CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-813

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	50813
Submission Code	000
Letter Date	March 23, 2007
Stamp Date	March 23, 2007
PDUFA Goal Date	January 23, 2008
Reviewer Name	Menfo Austin Imoisili, MD, MPH
Review Completion Date	January 23, 2008
Established Name	Amoxicillin/APC -111
(Proposed) Trade Name	Moxatag
Therapeutic Class	Penicillin Class of antimicrobials
Applicant	MiddleBrook Pharmaceuticals
Priority Designation	S
Formulation	Oral
Dosing Regimen	775 mg QD
Indication	Tonsillopharyngitis
Intended Population	Adolescents and Adults

Table of Contents

1.1 Recommendation on Regulatory Action 5
1.2 Recommendation on Postmarketing Actions 5
1.2.1 Risk Management Activity 5
1.2.2 Required Phase 4 Commitments 6
1.2.3 Other Phase 4 Requests 6
1.3 Summary of Clinical Findings 6
1.3.1 Brief Overview of Clinical Program 6
1.3.2 Efficacy 6
1.3.3 Safety 8
1.3.4 Dosing Regimen and Administration 9
1.3.5 Drug-Drug Interactions 10
1.3.6 Special Populations 10
2 INTRODUCTION AND BACKGROUND 11
2.1 Product Information 11
2.2 14
2.3 Availability of Proposed Active Ingredient in the United States 16
2.4 Important Issues with Pharmacologically Related Products 16
2.5 Pre-submission Regulatory Activity 17
1 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 18
3.1 CMC (and Product Microbiology, if Applicable) 18
3.2 Animal Pharmacology/Toxicology 19
4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 19
4.1 Sources of Clinical Data 19
4.2 Tables of Clinical Studies 19
4.3 Review Strategy 21
4.4 Data Quality and Integrity 22
4.6 Financial Disclosures 23
5 CLINICAL PHARMACOLOGY 23
5.1 Pharmacokinetics 23
Dose Selection and Duration Stipulated for APC-111 for Study 302 23
5.2 Pharmacodynamics 25
5.3 Exposure-Response Relationships 25
6 INTEGRATED REVIEW OF EFFICACY 25
6.1 Indication 25
6.1.1 Methods 25
6.1.2 General Discussion of Endpoints 28
6.1.3 Study Design 30
6.1.4 Efficacy Findings 39
6.1.5 Clinical Microbiology 52
6.1.6 Efficacy Conclusions 57
7 INTEGRATED REVIEW OF SAFETY 60
7.1 Methods and Findings 60
7.1.1 Deaths 66
7.1.2 Other Serious Adverse Events 66

7.1.3 Dropouts and Other Significant Adverse Events 67
7.1.3.1 Overall profile of dropouts 67
7.1.3.2 Adverse events associated with dropouts 68
7.1.3.3 Other significant adverse events 71
7.1.4 Other Search Strategies 71
7.1.5 Common Adverse Events 72
7.1.5.1 Eliciting adverse events data in the development program 72
7.1.5.2 Appropriateness of adverse event categorization and preferred terms 73
7.1.5.3 Incidence of common adverse events 73
7.1.5.4 Common adverse event tables 74
7.1.5.5 Identifying common and drug-related adverse events 74
7.1.5.6 Additional analyses and explorations 77
7.1.6 Less Common Adverse Events 77
7.1.7 Laboratory Findings 78
7.1.7.1 Overview of laboratory testing in the development program 78
7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values 79
Laboratory Testing in Phase 1 Studies 80
There were no clinically significant lab results reported in any of Phase 1 studies. 80
7.1.8 Vital Signs 81
7.1.8.1 Overview of vital signs testing in the development program 81
7.1.9 Electrocardiograms (ECGs) 85
7.1.9.3.1 Analyses focused on measures of central tendency 85
7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal 85
7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities 85
7. 1. 10 Immunogenicity 85
7.1.11 Human Carcinogenicity 85
7.1.12 Special Safety Studies 86
7.1.13 Withdrawal Phenomena and/or Abuse Potential 86
7.1.14 Human Reproduction and Pregnancy Data 86
7.1.15 Assessment of Effect on Growth 86
7.1.16 Overdose Experience 86
7.1.16 Overdose Experience 86
The product label indicates that "Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin." In addition "Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adults and pediatric patients." .. 86
7.1.17 Postmarketing Experience 86
7.2 Adequacy of Patient Exposure and Safety Assessments 87
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety 87
7.2.1.3 Extent of exposure (dose/duration) 88
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety 88
7.2.2.1 Other studies 88
7.2.2.2 Postmarketing experience 88
7.2.2.3 Literature 88

7.2.3 Adequacy of Overall Clinical Experience 93
7.2.4 Adequacy of Special Animal and/or In Vitro Testing 93
7.2.5 Adequacy of Routine Clinical Testing 93
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup 93
7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug 93
and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study 93
7.2.8 Assessment of Quality and Completeness of Data 94
7.2.9 Additional Submissions, Including Safety Update 94
7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions 94
7.4 General Methodology 95
7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence 95
7.4.1.1 Pooled data vs. individual study data 96
7.4.2 Explorations for Predictive Factors 96
7.4.2.1 Explorations for dose dependency for adverse findings 96
7.4.2.2 Explorations for time dependency for adverse findings 97
7.4.3 Causality Determination 97
8 ADDITIONAL CLINICAL ISSUES 98
8.1 Dosing Regimen and Administration 98
8.2 Drug-Drug Interactions 98
8.3 Special Populations 98
8.4 Pediatrics 99
8.5 Advisory Committee Meeting 99
8.6 Literature Review 99
8.7 Postmarketing Risk Management Plan 99
8.8 Other Relevant Materials 99
9 OVERALL ASSESSMENT 99
9.1 Conclusions 99
9.2 Recommendation on Regulatory Action 100
9.3 Recommendation on Postmarketing Actions 100
9.3.1 Risk Management Activity 100
9.3.2 Required Phase 4 Commitments 101
9.3.3 Other Phase 4 Requests 101
Labeling Review 101
9.5 Comments to Applicant 101
10 APPENDICES 101
10.1 Review of Individual Study Reports 130
10.2 Labeling Line-by-Line Labeling Review 130

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Advancis (now MiddleBrook) Pharmaceuticals submitted this NDA (#50813) application for ascertainment by the Agency of the efficacy and safety of their new once-daily dosing formulation of amoxicillin tablet (containing 775 mg) for the treatment of adolescent and adult patients with (b)(4) tonsillopharyngitis (b)(4) to Streptococcus pyogenes. In the studies conducted by the company, 550 patients received the new amoxicillin formulation (APC-111) in their two Phase 3 double-blind, double-dummy, randomized, multicenter studies; 112 subjects received the drug in their five Phase 1 studies (total, 662). No Phase 2 studies were conducted. As the application was submitted under section 505 (B)(2) of the Federal Food, Drug and Cosmetic Act, the company is also relying, in part, on data from published literature, as well as FDA's previous findings of safety and effectiveness of the drug product, for approval. All available data pertinent to the review have been evaluated. The Medical officer has determined that the data provided:

- Constitute substantial and supportive evidence of efficacy of APC-111 for the indication of (b)(4) tonsillopharyngitis (b)(4) to Streptococcus pyogenes in adolescent and adult patients;

- Have demonstrated that APC-111 is safe for use in the treatment of adolescent and adult patients with the indicated disease. The long history of use of amoxicillin has allowed accumulation of useful safety information known so far and contained in the product label for already marketed formulations of amoxicillin. The continuing safety surveillance maintained on this product in post marketing activities provides reassurance that safety information yet unknown, if any, can be uncovered over time.

- Have sufficiently given directions for use of the product. Other than once-daily dosing of the product, no additional information regarding, for example, dose adjustment for demographic, metabolic, or other differences is new.

Based on the above considerations, the reviewing Medical Officer recommends an action of approval for APC-111 and NDA #50813.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

As previously described, amoxicillin is a product with a long history of use. Nevertheless, postmarketing risk management should continue through postmarketing reporting of adverse drug experiences as outlined in 21 CFR314.80. Prescribing clinicians should be kept aware, through product labeling, of the clinical adverse events (AEs) and laboratory

abnormalities that potentially result from the receipt of APC-111. Examples include gastrointestinal AEs (diarrhea, vomiting), headache and skin reactions (rash/urticaria). Vigilance should be maintained regarding the development of in vitro resistance of clinical laboratory bacterial isolates to Amoxicillin.

1.2.2 Required Phase 4 Commitments

Studies of an amoxicillin extended release formulation in pediatric patients 2-11 years of age are required under Pediatric Research Equity Act (PREA). The sponsor will conduct a phase 3 study of a (b) (4) formulation in this age group and submit the results by March 31, 2013 as a post-marketing commitment.

1.2.3 Other Phase 4 Requests

No other Phase 4 requests are being made.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

- APC-111 tablet is a reformulation of amoxicillin, a penicillin-class antibacterial product. It is administered as one tablet (containing 775 mg) once daily for ten days for the treatment of tonsillopharyngitis (b) (4) to Streptococcus pyogenes in patients 12 years of age and older.
- Of the 2 Phase 3 studies referred to under section 1.1, one of them (study 302), was the pivotal study upon whose results the efficacy determination of APC-111 was based. Of the patients in this study, 302 received APC-111 tablet once daily for 10 days; the 306 patients in the comparator arm of the study received Penicillin VK, four times daily also for 10 days.
- In the other Phase 3 study 248 received APC-111 for 7 days; the 259 patients in the comparator arm received Penicillin VK, four times daily also for 10 days.
  In addition to the 550 patients who received APC-111 in the Phase 3 studies, 112 subjects received the product in Phase 1 studies. That is, 662 subjects/patients received APC in the Sponsor's studies.
- From Literature sources, 804 patients received amoxicillin from the studies of Shvartzman P et al and Feder HP et al (152, all on QD regimen); and the study of Clegg HW et al (652, either QD or BID). There were a total of 1466 amoxicillin-treated patients in the expanded database. The FDA findings of safety and efficacy for previous amoxicillin product submissions were also part of the consideration in the overall database evaluation.

1.3.2 Efficacy

As indicated under section 1.3.1, study 302 was the pivotal study and provided study results for efficacy determination of APC-111. The primary efficacy endpoint of the study was the bacteriologic eradication of Streptococcus pyogenes from the pharynx/tonsils of study patients at the test of cure (TOC) visit in the bacterial per protocol (PPb) and modified intent-to-treat (mITT) co-primary populations. Accordingly, as shown in table ExS 1, in the PPb population, 197/232 (85%) of APC-111-treated patients had a satisfactory (bacterial eradication) outcome compared to 189/227 (83%) patients who received Pen VK in the PPb population, with a 95% confidence interval (CI) around treatment difference of -5.0 , 8.4. Similarly, 211/256 (82%) APC-treated patients in the mITT co-primary population had satisfactory outcome compared to 207/ 266 (78%) Pen VK –treated patients, also with a 95% CI around treatment difference of -2.8, 10.8. As the chosen delta (δ) was -10, noninferiority was demonstrated. There was also clinical correlation with bacteriologic outcomes in the same study, as shown in table ExS 2.

Table EXS 1: Bacteriologic Outcome at the TOC visit in PPb and mITT Populations

Bacteriologic Outcome	PPb [n (%)]		mITT[n (%)]	
	APC-111	Pen VK	APC-111	Pen VK
N →	232	227	256	266
Total Satisfactory	197 (84.9)	189 (83.3)	211 (82.4)	207 (77.8)
Total Unsatisfactory	35 (15.1)	38 (16.7)	45 (17.6)	57 (21.6)
Point Estimate Difference	1.6		4.0	
95% Confidence Intervals	-5.0 , 8.4		-2.8, 10.8	

Table EXS 2: Clinical Outcome at the TOC visit in PPb and mITT Populations
[Sponsor's table - modified]

Analysis of Efficacy								
Clinical Outcome	PPb [n (%)]				mITT [n (%)]			
	APC-111	Pen VK			APC-111	Pen VK		
N →	233	229	Diff.	95% CI	256	264	Diff.	95% CI
Success (clinical cure)	213 (91.4)	212 (92.6)	-1.2	-6.1, 3.8	226 (88.3)	228 (86.4)	-1.9	-3.8, 7.6
Non-Success	20 (8.6)	17 (7.4)			30 (11.7)	36 (13.6)		
Clinical Failures	18 (7.7)	15 (6.6)			20 (7.8)	21 (8.0)		
Unable to evaluate	2 (0.9)	2 (0.0.9)			8 (3.1)	10 (3.8)		

An important secondary endpoint was a determination of bacteriologic outcome at late post therapy (LPT) visit. Consistent with results at the TOC visit, the trends in the in

bacteriological outcome at the LPT visit, as shown in table EXS 3, are similar across study arms in both the PPb and the mITT co-primary populations.

Ordinarily, one might consider it scientifically desirable to duplicate the results of this study to ensure that these results were not obtained by fluke. Again, as amoxicillin has a long history of use in clinical practice, the Agency's previous finding of efficacy and safety information about amoxicillin products served to a reliable degree, in lieu of a full-blown phase 3 duplicate study. Even many patients in the failed study 301 patients had satisfactory outcomes. Not enough patients had such outcomes to satisfy the endpoints stipulated in the study protocol. This was attributed (by the Sponsor) to insufficient treatment duration. Literature evidence was helpful by contributing some "proof-of-concept" data. The study of Clegg et al, to a respectable degree, was fairly supportive of the once-daily treatment regimen.

Table EXS 3: Number of Patients (%) and Bacteriological outcome at the LPT visit [Sponsor's table].

Bacteriological outcome	PPb		mITT(b]	
	APC-111	Pen VK	APC-111	Pen VK
N	219	217	256	264
Satisfactory	169 (77.2%)	164 (75.6%)	179 (69.9%)	179 (67.8%)
Eradication	169 (77.2%)	164 (75.6%)	175 (68.4%)	175 (66.3%)
Presumed Eradication	-	-	4 (1.6%)	4 (1.5%)
Unsatisfactory	50 (22.8%)	53 (24.4%)	77 (30.1%)	85 (32.2%)
Unsatisfactory at TOC	34 (15.5%)	38 (17.5%)	45 (17.6%)	57 (21.6%)
Persistence	29 (13.2%)	32 (14.7%)	29 (11.3%)	37 (14.0%)
Presumed Persistence	5 (2.3%)	6 (2.8%)	7 (2.7%)	8 (3.0%)
Indeterminate	-	-	9 (3.5%)	12 (4.5%)
Satisfactory at TOC with secondary failure at LPT	16 (7.3%)	15 (6.9%)	32 (12.5%)	28 (10.6%)
Carrier/Re-colonization	2 (0.9%)	7 (3.2%)	4 (1.6%)	8 (3.0%)
Recurrence	1 (0.5%)	1 (0.5%)	2 (0.8%)	1 (0.4%)
Presumed Recurrence	11 (5.0%)	6 (2.8%)	13 (5.1%)	8 (3.0%)
Reinfection	2 (0.9%)	1 (0.5%)	2 (0.8%)	1 (0.4%)
Indeterminate	-	-	11 (4.3%)	10 (3.8%)
Point estimate Difference	1.6		2.1	
95% CI	-6.4, 9.6		-5.8, 10.1	

The once daily administration of APC-111 was intended for convenience and to enhance compliance, and, perhaps, increase treatment effect. If this goal is realized, the product would have served as another weapon in the armamentarium for the treatment of streptococcal tonsillopharyngitis with convenience.

1.3.3 Safety

The size of safety database was discussed under Section 1.3.1. Study 301 patients received seven days of APC-111. Phase 1 patients received single or multiple doses, depending on which study they participated in. But all received less than 10 days of APC-111. Some patients in study 302
did not complete their 10 days of treatment – some discontinued their medication for insufficient efficacy, or secondary to adverse events (AEs). Most patients in study 302 completed 10 days of APC-111 treatment.

There were no deaths in any study. In 3 APC-treated patients, the reported serious adverse events (SAEs) appeared to be unrelated to study drug.

The most common AE leading to patient discontinuation from study was severity of pharyngeal pain and was less common among APC-treated patients than comparator-treated patients (0.6% vs 1.2%). Other AEs considered to be study drug related were similar across study arms.
Among the common all causality AEs occurring in ≥ 2% of study population, the frequency rates of AEs were similar in APC-111-treated and comparator-treated study patients. For these patients, the 4 most common AEs included worsening streptococcal tonsillopharyngitis (6.7% vs 7.3%), headache (4.9% vs 6.4%), pharyngo-laryngeal pain (4.5% vs 3.9%), and upper respiratory tract infection (4.4% vs 5.7%) in APC-treated and comparator-treated patients respectively.
Regarding study drug-related AE rates, it was slightly lower in APC-111-treated than in comparator-treated study patients, as shown in table EXS 4. The four most common in this category of patients included nausea (1.5% vs 1.4%), streptococcal tonsillopharyngitis (0.9% vs 1.8%), vulvovaginal candidiasis (0.9% vs 1.4%), and headache (0.7% vs 1.6%).

