 (Multiple-Dose)						
Mean	29.3	ND	6.57	3.05	13.4	56.0
SD	5.40	ND	1.10	1.26	2.70	11.2

[a] Based on protein-binding estimate of 18%.
[b] MIC_{90} for *S. pyogenes* (0.06 µg/mL)

Exposure-Response:

- The efficacy of β-lactam antibiotics, including amoxicillin, is correlated most closely with the PK/PD parameter T>MIC. The Sponsor has targeted a percent of the dosing interval above the MIC (%T>MIC) of 40% for APC-111, based on previous clinical and *in vitro* data demonstrating the efficacy of amoxicillin against respiratory pathogens at this value.
- A target MIC value of 0.06 µg/mL was identified by the Sponsor based on the MIC_{90} for *S. pyogenes* reported for amoxicillin in the literature. Of the 914 isolates of *S. pyogenes* identified in the two Phase III clinical trials conducted with APC-111, 905 isolates (99%) had baseline MIC values ≤ 0.06 µg/mL for amoxicillin.
- The Sponsor determined %T>MIC values for unbound amoxicillin plasma concentrations in four clinical PK studies in which APC-111 was administered to healthy volunteers (Table 1.3-3). Values were calculated using a protein binding estimate of 18%, based on previously published data.

Table 1.3-3 %T>MIC of Unbound Amoxicillin Plasma Concentrations in Healthy Volunteers

Conditions	Study	%T>MIC (0.06 µg/mL)		N
		Mean	Range	
Fasting	111	46.3	33.3 – 58.8	24
	112	46.3	37.7 – 56.5	23
Low-fat fed	109	55.5	43.7 – 92.7	20
	111	51.9	36.7 – 97.1	24
High-fat fed	110*	65.7	47.5 – 98.9	19
	111	62.4	41.7 – 99.3	24

*Without coadministration of lansoprazole

- There was no exposure data collected in the Phase III studies; as such, a relationship between amoxicillin exposure and clinical efficacy could not be determined.

Pharmacokinetics Summary:

Administration of APC-111 with a low-fat meal results in a 40% lower Cmax and 14% lower $AUC_{0-\infty}$ as compared to immediate-release amoxicillin suspension. The absolute time unbound amoxicillin concentrations remain above an MIC value of 0.06 μg/mL is approximately 13 hours following administration of APC-111 with a low-fat meal in healthy subjects. The elimination $T_{1/2}$ of amoxicillin is approximately 1.4 hours, similar to that of immediate release formulations. There is no accumulation of amoxicillin exposure following multiple doses of APC-111.

Absorption:

- Administration with food decreased the rate but not the extent of amoxicillin absorption from APC-111 (Study 111.111). The Cmax was 16% and 26% lower under low-fat and high-fat fed conditions, respectively, compared to fasted conditions, while AUC was unchanged. The $T_{1/2}$ of amoxicillin was unaffected by food. In general, T>MIC was prolonged by the administration of APC-111 with food, particularly a high fat meal. Mean unbound T>MIC (0.06 μg/mL) increased from 11.0 hours under fasting conditions to 12.2 hours with a low-fat meal and 14.6 hours with a high-fat meal.

Distribution:

- Previous studies have identified a protein binding rate of approximately 15 to 25% for amoxicillin. *In vivo* protein binding was not evaluated in any of the clinical PK studies submitted with this NDA.
- The apparent volume of distribution of amoxicillin is approximately 0.26 – 0.31 L/kg.

Metabolism:

- Amoxicillin is not appreciably metabolized.

Excretion:

- The urinary excretion of amoxicillin has previously been reported as 50 – 70% of the administered dose. The urinary excretion of amoxicillin following administration of APC-111 was not evaluated in any of the submitted PK studies.

Intrinsic Factors:

- Approximately 50 to 70% of amoxicillin is excreted unchanged in the urine. According to the product label for immediate-release amoxicillin, "patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe." The Sponsor is proposing a recommendation that APC-111 not be used to treat patients with severe renal impairment or patients on hemodialysis.

Extrinsic Factors:

- The administration of lansoprazole with APC-111 (under high-fat conditions) increased the Cmax of amoxicillin by approximately 35% and the $AUC_{0-\infty}$ by 18%. The mean T>MIC was not significantly affected by administration with lansoprazole.

List of Abbreviations

mITT	Modified intent-to-treat
PPb	Per-protocol bacteriological population
PPc	Per-protocol clinical population
TOC	Test-of-cure
LPT	Late post-therapy

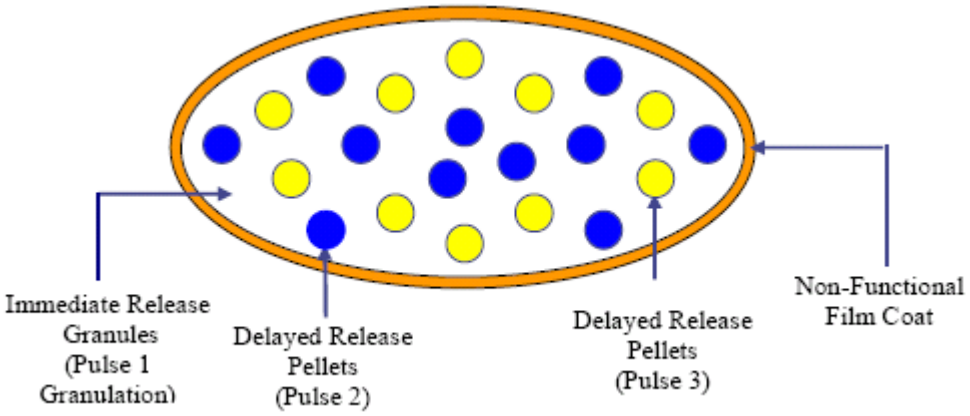
2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

APC-111 is a once-daily modified-release multiparticulate tablet formulation of amoxicillin, 775 mg. The tablet is a rapidly disintegrating formulation containing a mixture of three active components: an immediate-release granulation (45% of the dose) and two delayed-release pellets, Pulse 2 (30% of the dose) and Pulse 3 (25% of the dose). The tablet itself is designed to disintegrate rapidly in the stomach to release the three components. The immediate-release granule is formulated to dissolve rapidly. The remaining two intermediate components are designed to release amoxicillin in a different region of the intestinal tract subsequent to reaching the pH trigger for each of the respective film coats.

Figure 2.1.1-1 Schematic of APC-111 Tablet, 775 mg



2.1.2. What is the proposed mechanism of action and therapeutic indication?

Amoxicillin is a semisynthetic penicillin derivative that inhibits bacterial cell wall synthesis. APC-111 is a modified-release formulation of amoxicillin intended to provide a once-daily treatment alternative to currently approved penicillin and amoxicillin regimens for the treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes* in adults and adolescents.

2.1.1. What is the proposed dosage and route of administration?

The proposed dose of APC-111 is 775 mg (one tablet) orally once daily with food for 10 days.

2.2. General Clinical Pharmacology

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

Clinical Pharmacology Studies

The Sponsor submitted the results of five clinical pharmacology studies in support of the NDA, including a bioavailability study comparing APC-111 to amoxicillin oral suspension (111.109), a drug interaction study evaluating the effect of a proton pump inhibitor on the bioavailability of APC-111 (111.110), a food effect study (111.111) and a comparative bioavailability study comparing four different modified-release formulations (111.112). All of the clinical studies conducted with APC-111 in the final stages of development, including Studies 111.110, 111.111, 111.112 and the pivotal Phase III efficacy study, 111.302, utilized the same bulk batch of APC-111 manufactured at (b) (4) In bioequivalence Study 111.115, the (b) (4) batch of APC-111 was compared to a batch of APC-111 manufactured at (b) (4) the proposed commercial manufacturing facility.

Study 111.109 was an open-label, two period, sequential study in which 20 healthy males and females received a single dose of amoxicillin oral suspension, 750 mg, with a low-fat meal. Following a 7-day washout period, subjects received APC-111, 775 mg, once daily with a low-fat meal x 7 days. Dose-normalized amoxicillin PK parameters were compared between single doses of amoxicillin suspension and APC-111 in order to determine the relative bioavailability of APC-111. In addition, PK parameters on Day 1 and Day 7 of APC-111 administration were compared to evaluate potential accumulation of amoxicillin.

Study 111.110 was an open-label, two period, crossover study in which 20 healthy males and females received a single oral dose of APC-111, 775 mg, alone and following four days of treatment with lansoprazole 30 mg twice daily (BID). Lansoprazole was administered in the fasted state for 4 days; on the 5th day lansoprazole 30 mg was given in the fasted state, 30 minutes before a high fat breakfast and one hour prior to APC-111 dosing. Each dose of APC-111 was administered within 30 minutes of a high fat/high calorie meal. The periods were separated by a minimum 14-day washout period. The PK parameters of amoxicillin were compared between the two periods to characterize the effect of a proton pump inhibitor on the PK and bioavailability of APC-111 under fed conditions.

Study 111.111 was an open-label, 3-period, crossover study in which 24 healthy males and females received three single oral doses of APC-111, 775 mg, following an overnight fast (Treatment C), a low-calorie/low-fat meal (Treatment A) and a high-calorie/high-fat meal (Treatment B). Subjects were randomized to one of six treatment sequences. The periods were separated by a 7-day washout period. Amoxicillin PK parameters were compared between periods to characterize the effect of food (standard low-fat meal and high-fat meal) on the PK and bioavailability of APC-111.

Study 111.115 was an open-label, single-dose, two-way crossover study to establish the bioequivalence of APC-111, 775 mg, manufactured at two different manufacturing sites – (b) (4) . Twenty-six healthy males and females were enrolled in the study. APC-111 was administered under fasting conditions in both study periods. The periods were separated by a minimum 7-day washout period.

Phase III Studies

Two Phase III trials were conducted with APC-111, 111.301 and 111.302. Study 111.302 was conducted after Study 111.301 failed to demonstrate non-inferiority of APC-111 to the control treatment. Two key changes in the study methods in 111.302 were an increase in the duration of APC-111 treatment from 7 to 10 days and the administration of the test treatment with food (within 1 hour of completing a meal), as opposed to without regard to food:

Protocol Number	Study Population	Total N	Study Design	Treatments
111.301	Adolescent/ Adult Patients	513	Multi-center, double-blind, double-dummy, randomized, parallel group study to evaluate the safety and efficacy of 775 mg APC-111 orally once daily x 7 days compared to penicillin VK 250 mg orally 4 times daily x 10 days in the treatment of patients with tonsillitis and/or pharyngitis secondary to *S. pyogenes*.	APC-111 - 775 mg QD (without regard to food) x 7 days Pen VK - 250 mg QID x 10 days
111.302	Adolescent/ Adult Patients	618	Multi-center, double-blind, double-dummy, randomized, parallel group study to evaluate the safety and efficacy of 775 mg APC-111 orally once daily x 10 days compared to penicillin VK 250 mg orally 4 times daily x 10 days in the treatment of patients with tonsillitis and/or pharyngitis secondary to *S. pyogenes*.	APC-111 - 775 mg QD (with food) x 10 days Pen VK - 250 mg QID x 10 days

111.301

Study 111.301 was a double-blind, double-dummy, randomized, parallel-group, multicenter study to evaluate the safety and efficacy of 775 mg APC-111 orally once daily x 7 days compared to penicillin VK 250 mg orally 4 times daily x 10 days in the treatment of patients with tonsillitis and/or pharyngitis secondary to *S. pyogenes*. Study treatments were administered without regard to food. The study population included male and female outpatients ≥ 12 years of age with a clinical diagnosis of acute tonsillitis and/or pharyngitis defined by clinical signs and symptoms, as well as a positive rapid screening test for *S. pyogenes*.

The primary efficacy measure was satisfactory bacteriological outcome at the test-of-cure (TOC) visit (Days 14 – 18) in the per-protocol bacteriological (PPb) population (patients with a positive baseline throat swab culture for *S. pyogenes*, an evaluable throat swab culture at TOC and no major protocol deviations). Secondary efficacy measures included bacteriological and clinical outcomes at the TOC and late post-therapy (LPT) visits in the modified intent-to-treat (mITT) and per-protocol clinical (PPc) populations. The statistical analysis for the primary measure of efficacy was a non-inferiority test with a lower bound 95% CI of -10% for demonstrating non-inferiority of APC-111 to penicillin VK.