Table EXS 4	**Number (%) of Drug-related AEs occurring in ≥ 1% of Phase 3 Patients**						
Adverse events	**Study 302**		**Study 301**			**Pooled Studies**	
	APC-111 n= 302	**Pen VK n= 306**	**APC-111 n= 248**	**Pen VK n = 259**		**APC-111 n= 550**	**Pen VK n= 565**
Nausea	4 (1.3)	2 (0.7)	4 (1.6)	6 (2.3)		8 (1.5)	8 (1.4)
Strep Pharyngotonsillitis	6 (2.0)	10 (3.3)	-	-		6 (0.9)	10 (1.8)
Vulvovaginal Candidiasis	6 (2.0)	8 (2.6)	-	-		6 (0.9)	8 (1.4)
Headache	3 (1.0)	3 (1.0)	1 (0.4)	6 (2.3)		4 (0.7)	9 (1.6)
Diarrhea	5 (1.7)	6 (2.0)	2 (0.8)	6 (2.3)		3 (0.5)	7 (1.2)
Abdominal pain	1 (1.0)	3 (1.0)	2 (0.8)	4 (1.5)		3 (0.5)	7 (1.2)

1.3.4 Dosing Regimen and Administration

The regimen to be marketed is 775 mg once daily, orally, for 10 days. This was the dose used for 10 days in study in study 302 patients - the Sponsor's successful Phase 3 pivotal

study (i.e., study 302). The same dose used for 7 days in the other Phase 3 study (i.e., study 301) was unsuccessful.

1.3.5 Drug-Drug Interactions

As a drug with long history of use, drug-drug interaction was not evaluated for this application. However, current product label for amoxicillin contains the following drug-drug interaction information:
"Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of amoxicillin and probenecid may result in increased and prolonged blood levels of amoxicillin.
Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin." Although demonstrated in vitro, its clinical significance is unknown, per the label.

1.3.6 Special Populations

Similar to the reason in subsection 1.3.5, amoxicillin label reports: "This drug is known to be substantially excreted by the kidney, and the risk of (b) reactions to this drug may be greater in patients with impaired renal function. As elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function."
Also, Amoxicillin has been used in clinical practice in pediatric population, and frequently, for the treatment of bacterial upper respiratory illnesses, including streptococcal tonsillopharyngitis. The only precaution for pediatric use involves the neonatal population and those up to 12 weeks of age.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

This is a review of a 505 (B)(2) New Drug Application (NDA), # 50813, for a new formulation of amoxicillin tablet form. The product is designed to allow amoxicillin to be dispensed as a once daily tablet for a 10-day treatment course. It has been developed by Advancis Pharmaceutical Corporation (Advancis) for the treatment of (b) (4) tonsillitis and/or pharyngitis (TP) (b) (4) Streptococcus pyogenes (GAS), in adolescents and adults (age 12 and above). The tablet design utilizes a ph-sensitive property which allows its content to be released in three separate pulses (see figure 1). According to the Sponsor, each release is triggered by a gastrointestinal (GI) environmental pH changes as the tablet travels down the tract, following its ingestion. The first release involves the dissolution of its outer coating. This reportedly results in immediate release of the outermost 40% amoxicillin content. The remaining inner two groups of Amoxicillin pellets are released further along the GI tract - with 35% and 25% release with the second and third pulses respectively. The name "Pulsatile-release, multi-articulate" tablet refers to this mechanism of release. The tablet is designed to release a total amount of 775 mg of amoxicillin each day.

Amoxicillin is itself an amino-derivative of penicillin. Penicillin is a beta-lactam antibiotic, first produced on a large scale for human use in 1943. Amoxicillin was approved in the U.S. in January 1974. It is an approved alternative to penicillin for the treatment of ear, nose and throat infections, although administered as every 8-12 hours regimens.

Mechanism of Action

Amoxicillin is bactericidal against susceptible organisms through the inhibition of biosynthesis of cell wall mucopeptide during the stage of bacterial multiplication. GAS has remained uniformly sensitive to penicillin (and amoxicillin) despite development of resistance among common bacterial pathogens.

Clinical Pharmacology

Based on the Sponsor's pharmacokinetic (PK) studies, the following are among the important PK properties of APC-111 after administration of the tablet, per the clinical pharmacology review by Drs Sarah Robertson and Charles Bonapace:

- Time above MIC (T>MIC) was prolonged by administration with food. Mean unbound T>MIC of 0.06 μg/mL (minimum required for the inhibition of S. pyogenes) 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.
- Apparent volume of distribution of amoxicillin is approximately 0.26 – 0.31 L/kg.
- Following its administration, the absolute time unbound amoxicillin concentrations remained > MIC value of 0.06 μg/mL was ≈ 13 hours with a low-fat meal in healthy subjects. The elimination half-life was ≈ 1.4 hours, with no accumulation following multiple doses.

- The urinary excretion of APC- 111 (as amoxicillin) following administration was not evaluated in any of the submitted PK studies. That of amoxicillin was previously reported as 50-70% of administered drug, unchanged in the urine.
- Although the product label for amoxicillin (immediate-release) states that "patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe.", the Sponsor has proposed a recommendation that treatment of patients with severe renal impairment or on hemodialysis with APC-111 be avoided.
- The administration of lansoprazole with APC-111 (under high-fat conditions) increased the Cmax of amoxicillin by approximately 35% and the AUC 0-∞ by 18%. However, the mean T>MIC was not significantly affected by administration with lansoprazole.

For further details of APC PK, please refer to the clinical pharmacology review by Drs Robertson and Bonapace.

Current Indications of Amoxicillin
There is no specific indication appertaining only to APC-111 other than the one for this review.
APC-111 is released as amoxicillin; information provided in this section is applicable to all amoxicillin products. According to its current label, amoxicillin is indicated in the treatment of infections due to susceptible non-beta-lactamase producing strains of the designated microorganisms in the following conditions:

Infections of the ear, nose, and throat: due to Streptococcus spp. (alpha- and beta-hemolytic strains only), S. pneumoniae, Staphylococcus spp., or H. influenzae.

Infections of the genitourinary tract: due to E. coli, P. mirabilis, or E. faecalis.

Infections of the skin and skin structure: due to Streptococcus spp. (alpha- and beta-hemolytic strains only), Staphylococcus spp., or E. coli.

Infections of the lower respiratory tract: due to Streptococcus spp. (alpha- and beta-hemolytic strains only), S. pneumoniae, Staphylococcus spp., or H. influenzae.

Gonorrhea, acute uncomplicated (ano-genital and urethral infections): due to N. gonorrhoeae (males and females).

Amoxicillin is also recommended for use in the following conditions:

Gastritis and peptic ulcer disease caused by H. pylori (as adjunct treatment agent - in combination with metronidazole and bismuth subsalicylate/macrolide)

Lyme disease caused by B. burgdorferi

Typhoid fever caused by S. typhi.

Prophylaxis against endocarditis in patients undergoing dental, oral, upper respiratory tract or esophageal procedures, with congenital cardiac malformations, rheumatic and other acquired valvular lesions, prosthetic heart valves, previous history of bacterial endocarditis, hypertrophic cardiomyopathy, surgically constructed systemic pulmonary shunts or conduits, etc. Amoxicillin is also included in prophylactic regimens for certain genitourinary and non-esophageal gastrointestinal procedures.

Sponsor's rationale for a once-a-day amoxicillin dosing oral formulation

To date, no once-a-day amoxicillin formulation has been approved by the FDA for the treatment of TP. The Sponsor has based the rationale for this formulation on the following:

1. Two randomized, controlled studies reported in the literature that demonstrated that a single 750 mg daily dose of immediate release amoxicillin for 10 days was as effective as penicillin VK (Pen VK) TID for 10 days in the eradication of S. pyogenes. These studies will be further discussed later in this review;
2. AAP Redbook containing the report that orally administered amoxicillin given as a single daily dose for 10 days is as effective as orally administered penicillin VK given three times daily (TID) also for 10 days;
3. Advancis conducted pharmacokinetic studies which indicated that a single APC-111 MP Tablet, 775 mg, given with food, achieves a daily T>MIC of greater than 40% of a 24-hour dosing interval against S. pyogenes.

Application Type

This application has been submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the FDCA or the Act)(21 V.S.C. 355(b)(2). This means "an application that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference [section 505(b)(2) (a) application].

The Sponsor is relying on data from the following sources for their product safety evaluation:

1. Safety data from their two Phase 3 studies and all their Phase 1 studies;
2. FDA knowledge of the safety of the active ingredient of their product (amoxicillin);
3. Literature reports for safety information related to amoxicillin.

***Reviewer's comments**: The Sponsor is relying primarily on the result of their Phase 3 study III-302 to support their product efficacy. Study III-301 conducted earlier in their drug product development program was similar to study III-302 in design but with significant differences, among which were treatment duration (7 days for study 301 versus 10 days for study 302), administering medication with meal (study 301, optional;*

study 302, patients urged to do so), etc. Study 301, however, failed to meet the efficacy endpoint requirement for a TP indication claim.

Through the rest of the review, the outer borders of Sponsor's tables will be in single lines; tables derived by the reviewers will be in double lines starting from table G1. In labeling the review tables, the letter 'G' indicates "general", 'E' indicates "efficacy" and 'S', "safety".

2.2 Currently Available Treatment for Indications

Table G1 shows a list of current approved antibiotics for the treatment of Tonsillopharyngitis. They all fall into three antibiotic classes – the penicillins, the cephalosporins and the macrolides.

Table G1:	Current Approved antibiotics for the treatment of Tonsillopharyngitis		
Drug Group	**Pharmacological Name**	**Trade Name**	**Sponsor**
THE PENICILLINS	Amoxicillin	Amoxil Capsules	GlaxoSmithKline
	Amoxicillin	Amoxil Chewable Tablets	GlaxoSmithKline
	Amoxicillin	Amoxil Pediatric Drops/ Oral suspension	GlaxoSmithKline
	Amoxicillin	Amoxil Powder for Oral suspension	GlaxoSmithKline
	Amoxicillin	Amoxil Tablets	GlaxoSmithKline
	Penicillin V	Penicillin –VK Oral Tablet/ Suspension	Apothecon
	Penicillin V	Penicillin –VK Oral Tablet/ Suspension	Biochemie
	Penicillin V	Penicillin –VK Oral Tablet/ Suspension	Clonmel
	Penicillin V	Penicillin –VK Oral Tablet/ Suspension	Teva
	Benzathine Penicillin G	Bicillin L-A	King Pharms
	Benzathine Procaine Penicillin G	Bicillin C-R	King Pharms
THE CEPHALOSPORINS	Cefuroxime Axetil	Ceftin for Oral Suspension	GlaxoSmithKline
	Cefuroxime Axetil	Ceftin Tablets	GlaxoSmithKline
	Cefdinir	Omnicef Capsules	Abbott
	Cefdinir	Omnicef for Oral Suspension	Abbott
	Cefixime	Suprax	Lupin (India)
	Cefpodoxime Proxetil	Vantin Tablets and Oral Suspension	Pharmacia & Upjohn
	Cefadroxil monohydrate	Duricef	Warner Chilcott
THE MACROLIDES	Clarithromycin	Biaxin Filmtab Tablets	Abbott
	Clarithromycin	Biaxin Granules	Abbott
	Erythromycin Ethylsuccinate	EES 200 Liquid	Abbott
	Erythromycin Ethylsuccinate	EES 400 Liquid	Abbott
	Erythromycin Ethylsuccinate	EES 400 Filmtab Tablets	Abbott
	Erythromycin Ethylsuccinate	EES Granules	Abbott
	Erythromycin Ethylsuccinate	EryPed 200 & EryPed 400 Oral suspension	Abbott
	Erythromycin Ethylsuccinate	EryPed Drops	Abbott
	Erythromycin Ethylsuccinate	EryPed Chewable Tablets	Abbott
	Erythromycin	Ery-Tab Tablets	Abbott
	Erythromycin Stearate	Erythrocin Stearate Filmtab Tablets	Abbott
	Erythromycin	Erythromycin Base Filmtab Tablets	Abbott
	Erythromycin	Erythromycin Delayed – Release Capsules, USP	Abbott
	Erythromycin	PCE Dispertab	Abbott

2.3 Availability of Proposed Active Ingredient in the United States

Amoxicillin, the active ingredient of the product under review, is currently available and marketed in the United States, but as a BID/TID regimen.

2.4 Important Issues with Pharmacologically Related Products

Being a penicillin derivative, important issues with pharmacologically-related products include the following:

Hypersensitivity reactions

Serious and sometimes fatal hypersensitivity/anaphylactic reactions can occur, particularly if the individual has a history of hypersensitivity to penicillin. There can be occasional cross reactivity in persons on a cephalosporin agent or with a history of multiple allergens.

Antibiotic-associated colitis/ Pseudomembranous colitis

This has occurred with nearly all antibiotics, including the penicillin class of antibiotics. The tendency for antibiotic treatment, including antibiotics in the penicillin class, to alter normal colonic flora can allow Clostridium difficile overgrowth. Toxins produced by this organism are known to cause antibiotic-associated colitis.

Other general adverse events associated with the penicillins

- Bleeding manifestations – this has occurred in some patients receiving β-lactam antibiotics, including amoxicillin. This sometimes involves platelet aggregation, abnormal prothrombin and clotting times usually in the setting of renal failure.
- Neuromuscular excitability or convulsion – can occur if higher than recommended doses are given, especially if renal failure is present.
- Fever and Rash: as with other penicillins, these can occur with amoxicillin.
- Phlebitis or thrombophlebitis has occasionally been associated with the administration of penicillins (e.g. nafcillin).
- Serum Sickness has also occasionally been reported in association with the use of the penicillins. Erythema multiforme and Stevens-Johnson syndrome have also been reported.

Organ-Specific Adverse Events

- Hepatitis and liver enzyme elevations are toxic effects occasionally seen with administration of penicillins, particularly oxacillin or nafcillin. Hepatitis associated with cholestatic jaundice has also been reported.
- Interstitial nephritis has been reported with the use of the penicillin, particularly methicillin.

2.5 Pre-submission Regulatory Activity

APC-111 was originally filed with the Agency under IND 62,576 on April 30, 2001. The following table was provided by the Sponsor to chronicle the number and types of submissions to the Agency prior to the submission of this NDA.

Table G2: Sponsor's List of Submissions to IND 62,576

Serial Number	Date of Submission	Submission Type
000	04/30/2001	Original IND Application
001	05/08/2001	Response To FDA Request For Information
002	09/14/2001	General Correspondence
003	10/22/2001	Information Amendment
004	07/03/2002	Annual Report
005	10/09/2002	Information Amendment
006	10/10/2002	New Investigator
007	06/06/2003	General Correspondence
008	06/11/2003	Annual Report
009	06/12/2003	Information Amendment
010	08/28/2003	Information Amendment
011	10/27/2003	Information Amendment
012	02/27/2004	Information Amendment
013	03/05/2004	Information Amendment
014	03/16/2004	Information Amendment
015	03/25/2004	Information Amendment
016	04/06/2004	Information Amendment
017	06/23/2004	General Correspondence
018	07/09/2004	Information Amendment

A fair amount of discussion occurred between the Sponsor and the Division regarding the efficacy failure of their initial Phase 3 trial (Protocol 111.301). The Division suggested a re-evaluation of their product's PK data to determine if time above MIC90 was actually above MIC90 less than 40% of the time between consecutive product doses; to ascertain if that possibly contributed to inadequate bacterial killing; and therefore failure to reach efficacy goal. The Sponsor attributed the failure to the choice of seven rather than 10 days duration of treatment. Their subsequent Protocol 111.302 was a modification of Protocol 111.301 which extended TP treatment duration from 7 to 10 days.

2.6 Other Relevant Background Information

The additional reported adverse events (AEs) associated with the use of amoxicillin have been rare events and are included in product label. They include toxic epidermal necrolysis; crystalluria (after overdosage in adults and pediatric patients); leukopenia

/agranulocytosis, hemolytic anemia, thrombocytopenia; thrombocytopenic purpura; and tooth discoloration (brown, yellow, or gray staining) in pediatric patients. This last AE, tooth discoloration, was eliminated with brushing or dental cleaning in most cases.

Combination products with Amoxicillin

According to the product label, in clinical trials involving the use of combination therapies (e.g. triple therapy in combination with clarithromycin and lansoprazole, or double with lansoprazole alone against H. pylori–related duodenal ulcer disease), no AEs unique to these combinations were observed. Adverse reactions that have occurred have been those previously reported with amoxicillin, clarithromycin, or lansoprazole.

Drug Interactions include the following:

Probenecid: Concurrent amoxicillin use with this product or other inhibitors of the renal acid secretory system increases and prolongs blood amoxicillin concentrations.

Allopurinol: may increase the possibility of skin rash.

Others: Tetracyclines, chloramphenicol and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin. Whether amoxicillin decreases the effectiveness of oral contraceptives has not been fully elucidated.

Use in Pregnancy
In pregnancy, amoxicillin is considered a Category B drug. Its use in the treatment of infections in pregnancy has not yet been established in clinical trials. However, harmful effects have not been documented when the product has been used in pregnancy. Amoxicillin does cross the placenta. Its therapeutic benefits must be weighed against its possible hazards to mother and child.

1 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The Sponsor initially submitted the NDA for this product on February 12, 2007. After a preliminary review of the Sponsor's submission, the chemistry reviewer considered the application not fileable due to significant deficiencies in the CMC aspects of the application. To summarize their concerns, the outline of the deficiencies was as follows:

- A master batch record for commercial lot manufacture of drug product or a comparably detailed description of the process was not included as required in 21 CFR 314.50(d)(1)(ii)(c).

- The commercial-scale process was not defined yet and was still under development. Key processes were still at development-scale (b) (4) commercial-scale). No plan was outlined for developing a commercial-scale process from the current process.

- Pharmaceutical/process development and controls information did not demonstrate sufficient process knowledge to assure successful manufacture of commercial material.

In response to these concerns, the Sponsor revised the CMC portion of the application and resubmitted it NDA on March 23, 2007. It was accepted.

Microbiology
The microbiology data comprised throat cultures obtained from study patients at baseline. Following the receipt of study medications, the patients were re-cultured at the test of cure (TOC) as well as late post-therapy (LPT) visits. Organisms isolated during these last two visits were compared to baseline organisms, using Pulse Field Gel Electrophoresis. This enabled delineation of cases of reinfection from persistence.

3.2 Animal Pharmacology/Toxicology

No new animal pharmacology/ toxicology information was provided in this submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

a. Efficacy data: Efficacy data submitted by the Sponsor were gathered primarily from a Phase 3 study (Protocol 111.302) conducted in the U.S. and Canada (see Tables G3 and G4 and reviewer's comment under section 2.1). The Sponsor is relying on this pivotal study to provide data that would serve as substantial evidence of efficacy of APC-111, 775 mg QD for 10 days.

b. Safety Data: Safety data were gathered from all the studies listed in Table G3 as well as from literature reports (numbered "c" below) submitted by the Sponsor.

c. Literature reports
Safety reports in the literature submitted by the Sponsor or safety information known to the FDA were evaluated as part of the safety review for this NDA. The safety analyses of interest included AEs gathered from clinical, laboratory and vital signs abnormalities.

4.2 Tables of Clinical Studies

In table G3, the studies done by the Sponsors and the number of patients who received APC-111 are tabulated. In table G4, the studies done by the Sponsor are further are further described in details.

Table G3: Modified Sponsor's Table 2.7.4-3: Exposure to APC-111

[N = Number of Patients Who Received APC-111 in Sponsor's Phase 3 and Phase 1 Studies]

Phase of Study	Study Protocol	N
Phase III		
7 days regimen	Protocol 111.301	248
10 days regimen	Protocol 111.302	302
Total (Phase III)		**550**
Phase I		
Single dose	Protocol 111.110	19
	Protocol 111.111	24
	Protocol 111.112	23
	Protocol 111.115	26
Multiple dose	Protocol 111.109	20
Total (Phase I)		**112**
All Studies		**662**

Table G4: Description of Clinical Studies

#	Protocol / Study Type	Phase	APC-Treated Subjects	Study Description
1	111.302	3	302	A Phase III, Double-Blind, Double-Dummy, Randomized, Parallel-Group, Multicenter Study to Evaluate the Safety and Efficacy of APC-111 MP Tablet, 775 mg PO QD for 10 Days Compared to Penicillin VK, 250 mg PO QID for 10 Days in the Treatment of Tonsillitis and/or Pharyngitis Secondary to *Streptococcus pyogenes* in Adolescents and Adults.
2	111.301	3	248	A Phase III, Double-Blind, Double-Dummy, Randomized, Parallel-Group, Multicenter Study to Evaluate the Safety and Efficacy of 775 mg APC-111 MP Tablets PO QD for 7 Days Compared to Penicillin VK 250 mg PO QID for 10 Days in the Treatment of Patients with Tonsillitis and/or Pharyngitis Secondary to *Streptococcus pyogenes* in Adolescents and Adults.
3	111.109 Single dose & Mult dose Comparative Study	1	20	A Single Center, Open-Label, Non-Randomized, 2 Period Cross-over Study to Evaluate the Single- and Multiple-Dose Pharmacokinetics of APC-111 MP Tablet, 775 mg, and the Single Dose PK of Amoxil® Oral Suspension, 750 mg in the Fed State.
4	Protocol 110 Drug interaction	1	19	A Single Center, Open-Label, Randomized, Single-dose, 2-Way Crossover Study to Evaluate the Effect of a Proton Pump Inhibitor on Amoxicillin Pharmacokinetics and Bioavailability after Administration of a Single 775 mg, APC-III MP Tablet.
5	Protocol 111 Food Effect	1	24	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
6	Protocol 112 IVIVC	1	23	A Single Center, Open-Label, Randomized, 4-Way Crossover Study to Evaluate the Single Dose Pharmacokinetics of Two 775 mg Amoxicillin Pulsatile-Release Multiparticulate Tablet Formulations, and Two 775 mg Amoxicillin Pulsatile-Release Multiparticulate Sprinkle Formulations under Fasted Conditions
7	Protocol 115 BE	1	26	A Phase I Single Center, Open-Label, Single Dose, Randomized, 2-Way Crossover Study to Establish Bioequivalence of APC-111 MP Tablet, 775 mg Manufactured at Two Different Manufacturing Sites in Healthy Subjects under Fasted Conditions

Mult = Multiple; IVIVC= In vitro-in vivo comparison; BE = Bioequivalence (study)

4.3 Review Strategy

The Sponsor has submitted two Phase 3, and five Phase 1 studies for this application. Supportive literature materials were also provided. Data from Study 111- 302 were submitted for evaluation of product efficacy. Studies 301/-302 and all the Phase 1 study data were evaluated for safety-related information. Literature materials provided were

screened and the ones pertinent to the review were evaluated for additional safety information.

4.4 Data Quality and Integrity

The data submitted appears to be of good quality and seem generated from studies conducted with integrity. The data evaluated from the 10% random sample generated by the FDA statisticians seem to support data integrity. The Sponsor stated in their submission that the study was conducted in compliance with the "Declaration of Helsinki (Edinburgh, Scotland, 1989), the protocol, U.S. 21 CFR Part 312.20, current International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements. In addition, according to the Sponsor, several steps were taken to assure data integrity, including maintenance of good data collection (completing data collected on CRFs individually for each subject, with all data entry, processing, and quality control procedures performed by (b) (4) [redacted] reviewing all CRFs for missing pages, legibility, and consistency of subject identification on each page; performing Data Validating (defining validation criteria before data collection); maintenance of an audit log which documented changes made to database; and maintaining quality control of database. Other steps involved database locking, unblinding of randomization drug code and adequate properly archiving database, including retention of associated queries.

The Division of Scientific Investigation (DSI)

On completion of their inspection of study sites, the Division of Scientific Investigation (DSI), Office of Compliance provided the following report:
"This inspection was performed as a data audit for NDA #50-813. At this site, 117 subjects were screened; 58 subjects were randomized and 52 subjects completed the study. There were no deaths or SAEs reported. Six subjects discontinued due to lack of efficacy. An audit of 16 subjects' records was conducted. There were three instances of subjects who were enrolled who met exclusion criteria, and multiple instances of study interval telephone calls not being made. It is unlikely that any of these protocol violations affected data integrity. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4.5 Compliance with Good Clinical Practices

The initial clinical study was submitted by the Sponsor to IND 62,576. It was approved by FDA following the protocol review. In addition, according to the Sponsor, the clinical study protocol, protocol amendments, informed consent documents(s), and other appropriate study-related documents were reviewed and approved by two central Institutional Review Boards (IRB) and three local IRBs. The Sponsor further stated that "This study was conducted in accordance with Good Clinical Practice (GCP) as required by the guidelines in the European Community, the International Committee for Harmonization (ICH) harmonized tripartite guidelines 'Note for Guidance on Good Clinical Practice'(Committee for Proprietary Medicinal Products [CPMP]/ICH135/95), and standard operating procedures for clinical investigation and documentation at

Advancis Pharmaceutical Corp (Advancis) and their agent, (b) (4) . Compliance with these requirements also constitutes conformity with the ethical principles Declaration of Helsinki (Edinburgh, Scotland 1989). The trial master file containing essential documents for this study has been established and archived".

4.6 Financial Disclosures

The Sponsor submitted a completed FDA Form 3454, containing the names the investigators. The Sponsor has also certified that none of the listed investigators received significant payments and the financial relationship between the Sponsor and the investigator was consistent with the tenets of 21 CFR 54.2 (a), (b) and (f).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

See subsection 2.1 under Clinical Pharmacology

Dose Selection and Duration Stipulated for APC-111 for Study 302

The Sponsor provided the biopharmaceutical rationale for the 775 mg dose selected (and the 10- day treatment duration chosen) for the treatment of PT in study patients and is summarized by the reviewer as follows:

- that for an antibiotic the type of amoxicillin, time above minimum inhibitory concentration (T> MIC90) of 40% of a 24-hour dosing interval is traditionally considered adequate to provide efficacy against relevant sensitive respiratory pathogens;
- that APC-111 dose used in this study was calculated to provide amoxicillin concentrations that exceed the target MIC90 of GAS for 40% of the dosing interval after a single dose, based on their Phase I studies;
- that when administered with food, a single dose of APC-111 provides T> MIC90 coverage of at least 40% of a 24-hour dosing interval (table G5);
- that based on their experience with their previous study (study 301), when APC-111 was administered once-daily for 7 days, the < 80% bacterial eradication rate observed was comparable to 7-day Pen VK treatment course; therefore, a 7-day treatment duration was insufficient despite T> MIC90 exceeding 40% daily to confer efficacy against GAS;
- that this last point is supported by two randomized, controlled studies in which an immediate release amoxicillin formulation (750 mg) administered to study patients once daily for 10 days for the treatment of PT due to GAS resulted in 100% eradication rate in one study (N = 75) and 89% in the other (N=79) (Shvartzman P3 et al and Feder et al4
- that the AAP Redbook reports indicate that orally administered amoxicillin given as a single daily dose for 10 days is as effective as orally administered penicillin VK given TID for 10 days.

Table G5: (Modified Sponsor's Table 9-2): Mean (±SD) % T>MIC Values against *S. pyogenes* post receipt of APC-111 Under Various Conditions

Protocol	Food Administered	T>MIC (% of 24-hr Interval)[a]	
		MIC 0.06 µg/mL	MIC 0.015 µg/mL
111.109 (Day 1)	Low-Calorie Meal	55.4±11.3	67.5±11.3
111.109 (Day 7)	Low-Calorie Meal	56.6±11.1	70.7±10.6
111.111	Low-Calorie Meal	51.9±11.6	64.2±11.7
111.111	High-Fat Meal	62.3±15.3	75.4±15.2
111.110	High-Fat Meal	66.2±17.0	76.5±13.1

[a] **T>MIC determined using free, unbound plasma concentrations.**

For additional information on product pharmacokinetics and pharmacodynamics, the reader is referred to the clinical pharmacology NDA reviewed by Drs. Robertson and Bonapace.

Table G6 [Sponsor's Table 2.7.3 -22]: Literature Evidence to support Sponsor's once –daily Dose Selection.

Parameters	Shvartzman et al., 1993	Feder et al., 1997	Clegg et al., 2006
Design	Randomized, open-label, multi-center	Randomized, investigator-blinded, single center	Randomized, investigator-blinded, single center
Test Drug	Amoxicillin 50 mg/kg (max 750 mg) QD or 750 mg QD for 10 days	Amoxicillin 750 mg QD for 10 days	Amoxicillin 750 mg or 1000 mg QD for 10 days
Comparator	Penicillin V 250 mg TID/QID for 10 days	Penicillin V 250 mg QID for 10 days	Amoxicillin 375 mg BID or 500 mg BID for 10 days
Number centers	5	1	1
Location	Israel	US	US
Number of evaluable patients	157	152	590
Age of patients	≥ 3 years	4 – 18 years	2 – 17 years
Bacteriological eradication rate	Amoxicillin QD = 96% Penicillin V TID/QID = 87%	Amoxicillin QD = 89% Penicillin V QID = 84%	Amoxicillin QD = 79.9% Amoxicillin BID = 84.5%

MO comments: The above summary represents the key points in the Sponsor's rationale for the dose and duration chosen in their study 302. With regards to the fifth bullet, there is a major difference in the way amoxicillin was released in the studies conducted by Shvartzman et al Feder et al, and Clegg et al, on the one hand, and studies 302/301 done

by the Sponsor on the other. Whereas in the Sponsor's APC-111 tablet, amoxicillin was released in 3 pulses (45%, 30% and 25%) according to gastrointestinal PH, each of the ones reported in the literature was an immediate release formulation. The Sponsor's amoxicillin was released in diminishing quantities daily for each patient who received it. Given that amoxicillin is a time-dependent rather than concentration-dependent bacterial killer, the important issue is whether the product stays above MIC > 40% of a 24 hour period per dose taken. Table G6 shows eradication rates of S. pyogenes in patients who received once-daily dose of amoxicillin for treatment of PT.
The application also cites the Red Book (of the American Academy of Pediatrics) as endorsing the once-daily regimen.
Of note, the literature material reporting QD amoxicillin treatment of PT was done predominantly in pediatric patients. Although Study 302 had some pediatric patients (a total of 68, or 22.5% were between 12 and 18 years of age), study patients were predominantly adults.

5.2 Pharmacodynamics

Information related to pharmacodynamics is primarily in the review from Clinical Pharmacology by Drs Robertson and Bonapace.

5.3 Exposure-Response Relationships

Overall, 662 subjects/patients received APC-III in all studies conducted by the sponsor. Of these, 550 patients were enrolled in the Phase 3 studies (302 patients in study III-302, and 248 in study III-301).One hundred and twelve Phase 1 subjects received APC-III. The highest dose of APC-III received by any study enrollee was 775 mg. All received the tablet formulation except two subjects who received sprinkles from research batches of pulsatile-release MP formulation during their biopharmaceutical studies.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

In this NDA application, the Sponsor is seeking a claim for the indication of (b) (4) Tonsillitis and/or Pharyngitis (b) (4) Streptococcus pyogenes (PT) in adolescents and adults.

6.1.1 Methods

The primary clinical efficacy data submitted to support the above indication were those from Study 302 in which 302 patients who received APC-111 were evaluated compared with 306 patients who received Pen VK. The study report, case report forms, and datasets submitted by the Sponsor were reviewed to ascertain the efficacy of APC-111 relative to that of penicillin for noninferiority evaluation. The submission was reviewed as a 505 (b)(2) application (discussed in section 2.1, under "application type").

Protocol Amendment
During the Pre-NDA discussions between the Agency and the Sponsor, the populations from whom study data would be derived following treatment were defined, leading to a protocol amendment by the Sponsor.

MO comments: *The reviewer considered it helpful to outline the pertinent parts of the protocol amendment to provide a background to this efficacy review, including the primary efficacy endpoint, and how the populations to be evaluated for efficacy were determined and defined.*

The Sponsor provided a summary of the changes in the planned analyses as follows:

1. The primary efficacy analysis as stipulated by the protocol was originally to be conducted in the PPb population only. The SAP was amended based on FDA feedback to include both the PPb and mITT [b] populations as co-primary efficacy populations (where PPb referred to the PPb2 analysis population determined after treatment unblinding, see below). Furthermore, the analysis was to be presented unadjusted for region. The treatment groups were to be compared by calculating the asymptotic point estimate and two-sided 95% confidence interval for the difference in satisfactory bacteriological outcome rates (APC-111 – penicillin). No adjustment for region effect was to be made.

2. The process for determination of compliance prior and post unblinding were detailed in the SAP, and additional PPc (PPc1 and PPc2) and PPb (PPb1 and PPb2) populations were defined. Prior to unblinding of the randomized treatment allocated, the hierarchical analysis populations (ITT/Safety, mITT, PPc1 and PPb1) were discussed at the final data review meeting. Assessment of compliance and subsequent assignment to the PPc1 and PPb1 populations was based on tablet and capsule counts without regard to randomized treatment allocated. After database lock and unblinding of the randomized treatment allocated, two additional populations (PPc2 and PPb2) were determined. The two additional populations (PPc2 and PPb2) excluded those subjects considered to be noncompliant to their active study medication only, in accordance with the actual study medication that they were randomized to. The additional populations were defined after treatment unblinding; these were used in all efficacy analyses. PPc2 was referred to as the PPc analysis population and PPb2 was referred to as the PPb population in the body of the SAP and all tables and listings.

3. In addition to the co-primary analysis populations defined above, the presentation of the planned secondary efficacy analyses previously stated in the protocol to be presented for the mITT [a] population were revised to mITT [b] population. The unadjusted statistical analysis model presented for the primary efficacy analysis was to be implemented across the secondary efficacy analyses, where appropriate.

4. The study protocol stipulated that safety would be performed on a valid ITT population and defined the ITT population as all subjects who received at least one dose of study medication and presented with a positive enzyme immunoassay for S. pyogenes at baseline. The statistical analysis plan clarified that the same criteria were to be used to define both the ITT and Safety populations; therefore, these populations were combined into one population and titled ITT/Safety population. The ITT/Safety population was defined as all subjects who received at least one dose of study medication and who had at least one post-baseline clinical safety assessment.