111.302

Study 111.302 was a double-blind, double-dummy, randomized, parallel-group, multicenter study to evaluate the safety and efficacy of 775 mg APC-111 orally once daily x 10 days compared to penicillin VK 250 mg orally 4 times daily x 10 days in the treatment of patients with tonsillitis and/or pharyngitis secondary to *S. pyogenes*. The test treatment, APC-111, was to be administered with food (within 1 hour of completing a meal). The study population included male and female outpatients ≥ 12 years of age with a clinical diagnosis of acute tonsillitis and/or

pharyngitis defined by clinical signs and symptoms, as well as a positive rapid screening test for *S. pyogenes*.

The primary efficacy measure was satisfactory bacteriological outcome at the TOC visit (Days 14 – 18) in the PPb and mITT co-primary populations. Secondary efficacy measures included bacteriological and clinical outcomes at the TOC and LPT visits in the mITT, PPb and PPc populations. The statistical analysis for the primary measure of efficacy was a non-inferiority test with a lower bound 95% CI of -10% for demonstrating non-inferiority of APC-111 to penicillin VK.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in the pivotal Phase III study was bacteriological outcome at the TOC visit (Days 14 – 18) in the PPb and mITT co-primary populations. Bacteriological outcomes included "satisfactory" (bacterial eradication or presumed eradication), "unsatisfactory" (bacterial persistence or presumed persistence) or "indeterminate" (bacterial response indeterminate). The TOC visit was scheduled between Days 14 and 18 of the study. At the time of early withdrawal or at the TOC and LPT visits infection-related signs and symptoms were recorded and a clinical response was determined. In addition, a throat swab was obtained for culture to confirm the presence or absence of *S. pyogenes*. The non-inferiority margin was prespecified at 10% for the primary efficacy endpoint. Secondary efficacy measures included bacteriological and clinical outcomes at the TOC and LPT visits in the mITT, PPb and PPc populations.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

All of the plasma samples from the clinical pharmacology studies were analyzed for amoxicillin concentration by a validated HLPC/MS/MS method by **(b) (4)** No active or inactive metabolites were assessed, nor were other biological fluids other than plasma analyzed.

2.2.4. Exposure-Response

2.2.4.1. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for efficacy?

The efficacy of β-lactam antibiotics, including amoxicillin, correlates most closely with the PK/PD parameter T>MIC. The Sponsor has targeted a %T>MIC of 40% of the dosing interval for APC-111 based on previous clinical and *in vitro* data demonstrating efficacy of amoxicillin against respiratory pathogens at this target value. A target MIC value of 0.06 μg/mL was identified by the Sponsor based on the MIC_{90} for *S. pyogenes* reported for amoxicillin in the literature.

The Sponsor calculated the %T>MIC for unbound amoxicillin plasma concentrations in four clinical PK studies in which APC-111 was administered to healthy volunteers. Estimates of unbound amoxicillin were determined using a protein binding estimate of 18%, based on previously published data. Mean unbound %T>MIC estimates ranged from 46.3% to 65.7% across studies. The %T>MIC improved when APC-111 was administered with food, particularly with a high-fat meal. The mean (range) unbound %T>MIC estimates for an MIC value of 0.06

μg/mL were 46% (33 – 59%) under fasting conditions, 52 to 56% (37 – 97%) with a low-fat meal, and 62 to 66% (42 – 99%) with a high-fat meal.

Of the 914 isolates of *S. pyogenes* identified in the two Phase III clinical trials conducted with APC-111, 905 isolates (99%) had baseline MIC values ≤ 0.06 μg/mL for amoxicillin. Seven of the remaining isolates had baseline MIC values of 0.12 or 0.5 μg/mL and one isolate had an MIC value of 1 μg/mL. Five of the 9 patients with a baseline isolate MIC >0.06 μg/mL were randomized to treatment with APC-111 (all in Study 111.302). All five of the patients had bacterial eradication and clinical cure at the TOC visit.

There was no exposure data collected in the Phase III studies; as such, a relationship between amoxicillin exposure and bacterial eradication or clinical cure could not be determined.

2.2.4.2. Summary of Efficacy

Two Phase III trials were conducted with APC-111. Study 111.302 was conducted after Study 111.301 failed to demonstrate non-inferiority of APC-111 to the control treatment. Differences in the design of Study 111.302 included an increase in the duration of APC-111 treatment from 7 to 10 days, as well as the administration of APC-111 with food (vs. without regard to food). Both studies were multi-center, randomized, double-blind, double-dummy, parallel group controlled studies comparing APC-111 to penicillin VK. Both studies enrolled adults and adolescents ≥12 years of age with acute tonsillitis and/or pharyngitis due to *S. pyogenes*.

The results of the primary efficacy analysis in 111.301, bacteriological outcome at the TOC visit in the PPb population, failed to demonstrate non-inferiority of APC-111 to penicillin VK (Table 2.2.3.2-1). Several of the secondary outcome measures, including bacteriological outcome in the mITT population at TOC and bacteriological outcome in the PPc population at TOC, also had an upper bound 95% confidence limit less than zero.

Table 2.2.3.2-1 Bacteriological Outcome at TOC visit in PPb Population (Study 111.301)[a]

Bacteriological outcome / response	Number of patients (%)		Difference	95% CI[b]
	APC -111	Pen VK		
N	171	182		
Satisfactory	131 (76.6)	161 (88.5)	-11.9%	(-19.7, -4.0)
Eradication	131 (76.6)	161 (88.5)		
Unsatisfactory	40 (23.4)	21 (11.5)		
Persistence	37 (21.6)	20 (11.0)		
Presumed Persistence[c]	3 (1.8)	1 (0.5)		

[a] The PPb population consisted of all patients with a positive baseline visit throat swab for *S. pyogenes*, an evaluable throat swab at the TOC visit, and no major protocol deviations, as well as clinical failures who withdrew early from the study and started a new antimicrobial for the treatment of tonsillitis and/or pharyngitis.
[b] Two-sided 95% confidence interval.
[c] For the PPb population, presumed persistence included only those patients who started a new antimicrobial for the treatment of tonsillitis and/or pharyngitis.

Study 111.302 demonstrated non-inferiority of APC-111, 775 mg QD x 10 days, to penicillin VK 250 mg QID x 10 days for the primary efficacy endpoint of bacteriological outcome in the co-primary PPb and mITT populations at TOC. The lower bound of the 95% confidence interval was greater than the prespecified limit of – 10% (Table 2.2.3.2-2). For the co-primary efficacy population, no treatment-

by-region interactions were demonstrated when region was used as a stratification factor. Bacteriological outcome at TOC was also evaluated by subgroups based on gender, age, race, weight and infection characteristics. In general, the rates of bacteriological response across demographic groups and infection characteristics were similar to one another and consistent with the overall results. Analyses of the secondary efficacy endpoints were all consistent with the primary efficacy outcome.

Table 2.2.3.2-2 Bacteriological Outcome at TOC visit in PPb and mITT Co-Primary Populations (Study 111.302)

	Number of subjects (%)			
	PPb[a]		mITT [b][b]	
Bacteriological outcome / response	**APC-111**	**Pen VK**	**APC-111**	**Pen VK**
N	233	229	256	264
Satisfactory	198 (85.0)	191 (83.4)	211 (82.4)	207 (78.4)
Eradication	198 (85.0)	191 (83.4)	204 (79.7)	206 (78.0)
Presumed Eradication			7 (2.7)	1 (0.4)
Unsatisfactory	35 (15.0)	38 (16.6)	45 (17.6)	57 (21.6)
Persistence	30 (12.9)	32 (14.0)	30 (11.7)	37 (14.0)
Presumed Persistence	5 (2.1)	6 (2.6)	7 (2.7)	8 (3.0)
Indeterminate	-	-	8 (3.1)	12 (4.5)
Comparison				
Difference	1.6		4.0	
95% CI	-5.1, 8.2		-2.8, 10.8	

[a] The PPb population consisted of all subjects with a positive baseline visit throat swab for *S. pyogenes*, an evaluable throat swab at the TOC visit, and no major protocol violations, as well as clinical failures who withdrew early from the study and started a new antimicrobial for the treatment of tonsillitis and/or pharyngitis.
[b] The mITT population consisted of all subjects with a positive baseline visit throat swab for *S. pyogenes*, who received at least one dose of study medication and who had at least one post-baseline clinical safety assessment. The mITT [b] principal analysis included subjects with an indeterminate bacteriological response.

2.2.4.3. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety?

There was no PK data collected in the Phase III clinical trials. As such, a relationship between drug exposure and safety could not be assessed for APC-111.

Adverse Events

In Study 111.302 the most frequent treatment-emergent adverse events (AEs) in APC-111 and penicillin VK-treated patients, respectively, were as follows: streptococcal pharyngitis (10.6% vs. 10.1%), upper respiratory infection (3.6% vs. 5.6%), vulvovaginal mycotic infection (2.6% vs. 2.6%), diarrhea (3.6% vs. 2.9%), nausea (2.6% vs. 2.6%), headache (2.6% vs. 5.2%) and vomiting (1.7% vs. 2.9%). Two drug hypersensitivity reactions were reported, one in each treatment group. The mean duration of active study medication in the APC-111 treatment group was 9.7 days (median 10 days) and the mean duration of active study medication in the penicillin treatment group was 10 days (median 10 days).

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The primary concern regarding once-daily dosing of amoxicillin is the potential for loss of therapeutic efficacy if the optimal T>MIC of the target pathogen is not maintained. The Sponsor's target %T>MIC of 40% of the dosing interval is appropriate for the use of amoxicillin for *S. pyogenes*. Plasma concentration data from clinical PK studies involving single-dose administration of APC-111 to healthy volunteers (153 total doses), reveal mean unbound %T>MIC estimates of 46.3 – 65.7%. The %T>MIC estimates improved by 6-10% when APC-111 was administered with a low-fat meal (vs. fasting) and 16-20% when administered with a high-fat meal (vs. fasting). In addition to increasing the treatment duration from 7 to 10 days in Study 111.302, APC-111 was also administered with food, as opposed to without regard to meals. The Sponsor has proposed that APC-111 be administered with food.

2.2.5. What are the PK characteristics of APC-111?

Immediate release formulations of amoxicillin are absorbed with a bioavailability of approximately 89% up to a single oral dose of 2 g. Peak plasma concentrations occur around 1 to 2 hours after administration. Amoxicillin diffuses into most body tissues and fluids, with the exception of the central nervous system in the absence of inflamed meninges. It is approximately 15 – 25% protein bound in the serum. Amoxicillin is primary excreted unchanged in the urine. The elimination $T_{1/2}$ is around one hour.

The PK parameters of amoxicillin were evaluated following single and multiple (7 days) daily dosing of APC-111, 775 mg with a low-fat breakfast in healthy volunteers. There was no accumulation of amoxicillin in plasma after once-daily dosing of APC-111 for 7 days under fed conditions. There was a delay in the time to peak amoxicillin concentrations following APC-111; the T_{max} occurred at 3.1 hours post-dose versus 1.8 hours following administration of amoxicillin suspension (Figure 2.2.5-1). The dose-normalized Cmax was 40% lower for APC-111 versus amoxicillin suspension, while $AUC_{0-\infty}$ was 14% lower (90% CI 83.1 – 89.7). The dose-normalized $AUC_{0-\infty}$ for the oral suspension was similar to that previously reported for the 400 mg chewable tablet and the 875 mg tablet (Amoxil® product label). The elimination $T_{1/2}$ of amoxicillin was approximately 1.5 hours for both APC-111 and the oral suspension. This is similar to the $T_{1/2}$ reported previously for other immediate-release formulations (1 to 2 hours).

Table 2.2.5-1 Single Dose PK Parameters of Total Amoxicillin Following Single Doses of 750 mg Amoxil® Oral Suspension (Treatment A) and 775 mg APC-111 (Treatment B)

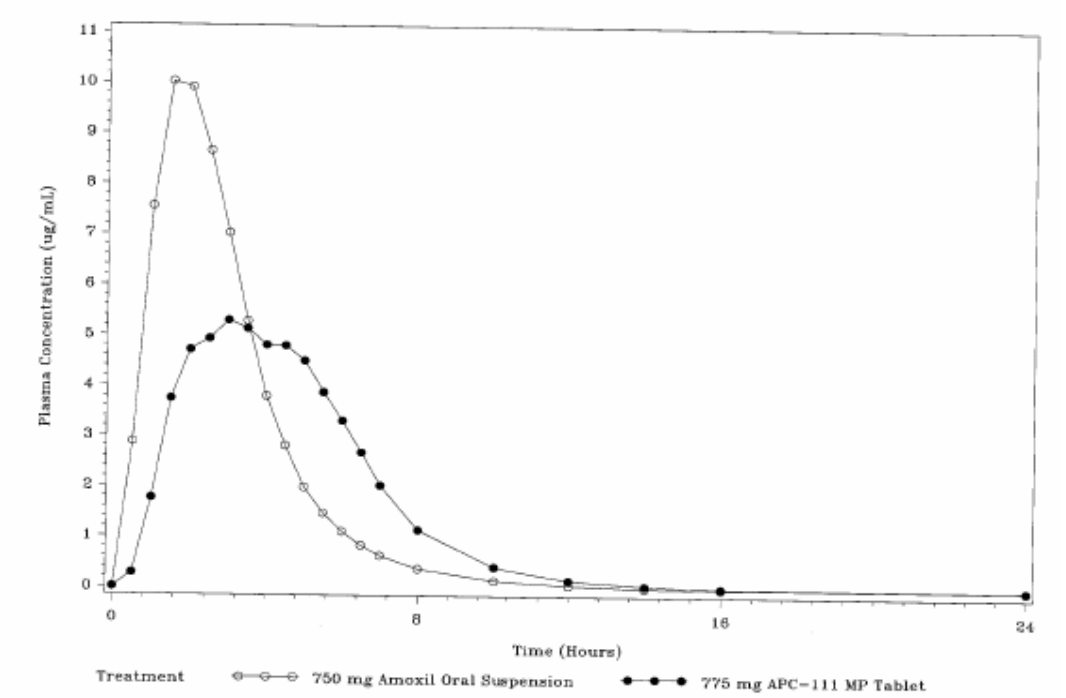
	AUC(0-t) (ug.hr/mL)	AUC(0-inf) (ug.hr/mL)	Kel (1/hr)	T1/2 (hr)	Cmax (ug/mL)	Cmin (ug/mL)	Tmax (hr)	T>MIC (hr)	% T>MIC
Treatment: (A) 750 mg Amoxil Oral Suspension									
N:	20	20	20	20	20	20	20	20	20
Mean:	33.10	33.28	0.4346	1.63	10.5700	0.0000	1.75	12.16	50.67
Median:	33.10	33.32	0.4374	1.58	10.7500	0.0000	1.54	11.91	49.62
SD:	5.78	5.77	0.0660	0.27	1.4801	0.0000	0.38	1.37	5.69
Min:	25.04	25.21	0.2883	1.20	8.0800	0.0000	1.00	9.34	38.92
Max:	45.36	45.60	0.5797	2.40	13.0000	0.0000	2.50	14.86	61.93
%CV:	17	17	15	16	14	.	22	11	11
GM:	32.64	32.81	0.4297	1.61	10.4701	.	1.71	12.09	50.36
Treatment: (B) 775 mg APC-111 MP Tablet									
N:	20	19	19	19	20	20	20	20	20
Mean:	29.40	29.79	0.4946	1.44	6.6230	0.0000	3.14	13.80	57.49
Median:	28.55	29.05	0.5006	1.38	6.5700	0.0000	2.75	12.68	52.82
SD:	5.28	5.35	0.0885	0.25	1.0466	0.0000	1.38	2.87	11.96
Min:	22.48	22.62	0.3772	1.02	4.5300	0.0000	1.50	10.78	44.91
Max:	42.91	43.11	0.6790	1.84	8.7000	0.0000	5.50	23.36	97.35
%CV:	18	18	18	17	16	.	44	21	21
GM:	28.98	29.37	0.4873	1.42	6.5408	.	2.86	13.57	56.53

Geometric Mean (GM)

The presence of food appears to affect the rate of absorption of one or more components of the tablet, resulting in a delay in Tmax and a blunted peak plasma concentration, but with no effect on the elimination $T_{1/2}$ (Section 2.5.3). In general, T>MIC is prolonged by the administration of APC-111 with food, particularly a high fat meal. Mean T>MIC (0.06 µg/mL) for total amoxicillin increased from 11.5 hours under fasting conditions to 12.7 hours with a low-fat meal and 15.1 hours with a high-fat meal.

The protein-binding of amoxicillin was not evaluated in any of the clinical studies of APC-111. However, unbound plasma concentrations were determined based on a protein-binding estimate of 18%. The mean time unbound amoxicillin concentrations remained above the target MIC of 0.06 µg/mL was 13.3 hours (range 10.5 – 22.2 hours) following administration of APC-111 with a low-fat meal (Study 111.109).

Figure 2.2.5-1 Mean (Total) Plasma Amoxicillin Concentration vs. Time Curves for Single Doses of 750 Amoxicillin Suspension and 775 mg APC-111.



2.3. Intrinsic Factors

2.3.1. What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Approximately 50 to 70% of amoxicillin is excreted unchanged in the urine. The product label for immediate release amoxicillin (Amoxil®) contains the following recommendation:

> *Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of < 30 mL/minute should not receive the 875-mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on the severity of the infection.*

The effect of renal impairment on the PK of amoxicillin following administration of APC-111 has not been evaluated. The Sponsor is proposing a recommendation that APC-111 not be used to treat patients with severe renal impairment or patients on hemodialysis.

In Phase III study 111.302 the primary efficacy outcome, bacteriological outcome at TOC, was evaluated by demographic subgroup, including gender, age, race, weight and infection characteristics. In general, the rate of satisfactory bacteriological response across demographic groups and infection characteristics was consistent with the overall results. The response rate for APC-111 was higher than penicillin in patients 12 to < 19 years old (85.1% vs. 78.7%) and lower than penicillin in 30 to < 40

year olds (77.8% vs. 82.5%); however, the numbers in each age group are too small to make any conclusions regarding differences in efficacy based on age.

2.4. Extrinsic Factors

Probenecid decreases the renal tubular secretion of amoxicillin. Therefore, concurrent use of probenecid and amoxicillin may result in increased levels of amoxicillin. APC-111 has not been studied in combination with probenecid.

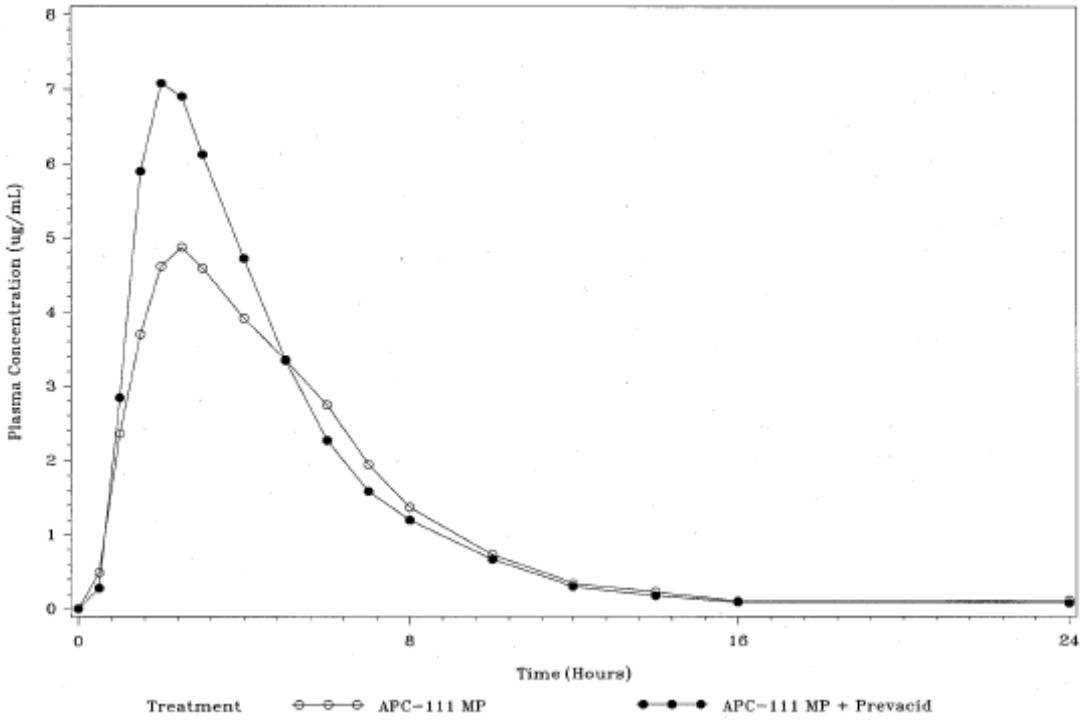
Following administration of APC-111 after 4 days of lansoprazole therapy, amoxicillin Cmax increased by approximately 33% relative to APC-111 alone (Table 2.4-1). Amoxicillin $AUC_{0-\infty}$ was more modestly affected (18% increase). The Tmax and elimination $T_{1/2}$ of amoxicillin were unaffected by lansoprazole, while T>MIC was slightly lower. The T>MIC estimate for unbound amoxicillin, using a protein binding estimate of 18%, was 15.3 hours for APC-111 alone versus 14.4 hours for APC-111 + lansoprazole.

Table 2.4-1 Total Amoxicillin PK Parameter Values (Geometric Least-Square Means [LSM] and LSM Ratios)

PK Parameter	Treatment B (N=18)	Treatment A (N=18)	Ratio (%) (B/A)	90% Confidence Interval
% T>MIC	61.3086	63.7139	96.22	91.49, 101.21
T>MIC	14.7141	15.2913	96.22	91.49, 101.21
AUC(0-inf)	32.6687	27.6656	118.08	113.74, 122.59
AUC(0-t)	32.3252	28.1501	114.83	109.60, 120.31
Cmax	8.2339	6.1738	133.37	118.52, 150.07

Treatment A: APC-111 MP Tablet
Treatment B: APC-111 MP Tablet + Previcid
For AUC(0-inf), N = 16 for Treatment A and N = 17 for Treatment B

Figure 2.4-1 Mean Plasma Amoxicillin Concentration vs. Time Curves for APC-111 Alone and APC-111 + Lansoprazole



2.5. General Biopharmaceutics

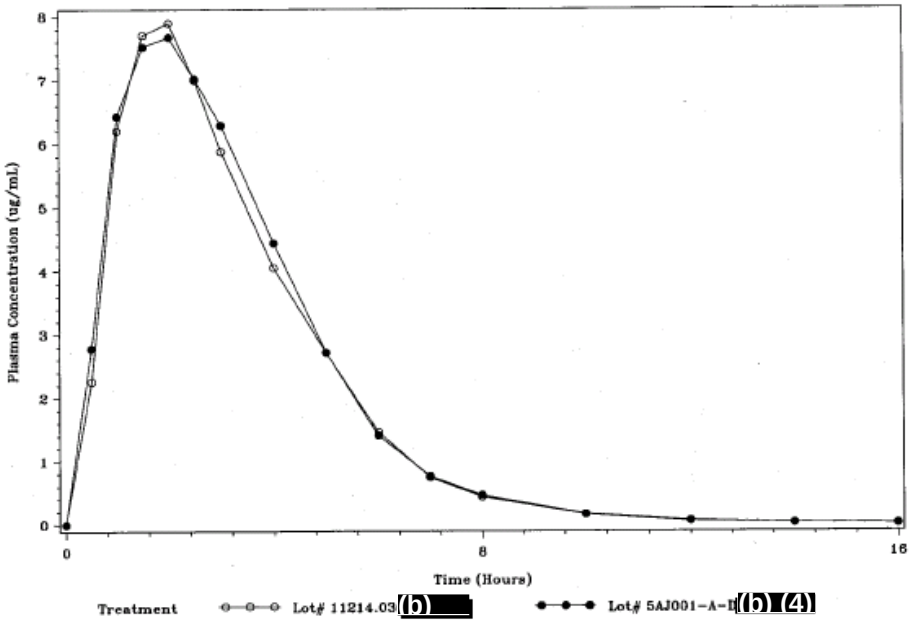
2.5.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not applicable to this modified-release product.