5. Similarly, the protocol defined the mITT population as all ITT subjects with signs and symptoms compatible with pharyngeal disease due to S. pyogenes and who had a positive culture for S. pyogenes at baseline. The statistical analysis plan clarified the definition for the mITT population to include all ITT/Safety subjects who had a positive baseline throat swab culture for S. pyogenes.

6. The study protocol defined the PPc population as all ITT subjects excluding those subjects with major protocol violations. The statistical analysis plan clarified the PPc population to describe a clinically evaluable group of patients. The PPc population included all ITT/Safety subjects with either a positive rapid Strep A Test at baseline or a positive baseline throat swab culture for S. pyogenes; excluding those with major protocol violations and excluding those who did not have a clinical assessment at the TOC visit except clinical failures occurring before the end of Day 23. Efficacy results for clinical failures were included in the PPc analyses.

Study Visits

Table E1 shows the schedule of study visits. There were four study visits for bacteriological and/or clinical assessments as shown in table E1: Visit 1 (Day 1) was the screening/baseline visit; Visit 2 (Day 3-5) was the "During Therapy" visit; Visit 3 (Day 14-18) was the Test- of -Cure (TOC) visit; and Visit 4 (Day 38-45) was the Late Post-Therapy (LPT) visit. The visits were in accordance with the FDA draft guidance document. In addition, the Sponsor reported that for analysis purposes, the upper limit of the TOC visit window was set at Day 23. A TOC visit beyond this upper limit was considered a major violation.

Table E1 (Modified Sponsor's Table 2.7.3.1): Schedule of Study Visits

	Study Design		
Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
Baseline/screening visit (Day 1)	During therapy visit (Day 3-5)	TOC visit (Day 14-18)	LPT visit (Day 38-45)
Assessment of subject eligibility, including clinical signs and bacteriology	Assessment of clinical signs and symptoms	Assessment of bacteriological and clinical outcome	Assessment of bacteriological and clinical outcome
LPT visit = Last Post-Therapy visit, TOC visit = Test-of-Cure visit.			

Sponsor's Communication with the Division

The Sponsor wanted the Agency's advice regarding what it might take for their product (APC-111) to be approved as a first line therapy for the indication of interest. They specifically wanted to know if their product would be required to achieve a minimum of 85% bacteriological eradication rate at the TOC visit in the PPb population while also demonstrating non-inferiority of APC-111 against penicillin in both the PPb and mITT populations at the TOC visit.

The Division's Response

"What seems implicit in your question is whether, to be approved as a first line therapy, a bacteriologic eradication rate in the mITT population < 85% is acceptable. We prefer to see a bacteriological eradication rate in the APC 111 MP arm of the study to be ≥ 85% in the mITT population at the TOC visit. While an eradication rate that is < 85% in the mITT population at the TOC visit does not necessarily preclude approval as a first line therapy, the sponsor should endeavor to limit controllable forces likely to serve as barriers to reaching the desired eradication rate in the population of interest."

6.1.2 General Discussion of Endpoints

In Phase 3 studies, the primary endpoint was to determine the rate of bacteriological eradication in APC-111-treated patients compared to penicillin VK-treated patients at the Test of Cure (TOC) visit (Day 14- Day 18) in the bacterial Per Protocol (PPb) and modified Intent-to-Treat (mITT) co-primary populations.

Secondary endpoints were many and are discussed under sections 6.1.4 (Efficacy Findings).

MO comment: *The endpoints used and the outcome definitions and assessment methods for studies 302 (and 301) are consistent with FDA's recommendations in the Draft Guidance for Industry document entitled "Streptococcal Pharyngitis and Tonsillitis-*

Developing Antimicrobial Drugs for Treatment" developed in July, 1998. The design of the Sponsor pivotal Study 302 was generally similar to study 301, the major difference being the extension of APC-111 treatment duration by three days in study 302. Bacterial eradication is of paramount importance. The value of treating this disease within nine days of onset is to avoid disease complications, particularly of non-suppurative nature – rheumatic fever and acute glomerulonephritis. Ascertainment of bacterial eradication in mITT co-primary population is to have a sense of the product's performance in uncontrolled settings (i.e., in the "real world" scenario). Another important issue is a measure of not only how effectively S. pyogenes isolates were eradicated but also how long the treatment effect was sustained. To get some measure of this, the bacterial isolates from throat cultures obtained at the Late Post-Therapy (LPT) visit (Day 35- Day 42) were compared to bacterial isolates obtained at baseline. The use of Pulse Field Gel Electrophoresis [PFGE] and bacterial comparison to baseline isolates enabled the bacterial strains cultured at the LPT visit to be identified as discordant strains/new growth (reinfection), or concordant/same strains as those cultured at baseline (persistence versus carrier/re-colonization status, according to other factors enumerated in the study protocol).

The Choice of 10% delta (δ) for study 302

The Sponsor has provided justification for the choice of -10% delta (δ) for non-inferiority margin. According to the company, in considering the difference in treatment effects between APC-111 and penicillin VK, if the lower limit of the 95% confidence interval was greater than –10.0%, APC-111 would be considered no worse than, or noninferior to, penicillin when both are administered at the study-specified doses and duration, in the treatment of TP due to S. pyogenes. The case is based on the International Conference on Harmonization (ICH) guidance document 'E9 – Statistical Principles for Clinical Trials' and 'E10 – Choice of Control Group and Related Issues in Clinical Trials'. Accordingly, a non-inferiority margin should be defined as the 'largest difference that can be judged clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator'. Furthermore, 'the non-inferiority margin cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo'. The Sponsor indicates that, from the literature, the penicillin treatment effect compared to placebo has been demonstrated in a randomized, double-blind, placebo controlled trial. The bacteriological eradication rate was 7% following placebo treatment, 41% following treatment with penicillin 500 mg TID for 3 days, and 72% following treatment with penicillin 500 mg TID for 7 days. For study 302, the Sponsor indicated, the expected response rate (proportion of 'satisfactory' bacteriological outcomes ['eradication']) of at least 85% for the test treatment (APC-111 750 mg QD for 10 days) is significantly greater than the spontaneous (placebo) response rate estimated to be 7%.

MO Comments: *The Sponsor referenced literature sources, including one which showed that the penicillin treatment effect compared to placebo has been demonstrated in a randomized, double-blind, placebo controlled trial 10. The bacteriological eradication rate was 7% following placebo treatment, 41% following treatment with penicillin 500 mg TID for 3 days, and 72% following treatment with penicillin 500 mg TID for 7 days.*

For study 302, the Sponsor indicated that the expected response rate (proportion of 'satisfactory', i.e. bacteriological eradication outcomes of at least 85% of the test drug treatment (APC-111 750 mg QD for 10 days) is significantly greater than the spontaneous (placebo) response rate estimated to be 7%. The Sponsor based their choice of -10% delta (δ) mainly on this, and, secondarily, two other literature sources. Based on this information, the non-inferiority margin of -10% appears clinically reasonable for this indication, as the margin is significantly smaller than the difference expected to be obtained in a superiority trial of amoxicillin/penicillin against placebo. Penicillin remains the drug of choice for the treatment of streptococcal tonsillopharyngitis, as the Sponsor rightly stated, particularly because of its long history of use for the treatment of this disease and with no report of resistance to the product. Penicillin is administered TID or QID, with potential for compliance difficulty. As a secondary matter, (or a matter of curiosity), however, it would have been interesting if amoxicillin, approved for the same indication but administered TID or BID daily, could have served as a comparator or used in a three- arm study design. Although, the paper by Clegg et al5 shed some light on this idea, their product was not released in a pulsatile fashion. The information gathered would have been informative and could influence a potential buyer's inclination whether to go for once a day APC-111 or the old three times a day regimen.

6.1.3 Study Design

Study 302 was a Phase III, double-blind, double-dummy, randomized, parallel-group, multicenter study to evaluate the safety and efficacy of APC-111 MP Tablet, 775 mg PO QD for 10 Days compared to Pen VK, 250 mg PO QID for 10 days in the treatment of tonsillitis and/or pharyngitis secondary to Streptococcus pyogenes in adolescents and adults. It is a noninferiority design to demonstrate that in the treatment of PT as described above, APC-111 is noninferior to Pen VK.

Sponsor's Justification of Their Study Design

The Sponsor presents the following argument to justify the noninferiority design used and their choice of 10% delta (δ) for study 302.

1. The choice of a non-inferiority design is justified as the use of placebo controlled studies in this indication is generally not considered ethical, based on the need to avoid post-streptococcal sequelae of carditis and nephritis.

2. The active comparator chosen, penicillin, is considered the drug of choice for the t treatment of streptococcal tonsillopharyngitis and has been used in a number of registrational studies for this indication, including Spectracef® and Omnicef®.

3. The dose and dosing regimen for penicillin VK were selected based on approved product labeling information with precedence for use as a comparator in registration t rials for this indication.

4. Maintaining of study blind throughout the study was facilitated by the availability and use of over-encapsulated penicillin VK tablets with matching penicillin VK

placebo capsules, and APC-111 placebo tablets identical in appearance to APC-111.

Study Objectives (see Study Protocol in Appendix 1)

MO comments: *The MO has reviewed the study protocol, including study objectives, endpoints, eligibility criteria, the efficacy variables, etc. All the protocol components have been described in great detail by the sponsor. A few items in the protocol, e.g. demographic characteristics, population analyzed, choice of -10% delta, protocol deviation, and concomitant medications are presented in the body of the review given their potential direct influence on data analyzed. The other "routines" of the protocol, however, have been placed under Appendix 1 of the review and are available for reference, as needed.*

On balance, the reviewer considers the protocol adequate.

Demographic Characteristics

Tables E2 and E3 display demographic characteristics of the two treatment groups in study 302. According to the Sponsor, there were no statistically significant differences between the two treatment groups in gender, race, age, weight, including age and weight distribution. Both treatment groups had slightly more females than males - i.e. 57.9% in the APC-111 treatment group versus 64.7% in the Pen VK treatment group. The population was made up predominantly of Caucasians – i.e. 90.4% (APC-111 group) versus 92.5% (Pen VK group). The mean weight was approximately 79.34 kg (APC-111 group) versus 76.95 kg (Pen VK group). The mean age was 29.9 years (APC-111 group) versus 29.3 years (Pen VK group). There were approximately
23 % adolescents between 12 and 18 years of age in both treatment groups. There was comparable age distribution of these patients as well as those in the age group ≥ 40 years. However, there was a greater proportion of patients in the age range 19 to < 30 years in the penicillin treatment group (33.7%) compared with the APC-111 treatment group (24.8%). There was also a greater proportion of patients in the age range 30 to < 40 years in the APC-111
treatment group (33.4%) compared with the penicillin treatment group (23.5%).
The PPb population had similar demographic and baseline characteristics.

Table E2 (Modified Sponsor's Table 10-6) Demographic and other Baseline Characteristics - ITT/Safety Population

(N = 306)	APC-111	Pen VK Demographic/baseline characteristic (N =302)	p-value[a]
Gender, n (%)			
Female	175 (57.9)	198 (64.7)	0.0873
Male	127 (42.1)	108 (35.3)	
Race, n (%)			
Caucasian	273 (90.4)	283 (92.5)	0.6488
African American	13 (4.3)	9 (2.9)	
Asian / Oriental	9 (3.0)	6 (2.0)	
American Indian / Alaskan Native	0 (0.0)	1 (0.3)	
Other	7 (2.3)	7 (2.3)	
Ethnicity, n (%)			
Hispanic	17 (5.6)	13 (4.2)	0.4323
Non – Hispanic	285 (94.4)	293 (95.8)	
Age group, n (%)			
12 to <19 years	70 (23.2)	69 (22.5)	0.4907
19 to <30 years	75 (24.8)	103 (33.7)	
30 to <40 years	101 (33.4)	72 (23.5)	
≥40 years	56 (18.5)	62 (20.3)	
Age (years)			
Mean (SD)	29.9 (12.07)	29.3 (12.43)	0.5377
Median (range)	30.0 (12 – 67)	28.0 (12 – 72)	

a: p-value calculated using a Cochran Mantel-Haenszel test for qualitative data and analysis of variance (ANOVA) with treatment groups as main effect for quantitative

Table E3 (Modified Sponsor's Table 10-6) Demographic and other Baseline Characteristics - ITT/Safety Population – Continued

Demographic/baseline characteristic	Pen VK		
Demographic/baseline characteristic	**(N =302)**	**(N = 306)**	**p-value[a]**
Weight group, n (%)			
Missing	1	1	0.0873
< 40 kg	3 (1.0)	3 (1.0)	
> 40 kg to < 80 kg	162 (53.6)	182 (59.5)	
> 80 kg to < 120 kg	122 (40.4)	112 (36.6)	
> 120 kg to < 160 kg	13 (4.3)	8 (2.6)	
> 160 kg	1 (0.3)	0 (0)	
Weight (kg)			
N	301	305	0.1074
Mean (SD)	79.34 (21.15)	76.66 (19.63)	
Median (range)	76.48 (39.0 – 160.8)	73.94 (38.6 – 142.0)	

a: p-value calculated using a Cochran Mantel-Haenszel test for qualitative data and analysis of variance (ANOVA) with treatment groups
as main effect for quantitative data.

MO Comments *– The Sponsor has enumerated the asymmetry between treatment groups regarding the demographic subgroups in tables E2 and E3, namely gender, weight and race. The racial proportions in the study groups are a reflection of the local racial demographics of the geographic regions of the study centers where patients were recruited. Otherwise, the overall distribution of demographic subgroups in the two study arms was fairly similar. Where a slight difference occurred, it was not significant enough to skew study results in either direction for this indication.*

Concomitant Antibacterial Medications

The majority of non-study antibiotics received by study patients were "rescue" treatments for clinical failure cases that showed no response (or poor response) to study antibiotic therapy. Such patients received macrolides, first to third-generation cephalosporins, or extended spectrum penicillins, including beta-lactamase inhibitors. Table E4 represents the Sponsor's tabulation of the overall antibiotic classes used by such patients while Table E5 is the reviewer's tabulation of the specific concomitant antibiotics received by patients for the infections under which they are listed in the table.

Table E4: Concomitant Systemic Antibacterial Medication Use in MITT Population

	APC-111 n (%)	**Pen VK n (%)**	**Total n (%)**
Subjects in ITT/Safety	**302 (100.0)**	**306 (100.0)**	**608 (100.0)**
Patients with at least one use of concomitant antibiotic	61 (20.2)	55(18.0)	116 (19.1)
Antibacterials	60 (19.9)	55(18.0)	115 (18.9)
Macrolides	20 (6.6)	13 (4.2)	33 (5.4)
Third-generation cephalosporins	10 (3.3)	13 (4.2)	23 (3.8)
Penicillins with extended spectrum	8 (2.6)	13 (4.2)	21 (3.5)
Comb of penicillins, incl. beta-lactamase inhib.	9 (3.0)	7 (2.3)	16 (2.6)
Beta-lactamase sensitive penicillins	6 (2.0)	4 (1.3)	10 (1.6)
First-generation cephalosporins	7 (2.3)	3 (1.0)	10 (1.6)
Fluoroquinolones	4 (1.3)	4 (1.3)	8 (1.3)
Comb.sulfonamides & trimethoprim incl. derivatives	1 (0.3)	1 (0.3)	2 (0.3)
Second-generation cephalosporins	0 (0.0)	2 (0.7)	2 (0.3)
Imidazole derivatives	1 (0.3)	0 (0.0)	1 (0.2)
Lincosamides	1 (0.3)	0 (0.0)	1 (0.2)
Nitrofuran derivatives	1 (0.3)	0 (0.0)	1 (0.2)
Tetracyclines	0 (0.0)	1 (0.3)	1 (0.2)

Concomitant systemic antibacterial medication was defined by the Sponsor as any antimicrobial agent started: 1.) after the first dose of study antibiotic, or 2.) prior to the first dose of study antibiotic and continued during the study.

The use of concomitant non-study systemic antibacterial agents in patients for concurrent ailments while also receiving study antibiotics for PT was considered a major protocol violation. In efficacy data analysis, any patient who committed such violation was evaluated as "indeterminate" regardless of bacteriological outcome. Each patient's

clinical response was characterized as 'unable to evaluate', as outlined in the Statistical Analysis Plan. The treatment effect of such concomitant antibiotic to which S. pyogenes may have been susceptible could not be separated from that of study drug product. According to the Sponsor, in the PPb population, no concomitant systemic antibacterial medication use was reported prior to TOC visit, with the exception of clinical failures who received a non-study systemic antimicrobial for the treatment of PT. Moreover, between the TOC and LPT visits, use of non-study concomitant systemic antibacterial medication was reported in a number of patients. Such patients were excluded from the PPb population at LPT, with the exception of clinical failures who received non-study systemic antibiotics for the treatment of PT. Protocol violations committed by study patients used certain antibiotics concomitantly (i.e., while also receiving study antibiotics) for the treatment of the following infections: urinary tract infection (APC-111, 3 patients; Pen VK, 3 patients), sinusitis (APC-111, 3 patients; Pen VK, 2 patients), bronchitis (APC-111, 3 patients ; Pen VK, 1 patient), skin and skin structure infections (APC-111, 3 patients ; Pen VK, 1 patient), upper respiratory infections (APC-111, 0 patient ; Pen VK, 2 patients), and other miscellaneous indications (APC-111, 3 patients ; Pen VK, 3 patients).