2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The formulation of APC-111 used in the clinical pharmacology studies and the pivitol Phase III clinical trial is the same as that proposed for final marketing. All of the clinical studies conducted with APC-111 in the final stages of development, including clinical PK studies 111.110, 111.111 and 111.112, and the pivotal Phase III study utilized the same bulk batch of product manufactured at (b) (4) The Sponsor proposes to manufacture commercial APC-111 at (b) (4) Study 111.115 established bioequivalence of the proposed to-be-marketed formulation of APC-111 manufactured at (b) (4) to the drug product manufactured at (b) (4) (Figure 2.5.2-1). The geometric least-square mean (LSM) ratios for AUC_{0-t}, $AUC_{0-\infty}$ and Cmax were 1.04, 1.05 and 1.00, respectively. The 90% CIs for all ratios fell within the range of 80% to 125%.

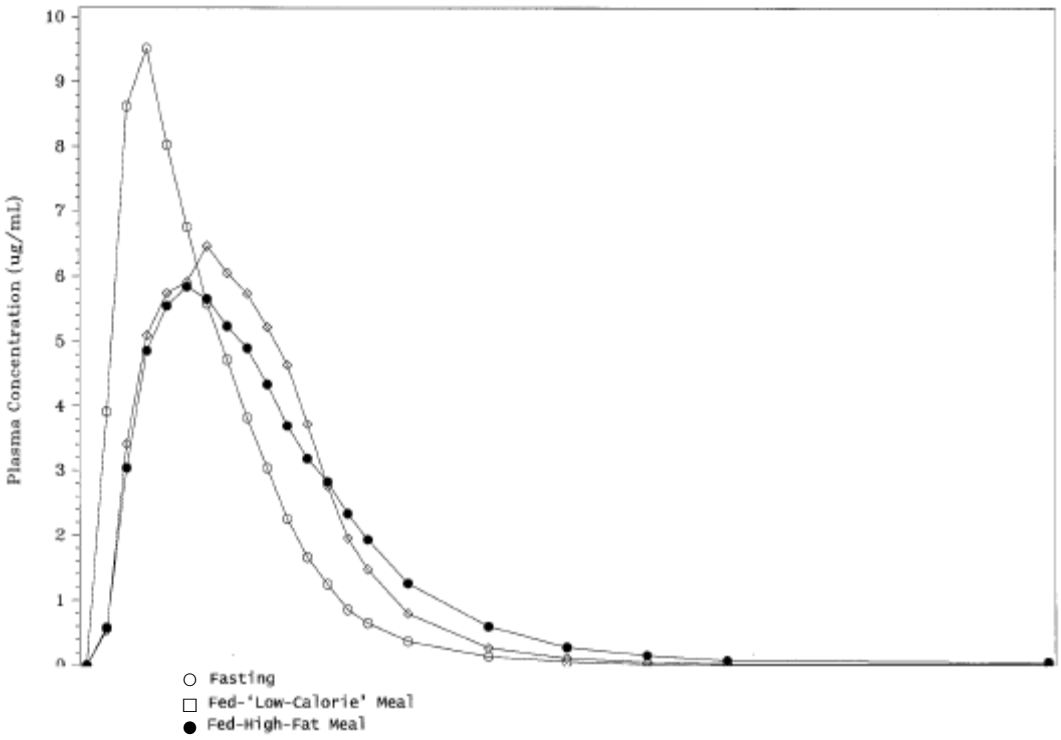
Figure 2.5.2-1 Mean (Total) Plasma Amoxicillin Concentration vs. Time Plots for APC-111 Manufactured at Two Different Sites (Study 111.115)



2.5.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Study 111.111 was a 3-way crossover study to evaluate the effect of a standard low-fat meal, a high-fat meal, or fasting conditions on the bioavailability and PK of APC-111. Administration of APC-111 with a low-fat meal or a high-fat meal did not affect overall amoxicillin exposure (AUC), while Cmax decreased by 16% and 26%, respectively, relative to administration in the fasted state (Figure 2.5.3-1). The presence of food appears to affect the rate of absorption of one or more components of the tablet, resulting in a delay in Tmax and a blunted peak plasma concentration following administration with food, with the magnitude of the effect related to the fat content of the meal. The elimination $T_{1/2}$ was not affected by food. However, food did prolonged the T>MIC of unbound amoxicillin. Based on a protein binding estimate of 18%, mean (range) T>MIC values for unbound amoxicillin were 11.0 (8.0 – 14.1) hours, 12.2 (8.8 – 23.3) hours and 14.6 (10.0 – 23.8) hours under fasted, low-fat fed and high-fat fed conditions, respectively. Consistent with the directions for administration of APC-111 in clinical study 111.302, the Sponsor has recommended that APC-111 be administered with food.

Figure 2.5.3-1 Mean (Total) Plasma Amoxicillin Concentration vs. Time Plots Under Fed and Fasted Conditions (Study 111.111)



2.5.4. When would a fed BE study be appropriate and was one conducted?

Study 111.115 evaluated the BE of APC-111 tablets manufactured at two different manufacturing sites under fasted conditions. A fed BE study was not conducted.

2.5.5. How do dissolution conditions and specifications ensure in vivo *performance and quality of the product?*

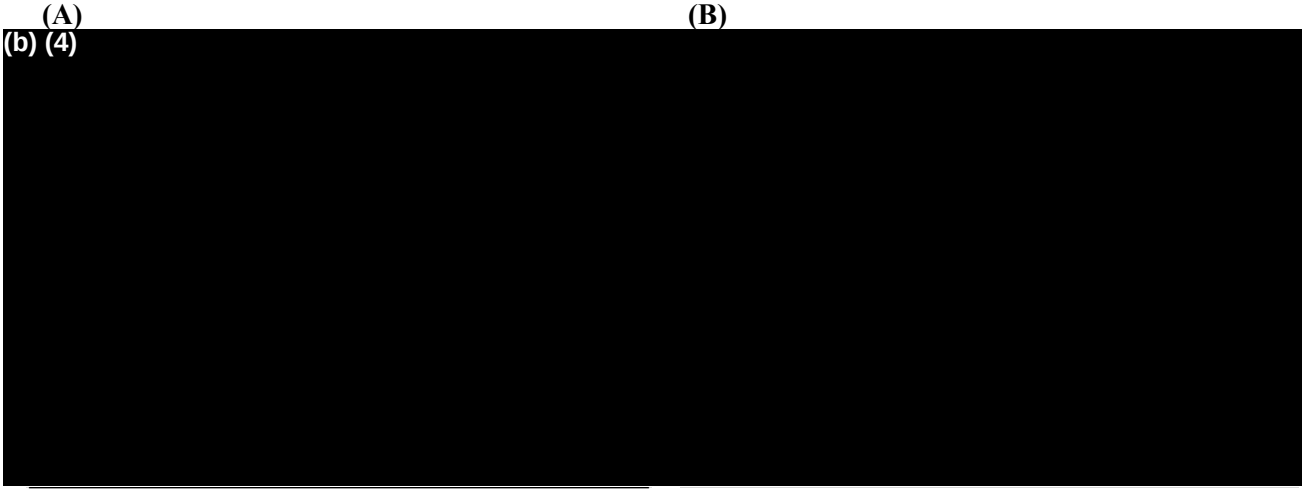
The delayed-release components of the formulation, **(b) (4)** The *in vitro* dissolution method employs USP Apparatus II (paddle) in 900 mL of 50 mM phosphate buffer with no surfactants (Table 2.5.5-1). **(b) (4)** The change in medium pH is designed to simulate the transit of the drug through the gastrointestinal tract. The proposed dissolution specifications are under review by ONDQA (see NDA review by Dr. Shrikant Pagay for final specifications).

The dissolution test method has been demonstrated to be **(b) (4)** The method was also applied to correlate the *in vitro* drug release with the *in vivo* performance of APC-111. The dissolution profiles for tablets manufactured at **(b) (4)** indicate that the amoxicillin release profile is consistent across batches at both manufacturing sites (Figure 2.5.5-1).

Table 2.5.5-1 Proposed *In Vitro* Dissolution Method and Specification for APC-111

Apparatus	USP Dissolution Apparatus II (Paddle)
Rotation Speed	100 RPM
Temperature	37.0° C ± 0.5° C
Medium	900 mL 50 mM Phosphate Buffer with changing pH: (b) (4)
No. of Test Unit	6 unless otherwise specified
Sampling Time	0.25, 0.5, 1.0, 2.0, 2.25, 2.5, 3.0, 4.0, 4.25, 4.5, 5.0 and 6.0 hrs
Filter	10 µm full flow (sampling), 35 µm full flow (evacuation)
Sample Volume	1.5 mL
Analytical Method	HPLC with UV detection at (b) nm
Specifications	(b) (4) at 120 minutes (b) (4) at 240 minutes NLT (b) at 360 minutes

Figure 2.5.5-1 Mean Drug Release Profiles for Multiple Batches of APC-111 Tablets Manufactured at (b) (4)



2.5.6. If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable.

2.5.7. If the NDA is for a modified release formulation of an approved immediate release product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated?

The active control product, penicillin VK, was blinded by encapsulation. The overencapsulated tablet met all USP release requirements for penicillin VK, including the dissolution specification.

2.5.9. What other significant, unresolved issues related to in vitro *dissolution or* in vivo *BA or BE need to be addressed?*

The Sponsor submitted a report to establish an *In Vitro*/*In Vivo* Correlation (IVIVC) for APC-111. Please refer to the ONDQA review of the NDA by Dr. Shrikant Pagay for further details.

2.6. Analytical Section

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Quantitation of amoxicillin in plasma was performed via a validated HPLC assay with MS/MS detection developed and validated by [redacted]

2.6.2. Which metabolites have been selected for analysis and why?

There are no metabolites to be quantitated.

2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total amoxicillin was measured in the clinical pharmacology studies. Protein binding was not assessed in any of the studies. The Sponsor used a protein binding estimate of 18% to determine the time unbound concentrations of amoxicillin remain above the target MIC.

2.6.4. What bioanalytical methods are used to assess concentrations?

A validated LC/MS/MS assay was developed by (b) (4) [redacted] for the analysis of amoxicillin in plasma for the clinical pharmacology studies.

2.6.4.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The calibration curve ranged from 0.050 to 25.0 µg/mL in plasma. Each calibration curve was calculated using a linear weighted ($1/x^2$) least-squares regression algorithm.

2.6.4.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The lower and upper limits of quantification for amoxicillin in plasma were 0.0500 µg/mL and 25.0 µg/mL, respectively.

2.6.4.3. What are the accuracy, precision, and selectivity at these limits?

The assay performance for the quantitation of amoxicillin in plasma in the clinical pharmacology studies is shown below:

Table 2.6.4.3-1 Summary of In-Study Assay Performance for Analysis of Amoxicillin in Human Plasma from Clinical Studies of APC-111

Clinical Study	**Quality Control Nominal Conc. (ng/mL)**	**Overall Inter-Assay Accuracy (%Bias)**	**Overall Inter-Assay Precision (%CV)**
111.109	150 1000 6000 15000 Calibration Standards[a]	0.64 (n=41) 1.19 (n=41) -0.071 (n=41) -2.89 (n=41) -1.25 to 1.71 (n=24)	5.20 (n=41) 5.21 (n=41) 4.73 (n=41) 5.07 (n=41) 3.30 to 5.92 (n=24)
111.110	150 1000 6000 15000 Calibration Standards	3.76 (n=20) 3.54 (n=20) 2.50 (n=20) 0.26 (n=20) -3.58 to 5.84 (n=8)	6.07 (n=20) 3.28 (n=20) 2.57 (n=20) 2.23 (n=20) 1.52 to 3.98 (n=8)
111.111	150 1000 6000 15000 Calibration Standards	1.72 (n=55) 1.92 (n=56) -1.11 (n=56) -1.21 (n=56) -3.16 to 4.11 (n=22)	3.49 (n=55) 11.4 (n=56) 5.04 (n=56) 9.11 (n=56) 2.94 to 4.55 (n=22)
111.112	150 1000 6000 15000 Calibration Standards	2.07 (n=39) 2.27 (n=39) 0.40 (n=39) -4.20 (n=39) -6.14 to 2.45 (n=26)	5.38 (n=39) 5.18 (n=39) 4.57 (n=39) 3.59 (n=39) 2.87 to 6.81 (n=26)

111.115	150 1000 6000 15000 Calibration Standards	-0.60 (n=16) 2.49 (n=16) -0.58 (n=16) 2.31 (n=16) -1.96 to 1.23 (n=8)	2.33 (n=16) 2.18 (n=16) 1.91 (n=16) 2.13 (n=16) 0.81 to 5.86 (n=8)

[a] Validated linear range = 50 to 25,000 ng/mL

2.6.4.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

The stability of amoxicillin in plasma with EDTA was established at - 80ºC for 183 days.