Table E5: Concomitant Antibiotic classes used by study patients

Indication	Concomitant Antibacterial Agent Used	Treatment Group		
		APC-111 n (%)	Pen VK n (%)	Total n (%)
		302 (100.0)	**306 (100.0)**	**608 (100.0)**
UTI	Moxifloxacin, Levofloxacin, ceftriaxone, Ciprofloxacin, Bactrim, Nitrofurantoin	3 (1.0)	4 (1.3)	
URI	Omnicef, Amoxicillin, Azithromycin	0 (0.0)	3 (1.0)	3 (0.5)
Bronchitis	Amoxicillin, Clarithromycin,	2 (0.7)	2 (0.7)	4 (0.7)
Sinusitis	Levofloxacin, Gatifloxacin	7 (2.3)	3 (1.0)	10 (1.6)
SSSI	Keflex, clindamycin, Zosyn, Augmentin, Kefzol	3 (1.0)	1 (0.3)	4 (0.7)
Others	Doxycycline, Amoxicillin, cephalexin, cefdinir, Bactrim	3 (1.0)	4 (1.3)	7 (1.2)

SSSI= skin and skin structure infection

Table E6: Reviewer's Assessment of Concomitant antibiotics Use (per dataset provided)

Indication	Sponsor	Reviewer		Sponsor	Reviewer
	APC 111	APC 111		Pen VK	Pen VK
	302 (100.0)	302 (100.0)		306 (100.0)	306 (100.0)
UTI	3	3		3	4 *
Sinusitis	3	6 *		2	2
ronchitis	3	2		1	2 *
SSI	3	2		1	1
URI	0	0		2	3 *
Others	3	3		3	3

UTI = urinary tract infection; URI = upper respiratory tract infection; SSSI = skin and skin structure infection; * = Disagreement in numbers (Reviewer's figures generated from datasets provided by the Sponsor)

MO comments: *Table E5 displays the concomitant antibiotics generally used for the various concurrent infections of study patients. There were agreements and some differences in count between the Sponsor and the reviewer with regards to the number of patients who received concomitant antibiotics for the treatment of concurrent infections. Table E6 shows the Reviewer's accounting of the number of patients and how it differs from the Sponsor's. For example, based on the dataset provided, six patients (rather than three, per the Sponsor's count) in the APC-111 arm of the trial received extra-study antibiotics for the treatment of sinusitis. Similarly, on the Penicillin VK arm of the study, the Sponsor and the reviewer differ in the number counts with respect to how many patients received concomitant antibiotics for the treatment of urinary tract infection (UTI), bronchitis, and upper respiratory tract infection (URI). However, the absolute numbers are small, as are the differences between figures across study arms.*

Table E6b: Patients Who Received Concomitant Antibiotics and their Analysis Group

Patient ID	Population	Concomitant Medication	Reason for Concomitant Drug use
APC 111 Group			
0401/3006	PPb	Amoxicillin	Rhinosinusitis
0298/3009	PPb	Amoxicillin/Clavulanate	Sinusitis
0314/3005	PPb	Azithromycin	Bronchitis
0443/3003	PPb	Clinda, Kefzol, Levaquin, Zosyn, Augmentin	SSSI
0461/3015	PPb	Keflex	SSSI
0450/3003	PPb	Macrobid (nitrofurantoin)	UTI
0314/3002	PPb	Bactrim	Others (Kidney Stone prophylaxis)
Pen VK Group			
291/3012	PPb	Avelox, Rocephin, Ciprofloxacin, Levofloxacin	Pyelonephritis
0461/3009	PPb	Septra	UTI
0316/3018	PPb	Omnicef	URI
0461/3002	PPb	Amoxicillin	URI
0453/3001	PPb	Levaquin	Sinusitis
0324/3010	PPb	Doxy-Caps	Left Breast Legion
0369/3004	PPb	Amoxicillin	Infected Tooth
0464/3012	PPb	Zithromycin	Pharyngitis – Worsening symptoms

UTI = urinary tract infection; URI = upper respiratory tract infection; SSSI = skin and skin structure infection; * = Disagreement in numbers (Reviewer's figures generated from datasets provided by the Sponsor)

MO comments: *Table 6B shows the patients who used concomitant antibiotics in the PPb population. The impact of patients' use of these antibiotics on the primary and co-primary efficacy results would depend on the type of antibiotics and the time of use relative to TOC visit. If some of these antibiotics were received long after TOC visit evaluation, such concomitant antibiotics would have no effect on primary efficacy evaluation. The impact of the use of these antibiotics by study patients on secondary efficacy results will be similarly evaluated.*

Sponsor's Population Subsets for Analysis of Study 302

The Sponsor defined their populations to be analyzed in their efficacy determination as follows:

1. **ITT (Intent-to-treat):** All patients who received at least one dose of study medication and who had at least one post-baseline clinical safety assessment.

2. **mITT (Modified intent-to-treat):** All ITT patients with a positive throat culture for *Streptococcus pyogenes* at baseline

3. **mITT [a]:** All mITT patients minus those with bacteriological response at TOC of 'indeterminate' and a clinical response of 'unable to evaluate'.

4. **mITT [b]:(Co-primary efficacy analysis population):** All mITT patients including those with bacteriological response at TOC of 'indeterminate' and a clinical response of 'unable to evaluate'. These patients were included in the analysis as an unsatisfactory outcome.

5. **PPc (Per-Protocol clinical):** All ITT patients who completed the study as specified by protocol and with no major protocol violation

6. **PPb (Co-primary efficacy analysis population):** All patients with a positive baseline throat culture for *S. pyogenes* and with throat culture results available at the TOC visit. Also includes clinical failures that withdrew early from the study and started a new antimicrobial for PT were included in the PPb analyses.

Patient Selection and Randomization

Screening: A total of 673 patients were screened out of which 618/673 (91.8%) were eligible for randomization. The most important reason for screening failure was negative (b) (4) Strep A Test (6.1% of screened patients).

Randomization: A total of 618 patients were randomized to receive study medication (see Sponsor's table E7). Of these, 306 received APC-111; 312 received Pen VK. A total of 608 were considered ITT/Safety evaluable patients (302 in the APC-111 arm, and 306 in the Pen VK arm). There were 10 patients (4 in the APC-111 arm, and 6 in the Pen VK arm) who were randomized and treated, but had no post baseline clinical safety assessment data available and were considered ineligible for inclusion in the ITT/Safety population. How the rest of the population subsets were derived (down to the two co-primary efficacy populations) have been tabulated (see reviewer's derived Table E8) and the following represents Sponsor's description of their analysis population subsets.

Table E7: (Sponsor's modified Table 10.2): Number (%) of Patients in Each Analysis population

Population	Number (%) of Subjects		
	APC-111	**Pen VK**	**Total**
Subjects randomized	306 (100.0)	312 (100.0)	618 (100.0)
ITT/Safety	302 (98.7)	306 (98.1)	608 (98.4)
mITT	256 (83.7)	264 (84.6)	520 (84.1)
PPb	233 (76.1)	229 (73.4)	462 (74.8)

Compliance with Study Medication and Dosing Requirements

As treatment duration was 10 days, if treatment study medication was started late on Day 1, such that not all of the first day's medication could be taken, the remaining Day 1 doses were to be completed on Day 11.

Per the Sponsor, about 93.7 % and 92.8 % of the ITT/Safety population in the APC-111 and Pen VK treatment groups, respectively, received study medications for 10 days. Only 1.0% of APC-111-treated patients versus 43.1% of Pen VK-treated patients received greater than 10 days of study medications because they either needed to complete their Day 1 doses (i.e., Pen VK capsules) on Day 11 as protocol-directed or took any missed dose (s) from another day. The mean duration of treatment with active study medication was 9.7 and 10 days for the APC-111 and penicillin VK treatment groups, respectively, of the ITT/Safety population. Duration of treatment was similar in the mITT population.

Table E8a: Sponsor's Table of Compliance to study medication and dosing requirement.

mITT Population	**APC-111 (N =256)**	**Pen VK (N = 264)**	**P-value [a]**
During first 3 days on study			0.0007
Compliance < 100%	4 (1.6)	21 (8.0)	
Compliance = 100%	252 (98.4)	243 (92.0)	
Overall compliance during study			< 0.0001
Compliance < 80%	12 (4.7)	18 (6.8)	
Compliance 80% - 89%	0 (0.0)	7 (2.7)	
Compliance 90% - 99%	1 (0.4)	67 (25.4)	
Compliance = 100%	243 (94.9)	172 (65.2)	
PPb Population	**(N =233)**	**(N = 229)**	
During first 3 days on study			
Compliance < 100%	0 (0.0)	0 (0.0)	
Compliance = 100%	233 (100.0)	229 (100.0)	
Overall compliance during study			< 0.0001
Compliance < 80%[b]	2 (0.8)	3 (1.3)	
Compliance 80% - 89%	0 (0.0)	2 (0.9)	
Compliance 90% - 99%	1 (0.4)	56 (24.5)	
Compliance = 100%	230 (98.7)	168 (73.4)	

Compliance = (Number active doses taken / Number of active doses planned)

a: p-value calculated using a Cochran Mantel-Haenszel test for qualitative data.
b For PPb population, compliance < 80% includes subjects regarded as clinical failures who withdrew from the study and started another non-study antimicrobial for the treatment of PT prior to TOC.

Major Protocol Violation

Table E 8b Summary (and Type) of Major Violations	APC-111	Pen VK
BL throat culture (-) for *S. pyogenes*, or culture result not available	46	42
Less than 100% compliance during the first 3 study days (72 hours)	16	32
No clinical assessment at TOC	14	26
No post-baseline clinical safety assessment data available	4	6
No throat swab culture results available at TOC	17	16
Overall compliance less than 80%	15	26
Previous or current medical condition	2	5
Throat swab culture sample collected after Day 23	1	2
Throat swab culture sample collected before Day 14	18	17
TOC visit not within Day 14 to 23, inclusive but unknown if < D14 or > D23	6	5
Use of prohibited prior and/or concomitant medication	6	2

BL = Baseline; (-) = negative.

MO comments: *Most of the patients affected by, or involved in, the above categories of protocol violations were in the ITT population. None was in the PPb population. As the table indicates, the categories with larger inter-treatment group differences involved compliance, absence of TOC visit assessment and, to a lesser degree, the category involving the use of prohibited medication. However, this last category involves a small number of patients.*

6.1.4 Efficacy Findings

Based on the study results derived from study 302 and displayed on the Sponsor's Table E9, and analyzed in the PPb and mITT co-primary populations indicate that, APC-111, at a dose of 775 mg QD, given orally for 10 days, was not worse than penicillin VK 250 mg QID, administered orally, for 10 days in bacteriological outcome at the TOC visit. Non-inferiority, per the Sponsor, has therefore been demonstrated.

The evaluation of the efficacy of APC-111 was based on study 302 efficacy results given that study 301 failed to meet efficacy requirement goal. The reasons for the different outcomes in the two similarly designed studies has been analyzed by the reviewer immediately before subsection 6.1.6 (Efficacy Conclusion).

Analysis of data in the PPb Population at the TOC visit

The primary efficacy analysis was performed on the primary efficacy variable - the bacteriological outcome at TOC in the PPb and mITT [b] co-primary populations (see General endpoint discussion, section 6.1.2). Ascertainment of product efficacy was based on bacteriological outcome at the TOC visit. Accordingly, for the PPb population at the TOC visit, only a bacteriological response of eradication was considered a

satisfactory outcome. For the mITT population at the TOC visit, a bacteriological response of eradication or presumed eradication was considered a satisfactory bacteriological outcome.

As shown in Table E9, the Sponsor indicated that 198/233 (85%) of study patients who received APC-111 in the PPb population had a satisfactory bacteriological outcome at the TOC visit compared to 191/229 (83.4%) who received comparator treatment. The 95% confidence intervals (CI) around the point estimates (treatment difference) was calculated as -5.1, 8.2. The lower bound of the 95% CI of -5 is greater than the pre-specified margin of -10 delta (δ).

Analysis of data in the mITT Co-Primary Population at the TOC visit
In the co-primary mITT population, 211/256 (82.4%) APC-111-treated patients had a satisfactory bacteriological outcome at the TOC visit versus 207/264 (78.4%) patients who were comparator-treated. The difference in point estimates, 4.0, is larger than that obtained in the PPb population. The 95% CI for the treatment difference in this population was -2.8, 10.8. Consequently the lower bound of the 95% CI for the treatment difference is greater than -10, the pre-specified δ.

The Sponsor performed a sensitivity analysis of product efficacy in the mITT population without the patients whose bacteriological status could not be determined ('indeterminate' cases). Then 211/248 (85.1%) APC-111-treated patients had a satisfactory bacteriological outcome at the TOC visit versus 207/252 (82.1%) comparator-treated patients. The difference in point estimates is 2.9 and 95% CI for the treatment difference in this sub- population being -3.5, 9.4. Consequently the lower bound of the 95% CI for the treatment difference is greater than -10, the pre-specified δ.

Based on these data analyses of study 302 by the Sponsor, the efficacy results in the two co-primary populations show corroboration and consistency. Accordingly, the data analyzed in the PPb and mITT co-primary populations indicate that APC-111, at a dose of 775 mg QD given orally for 10 days, was not worse than penicillin VK, 250 mg QID administered orally for 10 days, in bacteriological outcome at the TOC visit. Non-inferiority, per the Sponsor, has therefore been demonstrated.

Table E9 - (Modified Sponsor's Table 2.5.4-1): Sponsor's Analyses of Bacteriological Outcome at the TOC Visit in The Co- Primary Populations

Bacteriological outcome/	PPb[a] N (%)		mITT [b][b] N (%)	
	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[c]				
Difference[d]	1.6		4.0	
95% CI[e]	-5.1, 8.2		-2.8, 10.8	

a The PPb population: patients with positive baseline throat cultures for S. pyogenes, with evaluable throat cultures at the TOC visit, with no major protocol violations, and not clinical failures who withdrew early from the study and started on new antimicrobial agents for the treatment of tonsillitis and/or pharyngitis.
b The mITT population: patients with a positive baseline throat cultures for S. pyogenes, who received at least one dose of study medication and had at least one post-baseline clinical safety assessment. The mITT [b] principal analysis included patients with an indeterminate bacteriological response.
c Comparison between treatment groups: asymptotic point estimate and 95% confidence interval for the difference in satisfactory bacteriological outcome rates.
d Difference between treatment groups: calculated as (APC-111 – penicillin).
e Two-sided 95% confidence interval.

MO Comments: *Table E9 is the Sponsor's efficacy analysis table in the efficacy co-primary study populations. Table E10 displays the reviewer's detailed representation and accounting (using dataset information) of how the different analysis subpopulations*

were derived. Explanations are provided in italics under "Analysis Population Subsets" as to how the ITT population was "thinned" down in a step-wise manner to the PPb population. The reviewer agrees, prima facie, with the Sponsor's numbers, but will ascertain other factors that could also lead to differences between the reviewer and the Sponsor, e.g. after evaluating the case report forms (CRFs) of some patients in the PPb and mITT populations who received concomitant antibiotics or had any other major violations during the study.

Table E10: Study population and eligibility accounting at the TOC Visit (Derived from the Sponsor's Dataset)

Analysis Population Subsets *(Reasons for patient exclusion in italics)* ↓	**PPb Population**		**mITT Population**		
	APC-111	**Pen VK**	**APC-111**	**Pen VK**	**Comments**
	n (%)	n (%)	n (%)	n (%)	
ITT (Safety) population following randomization	**306 (100.0)**	**312 (100.0)**	**306 (100.0)**	**312 (100.0)**	Received ≥ 1 dose of study Med.
Post-BL safety evaluation data Unavailable	4 (1.3)	6 (1.9)	4 (1.3)	6 (1.9)	
Initial Modified Intention-to-treat (mITT)	**302 (98.7)**	**306 (50.3)**	**302 (98.7)**	**306 (50.3)**	
Baseline Throat culture (-) or not available	46 (15.0)	42 (13.5)	46 (15.0)	42 (13.5)	
Modified Intention-to-treat (mITT)	**256 (83.7)**	**264 (84.6)**	**256 (83.7)**	**264 (84.6)**	
Protocol violation	23 (7.5)	35 (11.2)	↓	↓	
Efficacy evaluable	**233 (76.1)**	**229 (73.4)**	**256 (83.7)**	**264 (84.6)**	
Bacterial Persistence	30 **(12.9)**	**32 (14.0)**	30 **(11.7)**	37 (14.0)	
Bacterial Presumed Persistence	5 (2.1)	6 (2.6)	7 (2.7)	8 (3.0)	
Indeterminate			8 (3.1)	12 (4.5)	
Total Number of Unsatisfactory Responses	35 (15.0)	38 (16.6)	45 (17.6)	57 (21.6)	
Bacteria Eradication	**198 (85%)**	**191 (83.4%)**	**204 (79.7)**	**206 (78.0)**	
Bacteria Presumed Eradication			7 (2.7)	1 (0.4)	
Overall Efficacy	**198 (85%)**	**191 (83.4%)**	**211 (82.4)**	**207 (78.4%)**	

Med. = Medication; BL = Baseline; ITT = Intent- to-Treat; Pen VK = Penicillin VK; APC-111 = Amoxicillin pulsatile release; (-) = negative

Reviewer's Analyses of data in the Co-primary populations

Table E11 is a tabulation of patients included in the PPb population who received concomitant antibiotics. Most of them did so between the TOC and LPT visits. One APC-111-treated patient (0401/3006) received a course of non-APC-111 amoxicillin for the treatment of rhinosinusitis. She received her last dose 23 days before receiving the first dose of APC-111 for the treatment of her PT, following documentation of positive rapid antigen test for S pyogenes while participating in study 302. Her enrollment into the study was a violation of exclusion criterion # 16 of the study protocol [which stipulated that patients be excluded if they had a history of "previous systemic antimicrobial therapy within 30 days prior to Screening/Baseline visit 1 (or Day 1)"].The patient ended up in the PPb population. Patient 0450/3003 (also in the APC-111 arm) received antibiotic (Macrobid) within 30 days prior to baseline. But Macrobid is inactive or weakly active against S pyogenes and is a case of minor protocol violation.