2.6.4.5. What is the QC sample plan?

Quality control samples (QCs) were prepared at four concentration levels in support of amoxicillin quantitative analyses: 0.150 µg/mL, 1.00 µg/mL, 6.00 µg/mL and 15.0 µg/mL. QCs were prepared in plasma and were assayed with unknown clinical samples during daily sample analysis.

3. LABELING RECOMMENDATIONS

See Appendix 4.1 for the proposed product label with reviewer annotations.

Appendix 4.1 Proposed Label with Reviewer Annotation

[redacted]

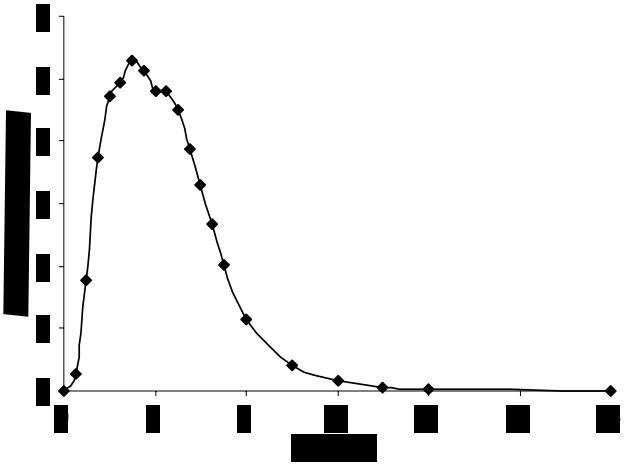
[redacted]

(b) (4)

[redacted]

[redacted] (b) (4) [redacted] (b) (4) [redacted]

(b) (4)



(b) (4)

(b) (4) [redacted]

[redacted] was non-mutagenic [redacted]

[redacted]

[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

[redacted] (b) (4) [redacted]

(b) (4)

Appendix 4.1 Individual Study Reviews

Study 111.109

A Single Center, Open-Label, Non-Randomized, 2 Period Study to Evaluate the Single and Multi Dose Pharmacokinetics of APC-111 MP Tablet, 775 mg, and the Single Dose Pharmacokinetics of Amoxil® Oral Suspension, 750 mg in the Fed State.

Study Dates: December 5 – 18, 2004

Study Sites: (b) (4) [redacted]

Objective:

The primary objective of this study was to compare the pharmacokinetics (PK) of 775 mg APC-111 administered for 7 days to the single dose PK of 775 mg APC-111 under fed conditions. The secondary objectives were to compare the single dose PK of 775 mg APC-111 and 750 mg Amoxil® Oral Suspension under fed conditions and to determine the safety and tolerability of APC-111 in healthy subjects.

Methods:

Study Design

Study 111.109 was a single center, open-label, two period, sequential study. Twenty healthy males and females were enrolled in order to obtain data from at least16 subjects. Each subject received a single dose of Amoxil® Oral Suspension 750 mg under fed conditions (Period 1) and seven daily doses of APC-111 775 mg under fed conditions (Period 2). The periods were separated by a minimum 7-day washout period. The first dose administered in Period 1 and the first and last doses administered in Period 2 were given 30 minutes after a low-calorie (approx. 470 total calories) breakfast (approx. 25 – 30% of calories from fat). On Days 3 – 6 of drug administration in Period 2, subjects were instructed to eat a light breakfast prior to drug administration.

Test Product

APC-111 (amoxicillin) Tablet, 775 mg
Manufactured by Advancis Pharmaceutical Corp.
Lot No: 13163.1
Manufactured August 31, 2004

Reference Product

Amoxicillin Suspension, 250 mg/5 mL (Amoxil® Oral Suspension)
Manufactured by GlaxoSmithKline
Lot No: AA0557
Exp. Date: June 2006

Inclusion Criteria

Healthy men or women between 19 and 55 years of age (inclusive), having a body weight within 20% of the ideal weight for their height and frame, and healthy by physical exam and laboratory results.

Pharmacokinetic assessment

Blood samples (3 mL) were drawn in lavender top (EDTA) blood collection tubes at the following time points on Day 1 of Period 1 and on Days 1 and 7 of Period 2: 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 14, 16 and 24 hours post-dose.

Analytical Methods
Concentrations of amoxicillin in plasma were quantified using a validated LC/MS/MS method with an analytical range of 0.05 – 25.0 μg/mL.

Pharmacokinetic Methods
Pharmacokinetic parameters were calculated from amoxicillin plasma concentrations using noncompartmental methods. The plasma PK parameters evaluated following single and multiple dose administration included: Cmax, Tmax, Cmin, AUClast, AUC_{τ}, $AUC_{0-\infty}$, t½, λz, T>MIC (time above MIC_{90} for *S. pyogenes* [0.06 μg/mL]) and %T>MIC (percent of 24-hour dosing interval above MIC_{90} for *S. pyogenes* [0.06 μg/mL]). Percent fluctuation ("Flux") was calculated following multiple dose administration of APC-111 as follows:

Flux 1: $(C_{max} - C_{min})/C_{ssav}$ (where C_{ssav} is the ratio of AUC_{τ} to the dosing interval, τ)
Flux 2: $(C_{max} - C_{min})/C_{min}$

Statistical Methods
Single-dose APC-111 vs. amoxicillin suspension: Analyses of variance (ANOVA) were performed on the ln-transformed AUClast, $AUC_{0-\infty}$, and Cmax and on the untransformed or ln-transformed parameters T>MIC or %T>MIC, where appropriate. The ANOVA model included formulation as a fixed effect and subject as a random effect. Each ANOVA included calculation of least-square means (LSM), the difference between formulation LSM and the standard error associated with this difference.

Multiple-dose APC-111 vs. single-dose APC-111: ANOVA were performed on the ln-transformed Cmax and on the untransformed or ln-transformed parameters T>MIC or %T>MIC, where appropriate. The ANOVA model included dose as a fixed effect and subject as a random effect. Each ANOVA included calculation of least-square means (LSM), the difference between dose LSM and the standard error associated with this difference. The PK parameter AUC_{τ} (Day 7) was compared with $AUC_{0-\infty}$ (Day 1) using ln-transformed values. The ANOVA model included Day 1 $AUC_{0-\infty}$ and Day 7 AUC_{τ} as fixed effects and subject as a random effect. The ANOVA included calculation of LSM, the difference between Day LSM and the standard error associated with this difference.

Results:
Study Population
A total of 20 subjects, 10 males and 10 females enrolled in the study; all subjects completed participation. All subjects were Caucasian. The mean age was 31 years (range 19 – 51 years), the mean height was 70.1 inches (range 65.0 – 76.0 inches) and the mean weight was 168.1 lbs (range 135.0 – 209.0 lbs). All 20 subjects were included in the PK analysis.

Analytical Performance
The LLOQ of the assay was 50.0 ng/mL. The precision of the calibration standards and quality control samples ranged from – 4.59 to 1.71%, and the overall accuracy was within 5.92%. Frozen-state stability was demonstrated for 183 days at -80 degrees C. Samples from this study were stored at – 80 degrees C for 52 days prior to analysis.

Pharmacokinetic Analysis

Single-Dose PK
Mean single-dose PK data following single doses of 750 mg Amoxil® Suspension (Treatment A) and 775 mg APC-111 (Treatment B) are shown below in Table 1. The results of the statistical analysis following dose-normalization are shown in Table 2. The dose-normalized C_{max} was 40% lower for APC-111 as compared to Amoxil® Suspension, with a 90% CI for the

ratio of 57 – 64%. Mean dose-normalized $AUC_{0-\infty}$ was 14% lower following APC-111 administration versus Amoxil® Suspension (90%CI 83.1 – 89.7%). The absolute T>MIC for total amoxicillin concentrations for an MIC value of 0.06 µg/mL was slightly longer for APC-111 (13.6 hours vs. 12.1 hours), as was the %T>MIC determined by the Sponsor (57% vs. 50%). However, the Sponsor used a 24-hour dosing interval for both formulations when calculating %T>MIC, despite a recommended dosing regimen of every 8 – 12 hours for Amoxil® Suspension. Based on a recommended Q12 hour dosing regimen, the mean %T>MIC would be approximately 100% for Amoxil® Suspension, as oppose to 50%. The similarity in absolute T>MIC for the two formulations is apparent in Figure 1.

The time to reach peak amoxicillin concentrations (T_{max}) was 1.2 hours longer for APC-111 than for Amoxil® Suspension. The elimination half-life of amoxicillin was similar for the two formulations – 1.44 and 1.63 hours, respectively, for APC-111 and Amoxil® Suspension

Table 1. Single Dose PK Parameters of Total Amoxicillin Following Single Doses of 750 mg Amoxil® Oral Suspension (Treatment A) and 775 mg APC-111 (Treatment B)

	AUC(0-t) (ug.hr/mL)	AUC(0-inf) (ug.hr/mL)	Kel (1/hr)	T1/2 (hr)	Cmax (ug/mL)	Cmin (ug/mL)	Tmax (hr)	T>MIC (hr)	% T>MIC
Treatment: (A) 750 mg Amoxil Oral Suspension									
N:	20	20	20	20	20	20	20	20	20
Mean:	33.10	33.28	0.4346	1.63	10.5700	0.0000	1.75	12.16	50.67
Median:	33.10	33.32	0.4374	1.58	10.7500	0.0000	1.54	11.91	49.62
SD:	5.78	5.77	0.0660	0.27	1.4801	0.0000	0.38	1.37	5.69
Min:	25.04	25.21	0.2883	1.20	8.0800	0.0000	1.00	9.34	38.92
Max:	45.36	45.60	0.5797	2.40	13.0000	0.0000	2.50	14.86	61.93
%CV:	17	17	15	16	14	.	22	11	11
GM:	32.64	32.81	0.4297	1.61	10.4701	.	1.71	12.09	50.36
Treatment: (B) 775 mg APC-111 MP Tablet									
N:	20	19	19	19	20	20	20	20	20
Mean:	29.40	29.79	0.4946	1.44	6.6230	0.0000	3.14	13.80	57.49
Median:	28.55	29.05	0.5006	1.38	6.5700	0.0000	2.75	12.68	52.82
SD:	5.28	5.35	0.0885	0.25	1.0466	0.0000	1.38	2.87	11.96
Min:	22.48	22.62	0.3772	1.02	4.5300	0.0000	1.50	10.78	44.91
Max:	42.91	43.11	0.6790	1.84	8.7000	0.0000	5.50	23.36	97.35
%CV:	18	18	18	17	16	.	44	21	21
GM:	28.98	29.37	0.4873	1.42	6.5408	.	2.86	13.57	56.53

Geometric Mean (GM)

Note: T>MIC is absolute time above MIC = 0.06 µg/mL

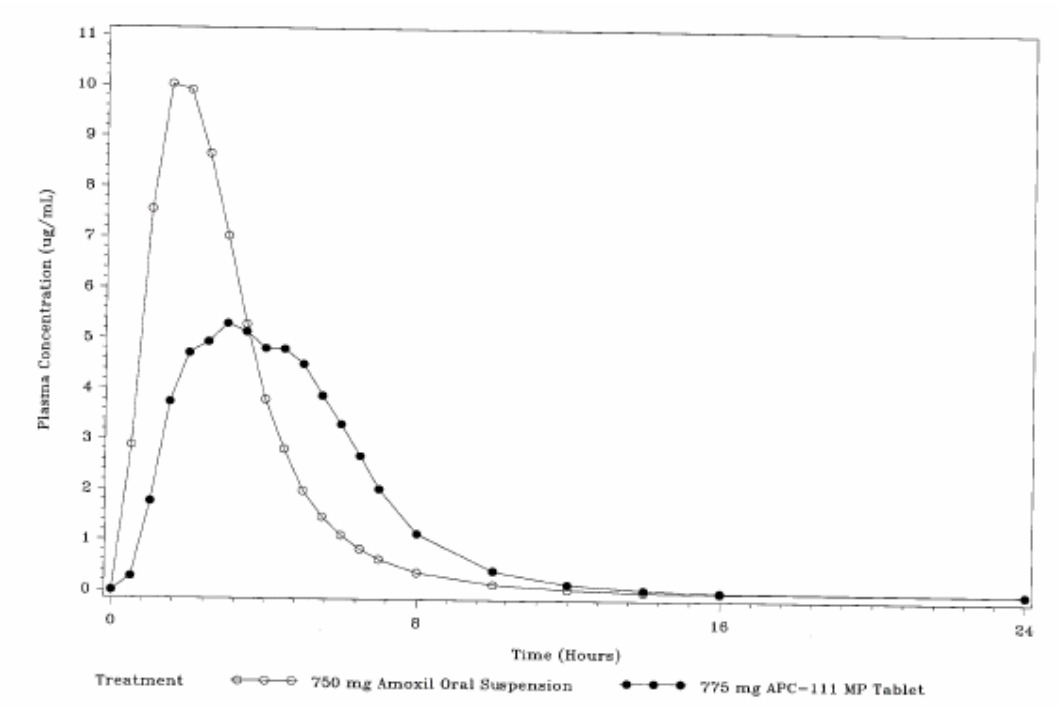
Table 2. Statistical Analysis of Total Amoxicillin PK for Single Doses of 750 mg Amoxil® Oral Suspension (Treatment A) and 775 mg APC-111 (Treatment B)