In the Pen VK arm, two patients (# 0316/3018 and # 0464/3012) had persistence of clinical symptoms of PT. The former received a dose of plain amoxicillin and a subsequent course of Ceftin. The second patient received azithromycin for worsening pharyngitis after 4 days on Pen VK. These patients were cases of evaluable failure but were included in the PPb population by the sponsor.There did not appear to be inappropriate inclusion or exclusions of patents in the mITT population.

MO Comment: *As noted in the text above, most of the patients who used concomitant antibacterial agents did so after the TOC visit, but before the LPT visit. The disagreement between the reviewer and the Sponsor with respect to patient adjudication involves only a small number of patients. It involves an APC 111-treated patient and the two Pen VK-treated patients whose use of concomitant antibiotics led to their removal from the PPb populations. The throat rapid antigen test was positive when enrolled into the study despite receiving a course of amoxicillin up to 23 days earlier. Although strict adherence to the eligibility criteria forbade her enrollment, her symptomatology combined with her positive throat culture seemed to make her inclusion in the study and treatment appropriate. There was no information provided to indicate that she was a S. pyogenes carrier who had an acute viral tonsillopharyngitis. Even if she was removed from the PPb co-primary population, the efficacy figures calculated by the Sponsor would still not be adversely affected. As Table E12 shows, the reviewer's efficacy re-analysis in the PPb population indicates that 197/232 (84.9%) of study patients who received APC-111 in the PPb population had a satisfactory bacteriological outcome at the TOC visit compared to 189/227 (83.3%) who received comparator treatment. The 95% confidence intervals (CI) around the point estimates were calculated as -5.0, 8.4. There were virtually no difference between the reviewer's and the Sponsor's analyses with regards to the efficacy evaluation in the mITT co-primary population at the TOC visit.*

The lower bound of the 95% CI of -5 is greater than the pre-specified margin of -10 (delta [δ]). Therefore, the reviewer agrees with the Sponsor's conclusion with regards to the non-inferiority of the APC--111, relative to the comparator, Pen VK, as analyzed in the co-primary populations at the TOC visit, and in the treatment of PT caused by S. pyogenes.

Although the treatment of patient 0401/3006 violated exclusion criterion # 16, was clinically appropriate.

Table E11: Concomitant Antibiotic Use by Patients in PPb Populations

APC 111	Population	Age/Gender	Study Abx Use /Date	Concomitant Antibiotic/Date	Reason	Comments
0401/3006	PPb	37 yo W♀	4.18 .06– 4.27.06	Amoxicillin/ 3.17 – 3.26.06	Rhinosinusitis	Abx within 30 days of Day 1; violated exclusion criterion #16.
0298/3009	PPb	44 yo W♂	01.07.06 –01.16.06 ;	Augmentin /02.01.06 – 02.11.06	Sinusitis	Abx use between TOC and LPT
0314/3005	PPb	65 yo W♂:	3.13.06 – 3.22. 06	Zithromax 2 mg (one dose on 3.28.06)	Bronchitis	Abx use between TOC and LPT
0443/3003	PPb	51 y/o H♂	2/31/06 – 3.10.06	Multiple Abx from 4.23.06	Cellulitis	Abx use between TOC and LPT
0461/3015	PPb	20 yo WM;	3.10.06 – 3.20.06	Keflex/1500 mg 4.18 .06 one dose)	Cellulitis	Abx use between TOC and LPT
0450/3003	PPb	24 yo W♀	Feb 6 – Feb 16, 2006;	Macrobid/ 01. 01.06- 01.17.06.	UTI	20 days to Day 1 but Macrobid is inactive against *S pyogenes*
0314/3002	PPb	28 yo W♀;	12.8.05 - 12.18.05;	Bactrim/01.07.06 – 0 1.13.06.	Renal calculi	Bactrim poorly active against *S pyogenes*
Pen VK Group						
0291/3012	PPb	34 yo W♀	05.04.06 –05.14.06	Multiple Abx 02.16.06. - 6.15.06	Pyelonephrtis	Abx use between TOC and LPT
0316/3018	PPb	14 yo W♀:	01.30.06–02.09.06;	Omnicef 02.16.06 (one dose).	URI	Abx use between TOC and LPT
0461/3002	PPb	15 yo W♀	12.14.05 - 12.24.05;	Ceftin:12.27.05–01. 05.06 Amox/12.25.05	Pharyngitis	Evaluable Failure
0453/3001	PPb	45 yo W♀	11.22.05 -12.2.05	Levaquin 12.14 -12-24.05	Sinusitis	Abx use between TOC and LPT
0324/3010	PPb	12 yo W♂:	2/22/06 -3/04/06	Doxy: 3.10.06 – 3.20.06	Breast lesion.	Abx use between TOC and LPT
0369/3004	PPb	23 y/o W♂	01.03 – 01.12.06;	Amox/ 01.25 – 02.3. 06	Infected tooth	Abx use between TOC and LPT
0464/3012	PPb	32 yo WM	3/13/06 - 3/17/06 failure	Received Azithromycin	Worsening Pharyngitis.	Evaluable Failure

Abx = **Antibiotics; Amox=** Amoxicillin; UTI = urinary Tract Infection; URI = upper respiratory infection

Table E12: Reviewer's Efficacy Recalculation.

Sponsor's Analysis of Efficacy in Co-primary Populations				
Bacteriological Outcome	**PPb [n (%)]**		**mITT[n (%)]**	
	APC-111	**Pen VK**	**APC-111**	**Pen VK**
N →	**233**	**229**	**256**	**264**
Total Satisfactory	**198 (85)**	**191 (83.4)**	**211 (82.4)**	**211 (78.4)**
Total Unsatisfactory	**35 (15.0)**	**38 (16.1)**	**45 (17.6)**	**57 (21.6)**
Point estimate Difference	**1.6**		**4.0**	
95% CI	**-5.1 - 8.2**		**-2.8, 10.8**	

Reviewer's Analysis of Efficacy in Co-primary Populations				
Bacteriologic Outcome	**PPb [n (%)]**		**mITT[n (%)]**	
	APC-111	**Pen VK**	**APC-111**	**Pen VK**
N →	**232**	**227**	**256**	**266**
Total Satisfactory	**197 (84.9)**	**189 (83.3)**	**211 (82.4)**	**207 (77.8)**
Total Unsatisfactory	**35 (15.1)**	**38 (16.7)**	**45 (17.6)**	**57 (21.6)**
Point Estimate Difference	**1.6**		**4.0**	
95% Confidence Intervals	**-5.0 , 8.4**		**-2.8, 10.8**	

Secondary Efficacy Results

Secondary efficacy analyses included patient responses at the TOC and LPT visits and in the following enumerated subpopulations.

Clinical Assessments
TOC visit [Table E13a & Table E13b]:
Clinical Outcome in the PPb Population
Clinical Outcome in the mITT [b] Population
Clinical Outcome in the ITT/Safety Population
Clinical Outcome in the PPc Population

LPT visit [Table E14]:
Clinical Outcome in the PPc Population
Clinical Outcome in the ITT/Safety Population

Bacteriological Assessments
LPT visit [Table E15]:
Bacteriological Outcome at the LPT Visit in the PPb and mITT [b]
Bacteriological Outcome vs Clinical Outcome at the TOC Visit in the PPb and mITT[b] Co-primary Populations

Clinical Outcomes at the TOC visit

The combined Tables E13a and E13b provide clinical assessments in all four subpopulations targeted for clinical assessments. Tables E13a displays clinical assessment results in the PPb and mITT populations. The assessments were made as an attempt to compare clinical resolution findings to bacteriological assessment results.

PPb Population

As Table E13a shows, 213/233 (91. 4%) APC-111-treated patients in the PPb population had the response of clinical cure during their TOC visit, which was similar to 212/229 (92.6%) patients who received Pen VK treatment. The difference between the point estimates, and the 95% confidence intervals between the two groups, are also shown in the table.

mITT Population

For the mITT [b] population at the TOC visit, a clinical response of cure was considered a successful clinical outcome, while responses of failure, unable to evaluate, or missing were considered as a non-successful clinical outcome.

The results of the clinical outcome analyses in the mITT [b] population are presented in the same Table E13a. As indicated by the data, 226/256 (88.3%) APC-111-treated patients had the outcome of cure compared to 228/264 (86.4%) study patients who received Pen VK. Further analyses (with regards to point estimate difference, 95% lower and upper bound confidence limits) are similar to the analyses in the PPb population above. With regards to the clinical failures, they are shown in the same Table E13a.

Table E13a: Clinical Outcome at the TOC visit in PPb and mITT Populations
[Modified Sponsor's tables 11-7 through 11-10]

Analysis of Efficacy

Clinical Outcome	PPb [n (%)]				mITT [n (%)]			
	APC-111	Pen VK			APC-111	Pen VK		
N →	233	229	Diff.	95% CI	256	264	Diff.	95% CI
Success/Clinical Cure	213 (91.4)	212 (92.6)	-1.2	-6.1, 3.8	226 (88.3)	228 (86.4)	-1.9	-3.8, 7.6
Non-Success	20 (8.6)	17 (7.4)			30 (11.7)	36 (13.6)		
Clinical Failures	18 (7.7)	15 (6.6)			20 (7.8)	21 (8.0)		
Unable to evaluate	2 (0.9)	2 (0.0.9)			8 (3.1)	10 (3.8)		

Table E13b: Clinical Outcome at the TOC Visit in the PPc and the ITT/Safety Population

Clinical Outcome	PPc [n (%)]				ITT/Safety [n (%)]			
	APC-111	Pen VK			APC-111	Pen VK		
N →	280	263	Diff.	95% CI	302	306	Diff.	95% CI
Success/Clinical Cure	257(91.8)	246 (93.5)	-1.8	-6.1, 2.6	265 (87.7)	264 (86.3)	1.5	-3.9, 6.8
Non-Success	23 (8.2)	17 (6.5)			37 (12.3)	42 (13.7)		
Clinical Failures	20 (7.1)	15 (5.7)			21 (7.0)	21 (6.9)		
Unable to evaluate	3 (1.1)	2 (0.8)			12 (4.0)	12 (3.9)		
Missing					4 (1.3)	9 (2.9)		

CI = Confidence interval

Bacteriological Outcome vs Clinical Outcome at the TOC Visit in the PPb and mITT[b] Co-primary Populations

According to the Sponsor, in the two Co-primary efficacy populations at the **TOC** visit the following occurred:
PPb – all 198/233 (85%) patients who received APC-111 and had bacteriological satisfactory response (i.e. eradication) also had satisfactory clinical response. Of the 191/229 (83.4%) Pen VK-treated patients who had bacteriological outcome of cure (eradication), two had a response of "unable to evaluate".
mITT – all 211/256 (82.4%) patients who received APC-111 and had bacteriological satisfactory response (i.e. eradication) also had satisfactory clinical response. Of the 207/264 (78.4%) patients who received Pen VK and had bacteriological outcome of cure (eradication), four had unsatisfactory outcomes (three were in the "unable to evaluate" category; the fourth had the response of failure).

The Sponsor analyzes these as corroborating the consistency of APC-111 and penicillin VK performance across the bacteriological and clinical efficacy endpoints.

MO's comments: *The two patients in the Pen VK arm in the PPb population were evaluable failures, not "unable to evaluate". Each of the two cases had received enough of study antibiotics for a cure of their disease or improvement of signs and symptoms. One case received penicillin for 10 days. Symptoms persisted, necessitating initiation of amoxicillin, which was then switched to Ceftin. Her illness resolved. The second patient received 5 days of Pen VK. He was switched to Azithromycin due to worsening signs and symptoms of pharyngitis. Despite our disagreement in the adjudication of these two cases, the reviewer agrees that, overall, a consistency between bacteriological eradication and clinical cure was apparent in the efficacy data.*

LPT Visits

Successful clinical response at the LPT visit required 1.) a cure at TOC, 2.) resolved or continued resolution of baseline clinical signs/symptoms, but with sufficient improvement at LPT visit, 3.) no appearance of new clinical signs/symptoms, and 4.) no further antimicrobial therapy required for tonsillitis and/or pharyngitis. Non-successful clinical response was considered a failure, unable to evaluate, or missing status. For the PPc population at the LPT visit, "missing" included patients who were lost to follow-up, discontinued due to Investigator discretion, non-compliance, violating protocol procedures, and withdrawal of consent.

Clinical Outcomes in the PPc and ITT/Safety Populations at the LPT Visit

The results of clinical outcome at the LPT visit in the PPc and ITT/Safety populations are presented in Table E14. For the ITT/Safety population, for example, 228/302 (75.5%) who received APPC-111 versus 230/306 (75.2%) who received Pen VK had successful clinical outcomes. The 95% lower confidence bound for the difference was -6.5%; the upper bound was 7.2. Clinical outcomes at the LPT visit were similar in both treatment groups. The clinical assessments in the ITT/Safety population show consistency with bacteriological efficacy analyses.
The analysis in the PPc population (on the left side of Table E14) indicates a similar trend.

Table E14: Clinical Outcome at the LPT visit in PPc and ITT/Safety Populations [Modified Sponsor's tables 11-11 and -12]								
Clinical Outcome	PPc Population [n (%)]				ITT/Safety Population [n (%)]			
	APC-111	Pen VK			APC-111	Pen VK		
N →	280	263	Diff.	95% CI	302	306	Diff.	95% CI
Success/Clinical Cure	222 (79.3)	216 (82.1)	-2.8	-9.5, 3.8	228 (75.5)	230 (75.2)	0.3	--6.5, 7.2
Non-Success	58 (20.7)	47 (17.9			74 (24.5)	76 (24.8)		
Clinical Failures	42 (15.0)	33 (12.5)			45 (14.9)	41 (13.4)		
Unable to evaluate	10 (3.6)	8 (3.0)			18 (6.0)	16 (5.2)		
Missing	6 (2.1)	6 (2.3)			11 (3.6)	19 (6.2)		
CI = Confidence interval								

Bacteriological Outcome at the LPT Visit in the PPb and mITT [b]

Bacteriological Outcome versus Clinical Outcome at the TOC Visit in the PPb and mITT[b] Co-primary Populations

In accordance with the study protocol, a bacteriological eradication at both the TOC and LPT visits was required to be assigned a satisfactory bacteriological outcome at LPT. An unsatisfactory outcome at LPT meant any of the following:
1. failure at the TOC visit (i.e., persistence or presumed persistence of PT),
2. secondary failure at LPT despite a bacteriological eradication at The TOC visit),
3. evidence of carrier state /re-colonization, recurrence, presumed recurrence, or re-infection at LPT. Presumed persistence and presumed recurrence included only those subjects who were clinical failures, withdrew early, and started a new antimicrobial for the treatment of PT.

For the mITT [b] population, responses of presumed persistence and indeterminate were counted as failures.
Table E15 displays bacteriological responses in the PPb and mITT populations. According to the Sponsor, for the bacteriological response at TOC in the mITT [b] population, presumed persistence was reported in 7/256 (2.7%) patients treated with APC-111 and was 8/264 (3.0%) in the Pen VK-treated arm of the study. Among those considered indeterminate 8/256 (3.1 %) received APC-111 compared to 12/264 (4.5%) who received Pen VK. These were assigned a bacteriological outcome of unsatisfactory at TOC that was carried forward to the LPT visit. In addition, mITT [b] subjects with a bacteriological response at LPT of presumed recurrence (APC-111, 5.1%; Pen VK, 3.0%) or indeterminate (APC-111, 4.3%; Pen VK, 3.8%) were assigned a bacteriological outcome of unsatisfactory. Patients who initially had satisfactory bacteriological

outcomes at TOC and subsequently became secondary failures due to an indeterminate response at LPT, included those who were lost to follow-up.

Table E15: (Sponsor's Table 11- 5): Bacteriological Outcome at the LPT Visit –PPb and mITT Populations

Bacteriological outcome/Bacteriological response	Number of Patients (%)			
	PPb		mITT(b]	
	APC-111	Pen VK	APC-111	Pen VK
N	219	217	256	264
Satisfactory	169 (77.2%)	164 (75.6%)	179 (69.9%)	179 (67.8%)
Eradication	169 (77.2%)	164 (75.6%)	175 (68.4%)	175 (66.3%)
Presumed Eradication	-	-	4 (1.6%)	4 (1.5%)
Unsatisfactory	50 (22.8%)	53 (24.4%)	77 (30.1%)	85 (32.2%)
Unsatisfactory at TOC	34 (15.5%)	38 (17.5%)	45 (17.6%)	57 (21.6%)
Persistence	29 (13.2%)	32 (14.7%)	29 (11.3%)	37 (14.0%)
Presumed Persistence	5 (2.3%)	6 (2.8%)	7 (2.7%)	8 (3.0%)
Indeterminate	-	-	9 (3.5%)	12 (4.5%)
Satisfactory at TOC with secondary failure at LPT	16 (7.3%)	15 (6.9%)	32 (12.5%)	28 (10.6%)
Carrier/Re-colonization	2 (0.9%)	7 (3.2%)	4 (1.6%)	8 (3.0%)
Recurrence	1 (0.5%)	1 (0.5%)	2 (0.8%)	1 (0.4%)
Presumed Recurrence	11 (5.0%)	6 (2.8%)	13 (5.1%)	8 (3.0%)
Reinfection	2 (0.9%)	1 (0.5%)	2 (0.8%)	1 (0.4%)
Indeterminate	-	-	11 (4.3%)	10 (3.8%)
Comparison				
Difference	1.6		2.1	
95% CI	-6.4, 9.6		-5.8, 10.1	

MO's Comments: *The Sponsor has tried to explain the disposition of patients who had the outcome of presumed persistence or categorization of indeterminate with respect to their inclusion in the mITT[b] population and not in the PPb population. While that is important, the other important review focus is the patients' comparable distribution in both arms of the study. An examination of Table E15 shows that in the various categories of the table, the responses to APC-111 treatment by study patients are similar to those of the Pen VK group across bacteriological outcomes analyzed.*

Efficacy Analyses in Subgroups in PPb Population

a. Subgroups evaluated – Region, Gender and Age Range

The Sponsor has also indicated that in their additional data analyses with regard to pharyngeal bacterial eradication in different demographic subgroups (not shown), consistency in treatment effect difference (i.e., APC-111 vs comparator) was unaffected by subgroup stratifications – i.e. by region, gender, and age in the PPb population. Such analyses in APC-111-treated versus (vs) comparator-treated patients included adjustment for region (85% vs 83.4%); gender effect, males (85.4% vs 81.0%), or females (84.7% v 84.8%); age range for 12 to <19 years (85.1% vs 78.7%), and 20 to <40 years (77.8% vs 82.5%) respectively.

b. Subgroups that could not be evaluated – Race, Weight, Food Effect, Current Infection

The Sponsor reported that race, ethnicity, and weight were not evaluated because of the predominance of Caucasian patients, non-Hispanic patients as well as patients in the 40 kg to 120 kg weight category, with too few patients in the other categories to allow adequate assessment of differences in bacteriological outcome in these subgroups in the PPb population. In addition,
the percentage of patients who took APC-111 with food <75% of the time was not large enough to allow for a meaningful interpretation of food effect on bacteriological outcome at the TOC visit in the APC-111 treatment group.

6.1.5 Clinical Microbiology

MIC of Baseline S. pyogenes Isolates and PFGE Testing

MIC of Baseline S. pyogenes Isolates

Per the Sponsor, susceptibility testing performed on all baseline S. pyogenes isolates was in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) and is summarized in the tabulated baseline isolate MIC data in Table E16.

Table E16 is the Sponsor's summary of the MIC range, including MIC50 and MIC90 values, of amoxicillin and penicillin for the baseline S. pyogenes isolates in the PPb population. The Sponsor reports that 92.2% and 96.2 % of isolates from patients in the APC-111 treatment group were sensitive to amoxicillin and penicillin respectively at MICs of 0.015μg/mL or less.
Among the S. pyogenes isolates from the penicillin VK treatment group, 94.3% were susceptible to amoxicillin and 97.0% to penicillin, also at MICs of 0.015 μg/mL or less.

Table E16: (Sponsor's Table 11-13): MIC Values at the Baseline Visit – PPb Population

Treatment group	Antibacterial agent	N	MIC Range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
APC-111	Amoxicillin	233	≤ 0.004 - 0.25	0.015	0.015
APC-111	Penicillin	233	≤ 0.004 - 0.12	0.015	0.015
Penicillin VK	Amoxicillin	229	≤ 0.004 – 0.25	0.015	0.015
Penicillin VK	Penicillin	229	≤ 0.004 - 0.12	0.015	0.015

Relationship Between S. pyogenes Baseline MICs and Efficacy Outcome At the TOC Visit

The Sponsor reports that in the PPb population at the TOC visit, the bacteriological response demonstrated no correlation between efficacy outcome and the S. pyogenes baseline MIC values for patients who received APC-111 or Pen VK. They further report, however, that 18/233 (7.7%) of patients in the APC-111 treatment group in the PPb population had baseline isolates with MIC values against S. pyogenes greater than the MIC90 of 0.015μg/mL. In the Pen VK treatment group, 6/229 (2.6%) of patients had isolates with MIC values against S. pyogenes greater than the MIC90 of 0.015μg/mL. Of

these, one patient in each treatment group had a bacteriological response of either persistence or presumed persistence at the TOC visit. Sixteen APC-111-treated patients and 5 patients who received Pen VK were found to have a bacteriological response of eradication.
Similar findings were reported in the mITT population in both treatment groups..

MO comments: *Penicillin is the drug of choice in the treatment of streptococcal tonsillopharyngitis. This is because of its proven efficacy, narrow spectrum, and low cost; its timely use is also known to prevent rheumatic fever. In spite of the widespread use of the product for over five decades, no clinical isolates of S. pyogenes showing in vitro resistance to penicillin have been reported*[5]*. The proportion of patients who had baseline S. pyogenes isolates with* MIC_{90} *values greater than 0.015μg/mL in the PPb population included 18/233 (7.7%) APC-111- versus 6/229(2.7%) pen VK-treated patients. Of these, 16/18 (89%) APC-treated and 5/6 (83%) had bacteriological response of eradication at the TOC visit. One in each group had a bacteriological response of either persistence or presumed persistence at the TOC visit. Overall, these figures are pointing to good susceptibility of S. pyogenes to both antibiotics. However, the meaning of persistence of S. pyogenes or presumed persistence in patients who receive Pen VK may seem to question the notion of universal susceptibility of S. pyogenes to penicillin. However, it is also known that factors exist that work against 100% cure rate of TP caused by S. pyogenes. Such factors, as reported in the literature include 1. the presence of beta-lactamase producing bacteria that "protect" S. pyogenes from penicillin, 2.the poor penetration of penicillin into the tonsillar tissues and the tonsillo-pharyngeal cells, 3. co-aggregation between S. pyogenes*
and Moraxella catarrhalis,4. the absence of bacteria that interfere with the growth of S. pyogenes, 5. poor compliance, 6. penicillin tolerance, 7. carrier state, and 8. re-infection are some of the reasons given in the literature for penicillin failure in the treatment of PT due to S. pyogenes

PFGE Testing
The Sponsor reports that in sixteen patients (APC-111, 6; Pen VK, 10) their throat culture results of were either positive at baseline, negative at TOC, and positive again at LPT for *S. pyogenes* or were positive at baseline, and having TOC sample not available were then assessed as clinical cure (presumed eradication) at TOC and, lastly, with their culture positive LPT visit for *S. pyogenes.*
PFGE testing done indicated that 4 APC-111-treated versus 8 patients who received Pen VK were found to be concordant, whereas, 2 APC-111-treated versus one Pen VK – treated patient were discordant strains of *S. pyogenes*. These strains were considered to have persistent colonization or recurrence of the baseline organism. The discordant strains of *S. pyogenes* were considered to represent a new infection with a new strain of *S. pyogenes*. The result of PFGE testing in LPT isolate of one Pen VK-treated patient was indeterminate as the *S. pyogenes* isolate at LPT could not be confirmed as concordant or discordant with the baseline isolate. All the cases were assessed as unsatisfactory bacteriological outcome. However, it did not affect the final bacteriological outcome at LPT.

Efficacy Assessment in Study 301
The efficacy of APC-111 has been based on bacteriological and clinical responses at the TOC visit in the PPb and mITT co-primary populations in study 302. That of Study 301 was based on similar outcomes in the PPb population. The study failed to meet the efficacy study goal.

One of the reviewer's objectives in this review is to ascertain the reason study 301 failed despite the fairly similar design of the two studies.

Bacteriological Outcome at the TOC Visit in the PPb Population
Table E17 displays the Sponsor's assessment of bacteriological outcomes at the TOC visit in the PPb population. Like study 302, for the PPb population at the TOC visit, a bacteriological response of eradication was considered a satisfactory bacteriological outcome, while responses of persistence or presumed persistence were considered unsatisfactory bacteriological outcomes. Presumed persistence was defined as was done in study 302.

As shown in Table E17, 131/171 (76.6%) patients in the PPb population who received APC-111 had satisfactory bacteriological outcome at the TOC visit compared to 161/182 (88.5%)
who received penicillin VK treatment. The point estimate of treatment difference was -12.2% and with 95% Confidence Interval of -20.0, -4.4 for the difference in mean percentage of patients with a satisfactory bacteriological outcome between the two treatment groups. The lower bound was less than the chosen delta of -10. The upper bound of the interval fell short of zero, indicating inferior performance of APC-111 QD for 7 days compared to penicillin VK QID for 10 days in bacteriological outcomes at the TOC visit.

Table E17 (Sponsor's table): Bacteriological Outcome at the TOC Visit – PPb Population

Bacteriological outcome/ Bacteriological response	Number of patients (%)		Difference	95% CI[b]	P- value[a]
	APC-111	Pen VK			
N	171	182			
Satisfactory	131 (76.6)	161 (88.5)	-12.2%	(-20.0; -4.4)	0.5406
Eradication	131 (76.6)	161 (88.5)			
Unsatisfactory	40 (23.4)	21 (11.5)			
Persistence	37 (21.6)	20 (11.0)			
Presumed Persistenced[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 or died due to 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 or died due to tonsillitis and/or pharyngitis.

Subgroup Analysis

Bacteriological outcome at the TOC visit was also summarized by subgroups of the PPb population based on demographic (gender, age, race, and weight; Text Table 11-2) and current infection characteristics (previous antimicrobial therapies within 30 days of study entry, *S. pyogenes* infections within 36 months of study entry, and current infection signs and symptoms; Text Table 11-3). In general, the rate of satisfactory bacteriological outcome at the TOC visit across demographic characteristics and current infection characteristics was consistent with results for the primary efficacy population (i.e., the overall PPb population).

Females (APC-111, 79.2%; Pen VK, 91.9%) had better outcomes than males (APC-111,72.3%; Pen VK, 81.0%) in both treatment groups. The younger patients from age 12-< 19 years of age had better outcomes than patients 19 years of age or older (figures not shown). The Sponsor stated that those patients who took APC-111 with food <75% of the time were not large enough to allow for a meaningful interpretation of the effect of food on bacteriological outcome at the TOC visit in the APC-111 treatment group. The Sponsor also stated that the effect of race, ethnicity, and weight on bacteriological outcome could not be assessed. There was a predominance of Caucasians, non-Hispanics, and patients in the 40 kg to 120 kg weight category, with too few patients in the other categories to adequately assess differences in bacteriological outcome in these subgroups of the PPb population.

Secondary Efficacy Results

The trends of APC-111 poor performance compared to Pen VK continued in the secondary efficacy analyses (see Table E18).

Table E18 (Sponsor's Table): Bacteriological Outcome at the TOC Visit – mITT[a] Primary and Sensitivity Analysis Populations

	Number of patients (%)					
	mITT [a][b]		mITT [b][c]		mITT [c][d]	
Bacteriological outcome/ Bacteriological response	**APC-111**	**Pen VK**	**APC-111**	**Pen VK**	**APC-111**	**Pen K**
N	183	192	192	203	192	193
Satisfactory	138 (75.4)	170 (88.5)	138 (71.9)	170 (83.7)	138 (71.9)	170 (88.1)
Eradication	138 (75.4)	169 (88.0)	138 (71.9)	169 (83.3)	138 (71.9)	169 (87.6)
Presumed Eradication	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)
Unsatisfactory	45 (24.6)	22 (11.5)	54 (28.1)	33 (16.3)	54 (28.1)	23 (11.9)
Persistence	40 (21.9)	21 (10.9)	40 (20.8)	21 (10.3)	40 (20.8)	21 (10.9)
Presumed Persistence	5 (2.7)	1 (0.5)	5 (2.6)	1 (0.5)	5 (2.6)	1 (0.5)
Indeterminate	–	–	9 (4.7)	11 (5.4)	9 (4.7)	1 (0.5)
Difference	-13.4%		-12.1%		-16.5%	
95% CI[e]	(-21.1; -5.8)		(-20.2; -4.0)		(-24.3; -8.7)	

a The mITT population consisted of all patients 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.

b Analysis excluding Indeterminate bacteriological response at TOC.

c Analysis including Indeterminate bacteriological response at TOC as Unsatisfactory.

d Analysis including all Indeterminate bacteriological response at TOC for APC-111 as Unsatisfactory and 11.5% of Indeterminate bacteriological response at TOC for Pen VK as Unsatisfactory.

e Two-sided 95% confidence interval.

Differences between Studies 301 and 302: Potential Impact on Efficacy Outcomes

Table E19: Differences between Studies 301 and 302 (Summarized).

	Characteristic	Study 301	Study 302	Effect on Study Outcome
1	Treatment duration (most study patients)	7 days	10 days	Longer exposure to treatment APC-111 in study 302
2	Taking medication with food	Optional	Advised	Food allowed better APC-111 absorption and more likely to attain time >MIC > 40% of day.
3	Eligibility criteria	≥ three clinical s/s required	≥ two clinical s/s required	Probably sicker patients in study 301 (minor difference?)
4	Eligibility criteria: Concurrent RTI	Concurrent RTI not excluded	Concurrent RTI excluded	Probably sicker patients in study 301
5	Steroids use within 7 days of baseline visit	Allowed in study	Excluded	Clinical recovery probably more dramatic in study 302 than 301
6	TOC Evaluation	Days 14 – Day 18	Day 12- Day 23	
	RTI: Respiratory tract infection (upper/lower, e.g., sinusitis, bronchitis, and acute otitis media or concurrent symptoms of viral etiology including conjunctivitis, coryza, and cough)			

MO comments: *As table E19 indicates, patients randomized to the APC-111 arm in study 302 who completed the study received* the *study drug for ten days. The corresponding patients in study 301 received their APC-111 tablets for seven days (plus three extra days of placebo - to maintain blinding). Thus, patients in study 302 generally had longer exposure to APC-111. In addition, assessment of patients' CRFs indicates that most patients in study 302 received their medication with meals. Table G5 (in earlier pages of the review) showed in the Sponsor's Phase 1 studies that in patients receiving APC-111 with meals, particularly fatty meals, their APC-111 stayed longer above MIC than if the product was taken without food. Thus the role of food in helping the efficacy of this product seems important and has labeling implications. Patient evaluation at the TOC visit was allowed up to Day 23 in study 302, but not in study 301. Evaluation of patients between Day 18 and Day 23 is not in the guidance document. This was apparently agreed to in the meetings between the Agency and the Sponsor preceding study 302. The number of patients with satisfactory responses during that evaluation period who could have failed if evaluated earlier was difficult to delineate as there were no dataset codes to pull up that subset of study population. Other factors, probably less important, as listed in table 18E may have also contributed to the success of study 302. In the labeling process, if the product is approved, the importance of taking APC-111with food, and the need to complete the 10 days course of therapy, should be underscored.*

6.1.6 Efficacy Conclusions

Reviewer's Efficacy Conclusions

The Sponsor has provided substantial evidence of efficacy of APC-111 tablet in the treatment of tonsillitis and/or pharyngitis due to *Streptococcus pyogenes* in adult and pediatric patients 12 years and older. The data were derived mainly from Study 302, a Phase III, double-blind, double-dummy, randomized, parallel-group, multicenter study to evaluate the safety and efficacy of APC-111 Tablet. The product is administered as a 775 mg tablet orally once daily for 10 days.
The Sponsor's primary objective was to demonstrate that the receipt of the tablet was bacteriologically and clinically non-inferior to receiving Pen VK, 250 mg orally QID for 10 days in the treatment of tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes* in adolescents and adults.
Based on the analyses of the data in study 302, and other accompanying information, the Medical Officer is able to make the following efficacy conclusions:

A: On Primary (Bacteriological) Efficacy Outcomes

1. In the PPb population, of the study patients who received APC-111 tablet (775 mg PO QD for 10 days) for the treatment of pharyngitis/tonsillitis due to S. pyogenes, 85 % had a satisfactory bacteriological outcome of cure at the TOC visit. This outcome was similar to the 83.3% study patients who received Pen VK tablet (at 250 mg PO QID) for the same duration when evaluated at the TOC visit. The lower bound of the 95% confidence interval (-5.0) is greater than the pre-specified delta (δ) of -10. The upper bound (8.4) crosses the Zero axis. Based this study results, a statistical non-inferiority has been demonstrated. Therefore, for the treatment of pharyngitis/tonsillitis due to S. pyogenes, APC-111 tablet, taken in the stated dose and duration, is non-inferior to Pen VK at the dose and duration used in the study.