(Geometric LSM, Geometric LSM Ratios and 90% CI)

PK Parameter	Treatment B (N=20)	Treatment A (N=20)	Ratio (%) (B/A)	90% Confidence Interval
% T>MIC	56.5312	50.3610	112.25	106.97, 117.80
T>MIC	13.5675	12.0866	112.25	106.97, 117.80
Dose Normalized AUC(0-inf)	0.03777	0.04375	86.33	83.12, 89.66
Dose Normalized AUC(0-t)	0.03740	0.04352	85.95	82.84, 89.17
Dose Normalized Cmax	0.00844	0.01396	60.46	57.07, 64.05

Note: AUC and C_{max} values are dose-normalized by dividing the geometric mean value from Table 1 by dose.

Figure 1. Mean Plasma Amoxicillin Concentration vs. Time Curves for Single Doses of 750 mg Amoxil® Oral Suspension and 775 mg APC-111



The PK/PD parameters T>MIC and %T>MIC were also determined based on unbound amoxicillin, using a protein binding estimate of 18% (Table 3). The results indicate a slightly lower T>MIC estimate than that determined for total amoxicillin – 13.3 hours vs. 13.8 hours for APC-111 and 11.7 hours vs. 12.2 hours for amoxicillin suspension.

Table 3. Single-Dose PK Parameters of Unbound Amoxicillin (Mean [%CV])

PK Parameter	N	750 mg Amoxil® Suspension (A)	775 mg APC-111 Tablet (B)
T>MIC (0.060 µg/mL)	20	11.7 hours (11.3%)	13.3 hours (20.4%)
%T>MIC (0.060 µg/mL)	20	48.6% (11.3%)	55.5% (20.4%)

Multiple-Dose PK

Multiple-dose PK parameters of amoxicillin following 7 days of APC-111 are shown below in Table 3. The PK parameters on Day 7, including C_{max}, T_{max}, AUC and T>MIC, are similar to those seen on Day 1, indicating no accumulation with multiple dosing. Mean unbound %T>MIC values were 56.0% and 55.5% following multiple-dose and single-dose administration, respectively.

Table 3. Multiple Dose PK Parameters of Total Amoxicillin Following 7 Days of APC-111 (775 mg Once Daily)

	AUC(0-tau) (ug.hr/mL)	Cmax (ug/mL)	Cmin (ug/mL)	Tmax (hr)	Flux 1 %	Flux 2 %	T>MIC (hr)	% T>MIC
N:	20	20	20	20	20	0	20	20
Mean:	29.27	6.5670	0.0000	3.05	544.77	.	13.98	58.26
Median:	27.76	6.6500	0.0000	3.00	545.88	.	13.68	56.99
SD:	5.40	1.1003	0.0000	1.26	82.38	.	2.61	10.89
Min:	21.27	4.4500	0.0000	1.50	389.80	.	11.47	47.79
Max:	43.55	8.2600	0.0000	5.50	694.60	.	23.35	97.29
%CV:	18	17	.	41	15	.	19	19
GM:	28.84	6.4745	.	2.81	538.79	.	13.79	57.48

Geometric Mean (GM)

Table 4. Statistical Analysis of Total Amoxicillin PK for Single vs. Multiple Doses of APC-111, 775 mg.

(Geometric LSM, Geometric LSM Ratios and 90% CI)

PK Parameters	Day 7	Day 1	Ratio (%) (Day7/Day1)	Lower 90% CI	Upper 90% CI
AUC(0-tau)(Day 7) vs AUC(0-inf)(Day 1)	3.3618	3.3757	98.62	96.17	101.12
Cmax	1.8679	1.8781	98.99	94.21	104.00
%T>MIC *	58.2623	57.4888	101.35	98.17	104.52
T>MIC *	13.9830	13.7973	101.35	98.17	104.52

* LSM Ratios and Confidence Intervals of %T>MIC and T>MIC were calculated from untransformed parameters.

Safety Analysis

Nine out of 20 subjects (45%) experienced at least 1 treatment emergent adverse event (AE). The majority of AEs were mild in severity and were consistent with the types and frequency seen in other Phase I studies. The most common AE was headache, reported by 6 (30%) of subjects. Other AEs included dizziness (10%) and administration site pain (5%). There were no clinically significant laboratory abnormalities.

Sponsor's Conclusions

- The PK profile of amoxicillin following administration of a single dose of APC-111 was different from that of a single dose of Amoxil® Suspension in the presence of a low-calorie meal.
- Dose-normalized amoxicillin C_{max} was substantially (40%) lower and AUC values were slightly (13%) lower for APC-111 than for Amoxil® Suspension.
- Amoxicillin T>MIC of 0.06 µg/mL following APC-111 was more than an hour longer than that following Amoxil® Suspension when administered with a low-calorie meal.
- Both formulations achieved a %T>MIC for *S. Pyogenes* (MIC_{90} 0.06 µg/mL) of greater than 50% of a 24-hour dosing interval.
- There was no accumulation of amoxicillin in plasma after once-daily dosing of APC-111 for 7 days under fed conditions.

Reviewer assessment:
The Sponsor's conclusion regarding a similar %T>MIC for APC-111 and Amoxil® Suspension after dose-normalization is based on a 24-hour dosing interval. However, the recommended dosing interval for Amoxil® Suspension is every 8 – 12 hours. Based on a 12-hour dosing interval, the estimated mean %T>MIC is approximately 100% for Amoxil® Oral Suspension, as oppose to 50%, as estimated by the Sponsor.

Study 111.110

A Single Center, Open-Label, Randomized, Single Dose, Two-Way Crossover Study to Evaluate the Effect of Lansoprazole on Amoxicillin Pharmacokinetics and Bioavailability after Administration of a Single APC-111 MP Tablet, 775 mg, in the Fed State.

Study Dates: October 27 – November 14, 2004

Study Sites: (b) (4) [redacted]

Objective:

The primary objective of this study was to characterize the effect of a proton pump inhibitor on the PK and bioavailability of APC-111 under fed conditions.

Methods:

Study Design

Study 111.110 was a single center, open-label, two period, crossover study. Twenty healthy males and females were enrolled. Each subject received a single oral dose of APC-111, 775 mg, under fed conditions, alone and following four days of treatment with lansoprazole 30 mg twice daily (BID). Lansoprazole was administered in the fasted state for 4 days; on the 5th day lansoprazole 30 mg was given in the fasted state, 30 minutes before a high fat breakfast and one hour prior to APC-111 dosing. Each dose of APC-111 was administered within 30 minutes of a high fat/high calorie meal. The periods were separated by a minimum 14-day washout period.

Treatments

APC-111 (amoxicillin) Tablet, 775 mg (administered as a single dose)
Manufactured by Advancis Pharmaceutical Corp.
Lot No: P0001
Manufactured August 31, 2004

Prevacid® (lansoprazole) 30 mg Delayed-Release Capsule (administered BID x 9 doses)
Distributed by TAP Pharmaceutical Products
Lot No: 190342E21
Exp Date: 4/1/ 07

Inclusion Criteria

Healthy men or women between 19 and 55 years of age (inclusive), having a body weight within 20% of the ideal weight for their height and frame, and healthy by physical exam and laboratory results.

Pharmacokinetic assessment

Blood samples (3 mL) were drawn in lavender top (EDTA) blood collection tubes at the following time points following each dose of APC-111: 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16 and 24 hours post-dose.

Analytical Methods

Concentrations of amoxicillin in plasma were quantified using a validated LC/MS/MS method with an analytical range of 0.05 – 25.0 μg/mL.

Pharmacokinetic Methods

The following pharmacokinetic parameters were calculated from amoxicillin plasma concentrations using noncompartmental methods: Cmax, Tmax, AUClast, $AUC_{0-\infty}$, t½, λz,

T>MIC (time above MIC_{90} for *S. pyogenes* [0.06 μg/mL]) and %T>MIC (percent of 24-hour dosing interval above MIC_{90} for *S. pyogenes* [0.06 μg/mL]).

Statistical Methods

ANOVA was utilized to compare the log-transformed PK parameters. The model included the following factors: sequence, subject within sequence, period and treatment. Ratios of least square means (LSM) were calculated from log-transformed PK values.

Results:

Study Population

A total of 20 subjects were enrolled in the study; seventeen subjects (5 males and 12 females) completed the entire study, while 19 completed at least one treatment. Subjects included Caucasians, Blacks and Asians. The mean age was 37 years (range 20 – 51 years), the mean height was 68.2 inches (range 60.0 – 74.0 inches) and the mean weight was 157 lbs (range 113.0 – 198.0 lbs).

Analytical Performance

Analysis of human plasma samples was conducted November 19 – 24, 2004. The precision (%CV) of the calibration standards and QC samples ranged from – 3.58 to 5.84%, and the overall accuracy was within 6.07%. Stability of amoxicillin in frozen human plasma was determined for a period of 83 days at – 70 degrees C. Samples from the study were frozen at – 70 degrees C for 25 days prior to sample analysis. The correlation coefficients from regression equations were ≤ 0.9987.

Pharmacokinetic Analysis

PK data analysis was performed on the 19 subjects that completed at least 1 treatment period using PK data from all subjects completing each treatment. Statistical analysis was performed on those 17 subjects completing both treatment arms of the study. Subjects reported 100% compliance with lansoprazole dosing outside of the clinic.

Following administration of APC-111 following 4 days of lansoprazole therapy, amoxicillin Cmax increased by approximately 35% relative to APC-111 alone (Tables 1 and 2). Amoxicillin $AUC_{0-\infty}$ was more modestly affected (18% increase). The Tmax and the elimination $T_{1/2}$ of amoxicillin were unaffected by lansoprazole, while T>MIC for total amoxicillin was only slightly decreased, from a geometric mean (GM) of 15.8 hours to 14.9 hours. The parameters T>MIC and %T>MIC were also determined based on unbound amoxicillin, using a protein binding estimate of 18%. The results indicate slightly lower T>MIC estimates – a GM of 15.3 hours for APC-111 alone and 14.4 hours with lansoprazole.

Table 1. Summary PK Parameters of Total Amoxicillin

	AUC(0-t) (ug.hr/mL)	AUC(0-inf) (ug.hr/mL)	Cmax (ug/mL)	Tmax (hr)	Kel (1/hr)	T1/2 (hr)	T>MIC (hr)	%T>MIC
Treatment: (A) APC-111 MP								
N:	19	16	19	19	16	16	19	19
Mean:	28.87	28.13	6.3026	2.58	0.4293	1.88	16.19	67.46
Median:	28.48	27.72	6.1200	2.50	0.4513	1.54	14.53	60.56
SD:	4.47	4.10	1.6163	1.36	0.1271	1.11	3.95	16.45
Min:	20.87	20.97	4.0900	1.00	0.1209	1.18	11.83	49.29
Max:	36.92	36.19	10.3000	7.00	0.5890	5.73	23.78	99.07
CV:	15.49	14.57	25.6443	52.60	29.6979	58.67	24.39	24.39
GM:	28.54	27.85	6.1214	2.32	0.4045	1.71	15.79	65.79
Treatment: (B) APC-111 MP + Prevacid								
N:	18	17	18	18	17	17	18	18
Mean:	32.59	32.95	8.6039	2.84	0.3871	2.15	15.33	63.85
Median:	32.53	32.71	8.9050	2.00	0.4049	1.71	14.24	59.34
SD:	4.29	4.67	2.6406	1.74	0.1378	1.19	3.89	16.20
Min:	25.95	26.09	4.1400	1.50	0.1314	1.03	10.48	43.65
Max:	39.33	40.21	12.9000	8.00	0.6745	5.27	23.48	97.82
%CV:	13	14	31	61	36	56	25	25
GM:	32.32	32.64	8.1909	2.48	0.3585	1.93	14.92	62.18

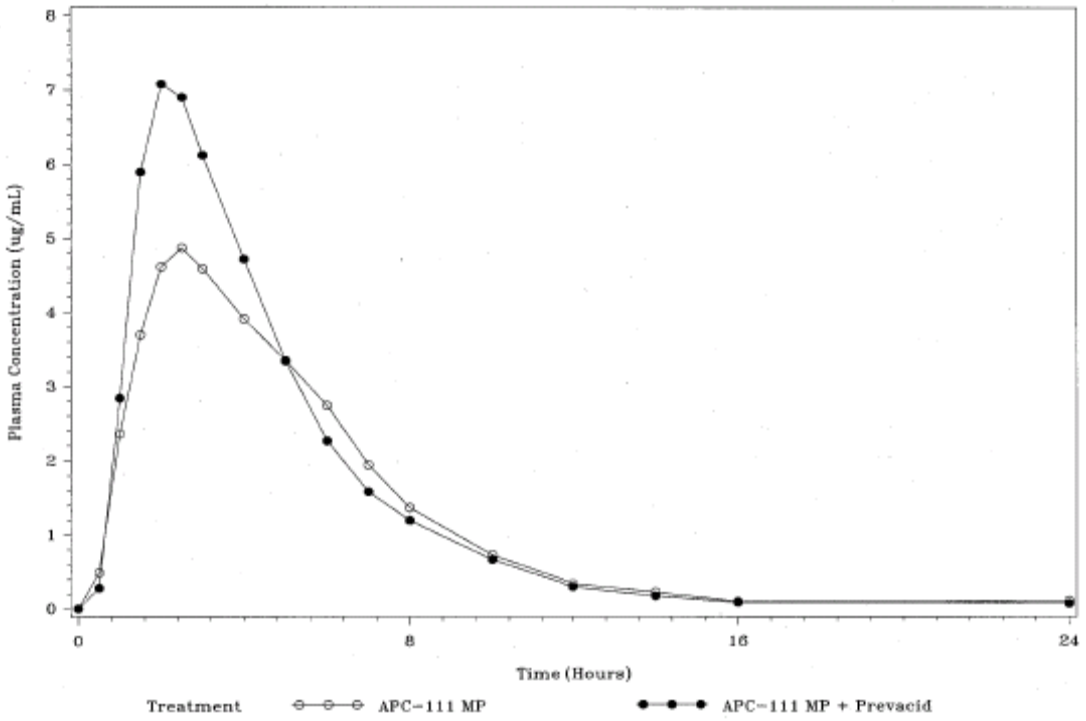
Geometric Mean (GM)

Table 2. Geometric Least-Square Means (LSM) and Geometric LSM Ratios with 90% Confidence Intervals for Total Amoxicillin PK Parameters

PK Parameter	Treatment B (N=18)	Treatment A (N=18)	Ratio (%) (B/A)	90% Confidence Interval
% T>MIC	61.3086	63.7139	96.22	91.49, 101.21
T>MIC	14.7141	15.2913	96.22	91.49, 101.21
AUC(0-inf)	32.6687	27.6656	118.08	113.74, 122.59
AUC(0-t)	32.3252	28.1501	114.83	109.60, 120.31
Cmax	8.2339	6.1738	133.37	118.52, 150.07

Treatment A: APC-111 MP Tablet
Treatment B: APC-111 MP Tablet + Previcid
For AUC(0-inf), N = 16 for Treatment A and N = 17 for Treatment B

Figure 1. Mean Plasma Amoxicillin Concentration vs. Time Curves for APC-111 Alone and APC-111 + Lansoprazole



Safety Analysis

A total of 3 subjects experienced treatment-emergent adverse events, including headache (n=3) and dizziness (n=1). All of the events were mild and considered to be possibly related to study drug.

Sponsor's Conclusions

- Lansoprazole 30 mg BID increased the peak amoxicillin plasma concentration (Cmax) by approximately 35% and had a more modest effect (18% increase) on overall mean amoxicillin exposure ($AUC_{0-\infty}$) following administration of APC-111 under fed conditions.
- The time to reach Cmax and $T_{1/2}$ of amoxicillin was not notably affected by coadministration of APC-111 with lansoprazole.
- Under fed conditions, APC-111 achieved a T>MIC for *S. Pyogenes* (MIC 0.06 µg/mL) for greater than 60% of the 24-hour dosing interval, with and without lansoprazole coadministration.
- APC-111 was well tolerated with and without lansoprazole.

Reviewer assessment:

The increase in Cmax following coadministration of APC-111 with lansoprazole suggests either an early release of some component of the delayed-release pulses or an increase in the absorption of the immediate-release pulse in the setting of an increased gastric pH. Regardless of the mechanism, sufficient delayed-release amoxicillin was absorbed in the setting of

concomitant lansoprazole therapy to maintain a similar T>MIC for the Sponsor's identified threshold of MIC = 0.06 μg/mL.

Study 111.111

A Single Center, Open-Label, Randomized, Single Dose, 3-Way Crossover Study to Evaluate the Effect of Food on Amoxicillin Pharmacokinetics and Bioavailability After Administration of a Single APC-111 MP Tablet, 775 mg

Study Dates: September 26 – October 10, 2004

Study Sites: (b) (4) [redacted]

Objective:

The primary objective of this study was to characterize the effect of food (standard low-calorie meal and high-fat meal) vs. fasting on the PK and bioavailability of APC-111.

Methods:

Study Design

Study 111.111 was a single center, open-label, 3-period, crossover study. Twenty-four healthy males and females were enrolled. Each subject received a three single oral doses of APC-111 775 mg following an overnight fast (Treatment C), a low calorie meal (Treatment A) and a high fat meal (Treatment B). Subjects were randomized to one of six treatment sequences. The periods were separated by a 7-day washout period.

Treatments

APC-111 (amoxicillin) Tablet, 775 mg (administered as a single dose)
Manufactured by Advancis Pharmaceutical Corp.
Lot No: P0001
Manufactured August 31, 2004

Inclusion Criteria

Healthy men or women between 19 and 55 years of age (inclusive), having a body weight within 20% of the ideal weight for their height and frame, and healthy by physical exam and laboratory results.

Composition of Meals

Low-calorie breakfast: Approx. 25 – 30% of total calories from fat, and a total of approx. 470 calories.

High-fat/high-calorie breakfast: Approx. 50% of total calories from fat, and a total of approx. 800 – 1000 calories.

Pharmacokinetic assessment

Blood samples (3 mL) were drawn in lavender top (EDTA) blood collection tubes at the following time points following each dose of APC-111: 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 14, 16 and 24 hours post-dose.

Analytical Methods

Concentrations of amoxicillin in plasma were quantified using a validated LC/MS/MS method with an analytical range of 0.05 – 25.0 μg/mL.

Pharmacokinetic Methods

The following pharmacokinetic parameters were calculated from amoxicillin plasma concentrations using noncompartmental methods: Cmax, Tmax, AUC_{0-t}, $AUC_{0-\infty}$, T½, λz, T>MIC (time above MIC_{90} for *S. pyogenes* [0.06 μg/mL]) and %T>MIC (percent of 24-hour dosing interval above MIC_{90} for *S. pyogenes* [0.06 μg/mL]).

Statistical Methods

ANOVA was utilized to compare the log-transformed PK parameters. The model included the following factors: sequence, subject within sequence, period and treatment. Ratios of least square means (LSM) were calculated from log-transformed PK values. The comparisons of interest were Treatment A vs. C, B vs. C, and B vs. A.

Results:

Study Population

A total of 24 subjects were enrolled in the study, and 23 subjects (10 males and 13 females) completed the entire study. Subjects were 92% Caucasians and 8% Hispanic. The mean age was 35 years (range 19 – 52 years), the mean height was 67.8 inches (range 61.0 – 76.0 inches) and the mean weight was 160.8 lbs (range 119.0 – 222.0 lbs).

Analytical Performance

Analysis of human plasma samples was conducted between September 30, 2004 and October 20, 2004. The precision (%CV) of the calibration standards and QC samples ranged from 2.94% to 11.4%, and the overall accuracy was within 4.11%. Stability of amoxicillin in frozen human plasma was determined for a period of 83 days at – 80 degrees C. Samples from the study were frozen at – 80 degrees C for a maximum of 24 days prior to sample analysis. The correlation coefficients from regression equations were ≤ 0.9962.

Pharmacokinetic Analysis

PK and statistical analyses were performed on the 23 subjects that completed study participation.

Administration of APC-111 with a low-calorie meal or a high fat meal did not affect overall amoxicillin exposure (AUC), while Cmax decreased by 16% and 26%, respectively, relative to administration in the fasted state (Tables 1 and 2). The presence of food appears to affect the rate of absorption of one or more components of the tablet, resulting in a delay in Tmax and a blunted peak plasma concentration following administration with food, with the magnitude of the effect related to the fat content of the meal. Amoxicillin elimination $T_{1/2}$ was not affected by food. However, food did prolonged the T>MIC of unbound amoxicillin. Based on an unbound estimate of 18%, T>MIC (geometric means) for unbound amoxicillin were 11.0, 12.2 and 14.6 hours under fasting, low-fat fed and high-fat fed conditions, respectively.

Table 1. Summary PK Parameters of Amoxicillin

	AUC(0-t) (ug.hr/mL)	AUC(0-inf) (ug.hr/mL)	Cmax (ug/mL)	Tmax (hr)	Kel (1/hr)	T1/2 (hr)	T>MIC (hr)	%T>MIC
Treatment: (A) Fed-'Low-Calorie' Meal								
N:	23	22	23	23	22	22	23	23
Mean:	31.71	31.67	8.3791	2.70	0.4812	1.53	12.96	54.01
Median:	30.66	30.23	7.8300	2.50	0.5041	1.38	12.35	51.46
SD:	7.39	7.52	2.2042	1.34	0.1082	0.46	2.82	11.75
Min:	19.22	19.32	5.9100	1.00	0.2209	0.98	9.19	38.31
Max:	51.50	51.74	14.0000	5.50	0.7058	3.14	23.35	97.29
%CV:	23	24	26	50	22	30	22	22
GM:	30.97	30.91	8.1392	2.39	0.4679	1.48	12.72	53.01
Treatment: (B) Fed-High-fat Meal								
N:	23	21	23	23	21	21	23	23
Mean:	31.57	31.74	7.4078	2.35	0.4433	1.69	15.47	64.47
Median:	30.35	30.60	7.0900	2.50	0.4116	1.68	14.82	61.74
SD:	6.39	6.69	1.9356	0.86	0.1388	0.46	3.65	15.22
Min:	21.74	21.84	4.9600	1.00	0.2614	0.89	10.28	42.84
Max:	48.01	48.45	14.0000	4.00	0.7789	2.65	23.86	99.43
%CV:	20	21	26	37	31	27	24	24
GM:	31.01	31.13	7.2071	2.19	0.4253	1.63	15.09	62.88
Treatment: (C) Fasting								
N:	23	23	23	23	23	23	23	23
Mean:	31.29	31.45	9.9326	1.57	0.4812	1.49	11.56	48.16
Median:	30.05	30.22	10.1000	1.50	0.4762	1.46	11.79	49.14
SD:	6.53	6.55	1.8550	0.64	0.0860	0.28	1.64	6.82
Min:	20.60	20.76	6.3000	1.00	0.3331	1.06	8.29	34.55
Max:	46.63	46.85	13.0000	3.50	0.6542	2.08	14.69	61.22
%CV:	21	21	19	41	18	19	14	14
GM:	30.66	30.82	9.7563	1.47	0.4737	1.46	11.45	47.69

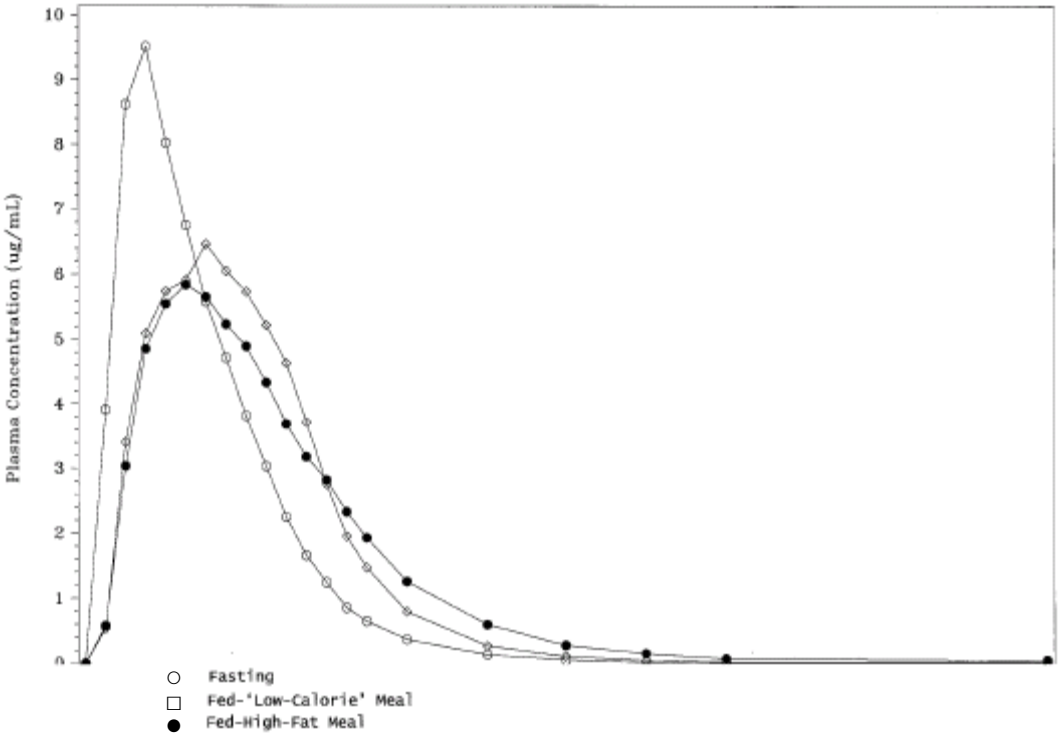
Geometric Mean (GM)

Table 2. Geometric Least-Square Means (LSM) and Geometric LSM Ratios with 90% Confidence Intervals for Amoxicillin PK Parameters

PK Parameter	Treatment B (N=23)	Treatment A (N=23)	Ratio (%) (B/A)	90% Confidence Interval
%T>MIC	62.9922	53.1420	118.54	110.86, 126.74
T>MIC	15.1181	12.7541	118.54	110.86, 126.74
AUC(0-inf)	31.1056	31.3019	99.37	94.11, 104.93
AUC(0-t)	31.2576	31.3319	99.76	94.74, 105.05
Cmax	7.2768	8.2458	88.25	82.13, 94.83
PK Parameter	**Treatment A (N=23)**	**Treatment C (N=23)**	**Ratio (A/C)**	**90% Confidence Interval**
%T>MIC	53.1420	47.9240	110.89	103.71, 118.56
T>MIC	12.7541	11.5018	110.89	103.71, 118.56
AUC(0-inf)	31.3019	31.1073	100.63	95.41, 106.13
AUC(0-t)	31.3319	30.9428	101.26	96.16, 106.62
Cmax	8.2458	9.8244	83.93	78.11, 90.19
PK Parameter	**Treatment B (N=23)**	**Treatment C (N=23)**	**Ratio (B/C)**	**90% Confidence Interval**
%T>MIC	62.9922	47.9240	131.44	122.94, 140.54
T>MIC	15.1181	11.5018	131.44	122.94, 140.54
AUC(0-inf)	31.1056	31.1073	99.99	94.72, 105.57
AUC(0-t)	31.2576	30.9428	101.02	95.93, 106.37
Cmax	7.2768	9.8244	74.07	68.93, 79.59

Treatment A: 775 mg APC-111 MP Tablet Administered with a 'Low-Calorie' Meal.
Treatment B: 775 mg APC-111 MP Tablet Administered with a 'High-Fat' Meal.
Treatment C: 775 mg APC-111 MP Tablet Administered under Fasting Conditions.
For AUC(0-inf), T1/2, and Kel, N = 22 for Treatment A and N = 21 for Treatment B

Figure 1. Mean Plasma Amoxicillin Concentration vs. Time Curves for APC-111 Under Fasting, Low-Calorie Fed and High-Fat Fed Conditions.



Safety Analysis

A total of 9 subjects (37.5%) experienced at least one adverse event (AE) possibly related to study medication. The most frequent AE was headache (n=4). All other AEs were experienced by only one subject each.

Sponsor's Conclusions

- Food decreases the rate, but not the extent of amoxicillin absorption from the APC-111 tablet.
- Elimination $T_{1/2}$ of amoxicillin was not influenced by the presence of food.
- Food increased unbound T>MIC by 1.2 to 3.6 hours, depending on the fat content of the meal.
- APC-111 tablet achieved an unbound %T>MIC for MIC=0.06 μg/mL for greater than 45% of the 24-hour dosing interval, regardless of meal conditions.
- APC-111 was well tolerated.

Reviewer assessment:

The Sponsor's conclusions are consistent with the results of the study.

Study 111.115

A Phase I Single Center, Open-Label, Randomized, Single Dose, 2-Way Crossover Study to Establish Bioequivalence of APC-111 Tablet, 775 mg Manufactured at Two Different Manufacturing Sites in Healthy Subject Under Fasting Conditions

Study Dates: February – March 2006

Study Sites: (b) (4) [redacted]

Objective:

The primary objective of this study was to establish bioequivalence of an APC-111 Tablet, 775 mg, manufactured at two different manufacturing sites in healthy adults in the fasted state.

Methods:

Study Design

Study 111.115 was a single center, open-label, randomized, 2-period, crossover study. Twenty-six healthy males and females were enrolled. Each subject was randomized to receive one of each treatment under fasting conditions. The dosing periods were separated by a 7-day washout period.

Treatments

(A) APC-111 Tablet, 775 mg (administered as a single dose)
Manufactured by (b) (4) [redacted]
Lot No: 11214.03 (b) (4) [redacted]

(B) APC-111 Tablet, 775 mg (administered as a single dose)
Manufactured by [redacted]
Lot No: 5AJ001-A-D [redacted]

Inclusion Criteria

Healthy men or women between 19 and 55 years of age (inclusive), having a body weight within 20% of the ideal weight for their height and frame, and healthy by physical exam and laboratory results.

Pharmacokinetic assessment

Blood samples (3 mL) were drawn in lavender top (EDTA) blood collection tubes at the following time points following each dose of APC-111: 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 16 hours post-dose.

Analytical Methods

Concentrations of amoxicillin in plasma were quantified using a validated LC/MS/MS method with an analytical range of 0.05 – 25.0 μg/mL.

Pharmacokinetic Methods

The following pharmacokinetic parameters were calculated from amoxicillin plasma concentrations using noncompartmental methods: Cmax, Tmax, AUC_{0-t}, $AUC_{0-\infty}$, T½ and λz.

Statistical Methods

An analysis of variance (ANOVA) was performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and Cmax values. The ANOVA model included sequence, treatment and period as fixed effects and subject nested within sequence as a random effect.

Results:

Study Population

A total of 26 subjects were enrolled in the study, and 24 subjects (10 males and 13 females) completed the entire study. The mean age of subjects was 30 years (range 19 – 52 years), the mean height was 67.7 inches (range 58.0 – 75.0 inches) and the mean weight was 151.3 lbs (range 100.0 – 190.0 lbs).

Analytical Performance

Analysis of human plasma samples was conducted between March 6 and March 11, 2006. The precision (%CV) of the calibration standards and QC samples ranged from 0.809 – 5.86%, and the overall accuracy was within 2.49%. Stability of amoxicillin in frozen human plasma was determined for a period of 183 days at – 70 degrees C. Samples from the study were frozen at – 80 degrees C for a maximum of 30 days prior to sample analysis.

Pharmacokinetic Analysis

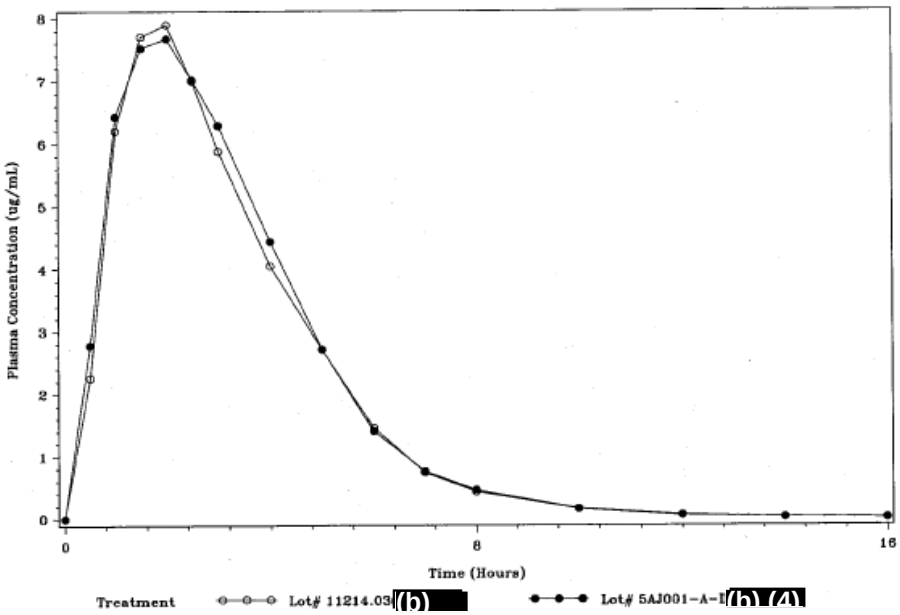
Statistical analyses were performed on the 24 subjects that completed study participation. PK parameters of amoxicillin from the reference tablet (Treatment A (b) (4)) and test tablet (Treatment B, (b) (4)) were comparable. The geometric least-square mean (LSM) ratios for AUC_{0-t}, $AUC_{0-\infty}$ and Cmax (Treatment B vs. A) were 104%, 105% and 100%, respectively (Table 1). The 90% CIs for all ratios fell within the range of 80% to 125%. Amoxicillin half-life was comparable between the two treatments (1.46 hours vs. 1.55 hours).

Table 1. Summary of Statistical Analysis of Amoxicillin PK Parameters

PK Parameter	Treatment B (N=24)	Treatment A (N=24)	Percent (B/A)	90% Confidence Interval
ln AUC(0-inf)	30.86	29.50	104.60	99.55, 109.91
ln AUC(0-t)	30.63	29.35	104.36	99.30, 109.68
ln Cmax	8.39	8.38	100.03	92.97, 107.62
T 1/2 (hr)	1.57	1.46	107.50	86.52, 128.48
Kel (1/hr)	0.49	0.49	100.03	90.33, 109.74
Tmax (hr)	1.95	1.94	100.54	83.03, 118.06

Treatment A = (b) (4)
Treatment B = (b) (4)

Figure 1. Mean (Total) Plasma Amoxicillin Concentration vs. Time Plots



Safety Analysis

A total of three subjects reported at least one adverse event (AE) – one subject report an AE during Treatment A [redacted]) and three subjects reported an AE during Treatment B [redacted]). The AEs reported with Treatment A were abdominal pain, diarrhea and nausea, while those reported with Treatment B were nausea, dizziness and headache. All AEs were mild or moderate in severity.

Sponsor's Conclusions

- The 775 mg APC-111 tablets manufactured at (b) (4) [redacted] are bioequivalent, as determined by measurement of amoxicillin AUC_{0-t}, $AUC_{0-\infty}$ and Cmax following administration of the APC-111 tablets under fasting conditions.
- All APC-111 treatments were well tolerated.

Reviewer assessment:

The Sponsor's conclusions are consistent with the results of the study.

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/s/

Sarah M. Robertson
11/30/2007 09:53:11 AM
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Chuck, this is the correct document

Charles Bonapace
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