2. In the bacteriological mITT co-primary population, 82.4% of APC-111-treated patients had a satisfactory bacteriological outcome of cure at the TOC visit. Similarly, 77.8% Pen VK- treated patients had a satisfactory bacteriological outcome of cure at the same visit. These are comparable. The lower bound of the 95% confidence interval, -2.8, is greater than the pre-specified delta (δ) of -10. The upper bound (10.8) also crosses the Zero axis. This outcome is consistent with and supports the findings in the PPb primary population.

B: On Secondary (Clinical) Efficacy Outcomes

In study 302, and in the treatment of pharyngitis/tonsillitis due to S. *pyogenes,* the clinical cure rates at the TOC and LPT visits, and the bacteriological cure rates at the LPT visit in the APC-111-treated study patients were comparable to the rates in the Pen VK-treated patients as shown in the following population subsets evaluated:

<u>Clinical at the TOC Visit</u>

- PPb population: 91.4% versus 92.6% respectively; 95% CI = -6.1, 3.8
- mITT population: 88.3% versus 86.4% respectively; 95% CI = -3.8, 7.6

- ITT population: 87.7% versus 86.3% respectively; 95% CI = -3.9, 6.8
- PPc population: 91.8% versus 93.5% respectively; 95% CI = -6.1, 2.6

Clinical at the LPT Visit

- PPc population: 79.3% versus 82.1% respectively; 95% CI = -9.5, 3.8
- ITT population: 75.5% versus 75.2% respectively; 95% CI = -6.5, 7.2

Bacteriological at the LPT visit

- PPb population: 77.2% versus 75.6% respectively; 95% CI = -6.4, 9.6
- mITT population: 69.9% versus 67.8% respectively; 95% CI = -5.8, 10.1

Post-Infection Sequelae at the LPT visit

There were no reports of development by any study patients of post-infection nephritis or carditis.

C. Other Concluding Comments

In its discussion of the Agency's expectations regarding study results conducted by applicants for claims for *S. pyogenes* pharyngitis/tonsillitis, the FDA Guidance for Industry (July 1998), stated "Any product with an absolute eradication rate at test of cure of <85% should not ordinarily be approved as a first line therapy for this infection." The bacterial eradication rate for study 302 was 84.9% (per the reviewer's assessment) in APC-111-treated patients compared to 83.3% in the Pen VK-treated patients, in the PPb population. It is, perhaps, fair to state that 84.9% is borderline result but close enough to 85%, particularly when results in the mITT co-primary population are trending in the same direction. The reviewer should point out that, if approved, consumers should be aware that these results were obtained with the following conditions as part of the study:

- ❖In taking this medication for the treatment of pharyngitis/tonsillitis due to *S. pyogenes,* patients who would take APC-111, if approved, should be aware that chances of a cure can are enhanced by completing a full 10-day course of treatment. Although this can be said of any antibiotic product, it is particularly pertinent for this product in light of the efficacy results of study 301 whose failure to meet efficacy goal was principally attributed to 7 (rather than 10) days of treatment.

- ❖ Patients in this study were required to take the medication with food (better if food was fatty) to enhance absorption and to increase the chances of the daily serum concentration of absorbed product to exceed MIC_{90} for *S. pyogenes* greater than 40% of the time of a 24 hour dosing interval.

- ❖There are studies (including the ones cited by the Sponsor) where a 750 mg once-daily dose of immediate-release plain amoxicillin administered to patients for the treatment of pharyngitis/tonsillitis due to *S. pyogenes* accomplished efficacy results similar to or better than the results seen in study 302. However, two of three

of those studies had smaller numbers of patients and most of them were not necessarily adequate and well controlled, double-blind, randomized, multi-center studies in design. Cost considerations sometimes influence Prescribers' choice of a product versus an alternative for the treatment of a non-life threatening disease in terms of study adequacy or cost alone.

- Pharyngitis/Tonsillitis has its peak incidence in pediatric age 5 through 11 years. The lowest age for eligibility for study 302 was 12 years. Recipients of APC-111 in study 302 included 63 (20.9%) pediatric patients age 12 to 17 years. They had no significant differences in treatment response or adverse reactions from adult patients in the study.

  For age group < than 12 years of age, safety and efficacy of APC-111 has not been demonstrated in an adequate and well-controlled study. That means, in the pediatric population subset most at risk for this disease, APC-111 (or a modification of it) has not been studied at this time.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

General information

This safety review is a description of adverse events (AEs) experienced and reported by patients who participated and developed any such events in any of the studies submitted by the Sponsor. The reviewer ascertained and evaluated such safety information as reported by the Sponsor and/or investigators in their submitted application. Datasets provided by the Sponsor was the major source of reported AEs. The information was presented in accordance with the FDA clinical template format. For the two Phase 3 comparative studies, the AEs reported after receiving at least one dose of APC-111 (or pen VK, the comparator) during the study period or/and post study observation period, were assessed. The severity, duration and time to resolution (depending on the AE type) were also evaluated. The temporal relationship to the receipt of the study drug was determined. Any concomitant drug that the patient may have taken, or was taking, was evaluated. For these comparative studies, the frequency of occurrence of AEs was compared in both study arms.

For the non-comparative (Phase 1) studies, reported AEs were evaluated by the type and severity of the event. The temporal relationship to the study drug was also determined. As needed, the appertaining CRF was located and assessed.

Other sources of reported AEs, including literature reports provided by the Sponsor, or other sources of reported AEs related to the product under review were sought, and when available, examined.

Review Tool (s) - The JMP computer program was the main review tool used to perform independent analysis of data.

Mortality Analysis
If any death occurred that was directly or indirectly related to the receipt of study medication, then study reports, sponsor's narratives (if provided), summaries and CRFs describing patient deaths was to be reviewed. In addition, events surrounding death were expected to be examined for evidence relating death to drug exposure or to lack of drug efficacy. Patients were considered to have died from the initial infection if death occurred before the end of follow-up period and:
a. the investigator indicated that the initial infection was the cause of death, and
b. the investigator documented the cause of death as: 1) directly correlated with an ongoing deteriorating infectious process and 2) the observed clinical course of illness was consistent with persistence or progression of the original infection

Discontinuations
All cases of discontinuations due to AEs were examined for evidence of a relationship to study drug, or its lack of efficacy. In addition, discontinuation rates were compared among treatment groups in the comparative studies and each group were examined to identify any specific subgroups of interest.

Laboratory values
Laboratory values were evaluated from the information in the database (using the review tool mentioned above) to allow comparison between treatment groups and specific subgroups of interest, as applicable. Outliers were identified and reviewed for evidence of a drug-effect relationship.

Patients' Exposure to APC-111
Table S1 shows the 662 subjects/patients treated with APC-111 who participated in the studies submitted for this review. All study participants received the drug orally. Of these, 550 patients were enrolled in the Phase 3 studies (302 in study III-302; and 248 in study III-301). One hundred and twelve subjects in Phase 1 studies received APC-III. The highest dose of APC-III received by any study enrollee was 775 mg. All received the tablet formulation, except two subjects who received sprinkles from research batches of pulsatile-release MP formulation during their Phase pharmacokinetic studies.

Table S1: Modified Sponsor's Table 2.7.4-3: Patients' Exposure to APC-111

Phase	Study Protocol	N
Phase III		
7 days regimen	Protocol 111.301	248
10 days regimen	Protocol 111.302	302
Total (Phase III)		**550**
Phase I		
Single dose	Protocol 111.110	19
	Protocol 111.111	24
	Protocol 111.112	23
	Protocol 111.115	26
Multiple dose	Protocol 111.109	20
Total (Phase I)		**112**
All Studies		**662**

N = Number of subjects and patients who received APC- 111 -Treated

Reviewer Identification of Study by number Designation
During efficacy review, the phase 3 studies were referred to as study 302, and when mentioned, study 301. For the rest of the review, the Phase 3 study designations remained unchanged. The designations for Phase 1 studies, which were now to be

evaluated for safety information for the rest of the review, were changed for ease of reference, as shown in Table S2.

In addition, data from studies 301 and 302 were pooled for safety evaluation, given similarity of design. Phase I studies were reviewed separately.

Table S2	**Sources of Safety Review data: Re-assigning numbers to Studies for Review Purposes.**	
Study Grouping	**Protocol Number**	**Reviewer-Assigned Study Number**
Phase 3 Studies (Phase 3 patients)	Protocol 111.301 Protocol 111.302	**Study 301** **Study 302**
Phase 1 Studies (Phase 1 Subjects)	Protocol 111.109 Protocol 111.110 Protocol 111.111 Protocol 111.112 Protocol 111.115	**Study 109** **Study 110** **Study 111** **Study 112** **Study 115**
Literature review	Literature materials submitted by the Sponsor were reviewed for AE reports associated with the use of amoxicillin products.	

Brief Overview of AEs

Tables S3a and S3b represent an AE overview displaying the numbers and percentage rates of patients that reported AEs in the comparative Phase 3 studies while table S3c represents a similar display for Phase 1 subjects. Multiple occurrences of a particular AE in the same individual was counted only once in the tables.

Phase 3 Study Patients

Overall, 263/550 (47.8 %) patients who received APC-111 reported at least one AE compared to 300/565 (53.1%) Pen VK-treated patients. This indicates that AEs were reported at a slightly higher rate in Pen VK-treated patients than in APC-111-treated patients.

With regards to patients whose AEs were considered study drug related, 57/550 (10.4%) APC-111-treated patients had such AEs compared to 91/565 (16.1%) comparator-treated patients. The rate differences parallel the overall reported AE frequencies in the two study arms as stated above.

Regarding SAEs, 3/550 (0.5%) who received APC-111 reported at least one SAE compared to 1/565 (0.2 %) who received Pen VK. These numbers were small for any meaningful comparison. None of the SAEs reported by these patients was thought to be study drug related.

Some patients developed AEs that led to discontinuation of either their study medication or from the study altogether. The reasons for discontinuation were generally similar in both study arms. Discontinued in most of the patients involved cases whose streptococcal pharyngitis worsened; such cases were attributed to study drug ineffectiveness. In some

cases, the patients had hypersensitivity to study drug. Yet others were discontinued due to severity of the concomitant illnesses they developed before or during the study, e.g. urinary tract infection, upper abdominal pain, muscle spasm, infectious mononucleosis, etc. This is further discussed in greater detail under section 7.1.3.

Phase 1 Study Subjects

In all 5 Phase 1 studies, 29/112 (25.9%) who received APC-111 reported at least one AE. Out of these, 11/112 (9.8%) reported AEs that were considered related to study drug. There were no subjects who received Pen VK, as these were non-comparative studies.

There were no deaths or other SAEs reported. There were no cases reported that developed AEs leading to discontinuation of study medication (for subjects receiving multiple doses), nor were there subjects discontinued from any study as a result of AEs.

Table S3a	Overview of Adverse Events in Phase 3 Patients			
Patient AE category	**APC-111** [n (%)]		**Pen VK** [n (%)]	
At least one AE	**Safety Population**	**Patients with AEs**	**Safety Population**	**Patients with AEs**
Study 302	n-1 = 302	137 (45.4)	n-1 = 306	163 (53.3)
Study 301	n-2 = 248	126 (50.8)	n-2 = 259	137 (52.9)
Combined	n-1 + n-2 = 550	263 (47.8)	n-1 + n-2 = 565	300 (53.1)
Study drug-related AEs				
Study 302	n-1 = 302	32 (10.6)	n-1 = 306	45 (14.7)
Study 301	n-2 = 248	25 (10.1)	n-2 = 259	46 (17.8)
Combined	n-1 + n-2 = 550	57 (10.4)	n-1 + n-2 = 565	91 (16.1)
Death				
Combined	n-1 + n-2 = 550	0 (0.0)	n-1 + n-2 = 565	0 (0.0)
At least one SAE				
Study 302	n-1 = 302	2 (0.7)	n-1 =306	1 (0.3)
Study 301	n-2 = 248	1 (0.4)	n-2 = 259	0 (0.0)
Combined	n-1 + n-2 = 550	3 (0.5)	n-1 + n-2 = 565	1 (0.2)

AE = Adverse event; SAE = Serious adverse event; TEAE = Treatment-emergent AE [defined as those reported as AEs possibly related, probably related, or related to study drug].

Table S3b	Overview of Adverse Events in Phase 3 Patients			
At least one Study drug-related SAE				
Study 302	n-1 = 302	0 (0.0)	n-1 = 306	0 (0.0)
Study 301	n-2 = 248	0 (0.0)	n-2 = 259	0 (0.0)
Combined	n-1 + n-2 = 550	0 (0.0)	n-1 + n-2 = 565	0 (0.0)
Study drug discontinuation due to at least one AE				
Study 302	n-1 = 302	14 (4.6)	n-1 = 306	16 (5.2)
Study 301	n-2 = 248	8 (3.2)	n-2 = 259	9 (3.5)
Combined	n-1 + n-2 = 550	22 (4.0)	n-1 + n-2 = 565	25 (4.4)

AE = Adverse event; SAE = Serious adverse event; TEAE = Treatment-emergent AE [defined as those reported as AEs possibly related, probably related, or related to study drug].

Table S3c	Overview of Adverse Events in Phase 1 study subjects					
Subjects:	**Study 109 n (%)**	**Study 110 n (%)**	**Study 111 n (%)**	**Study 112 n (%)**	**Study 115 n (%)**	**Group total n (%)**
	n = 2 0	n = 19	n = 24	n = 23	n = 26	N = 112
with at least one AE	9 (45.0)	3 (15.8)	9 (37.5)	5 (21.7)	3 (11.5)	29 (25.9)
with treatment-related AEs	0	3 (15.8)	4 (16.7)	1 (4.3)	3 (11.5)	11 (9.8)
who died	0	0	0	0	0	0
with at least one SAE	0	0	0	0	0	0
with at least one treatment-related SAE	0	0	0	0	0	0
with at least one AE leading to study drug discontinuation	0	0	0	0	0	0
with at least one TEAE leading to withdrawal from study	0	0	0	0	0	0

AE= Adverse event; TEAE = Treatment-emergent AE

7.1.1 Deaths

There were no deaths reported in any of the studies conducted for this application.

7.1.2 Other Serious Adverse Events

SAEs in Phase 3 patients
Reported SAEs were related to seriousness of signs and symptoms, patient hospitalizations or extended hospitalizations. Table S4 displays the number and rates of SAEs in Phase 3 patients; SAEs were reported in 3/550 (0.5%) - APC-111- treated and 1/565 (0.2%) - Pen-VK- treated patients respectively. None of these events was considered related to study drug.

Of the three SAE cases reported in study 302, two received APC-111; the third was Pen VK–treated. Of the two who received APC-111, one (# 0443-3003) was a 51-year old diabetic who was hospitalized for severe dorsal right foot cellulitis due to S. aureus 21 days after completing his course of APC-111 for PT treatment. In addition, he received treatment for tenosynovitis also involving the right foot. After multiple antibiotics for his cellulitis, he developed Clostridium difficile –related diarrhea. All signs/symptoms of disease improved. Patient was discharged after 11 days of hospitalization. The second patient (#0314-3002) was a 28-year old female, also hospitalized for severe right lower quadrant and flank pain 19 days after completion of her APC-111. Patient evaluation revealed ureterovesical junction obstruction from kidney stone (with calcification). She was discharged the following day on Bactrim and additional medications for prophylaxis against kidney stones. The third patient (# 0297-3003) was withdrawn from the study and categorized as 'indeterminate'. He was a 19-year-old male whose sore throat persisted with significantly enlarged tonsils despite 10 days course of Pen VK. Although his rapid streptococcal test and culture were positive, his monospot test (necessitated by persistence of sore throat and development of additional symptoms) was positive. This was subsequently accompanied by a peak alanine aminotransferase (ALT) elevation up to 10 x upper limit of normal (ULN). He was discharged home after two days of hospitalization, following improvement in his clinical symptoms and laboratory parameters; he responded to Decadron. His ALT decreased from 428 U/L to 260 U/L.

The one reported case of SAE in study 301 (# 0277/0025) was a 14-year old female who developed bilateral jerky movements of her extremities 33 days after her last dose APC-111.
Her work up on hospitalization revealed epileptiform abnormalities in her left posterior temporal area.

Table S4	Number (%) of patients with SAEs in Phase 3 studies					
	Study 302		Study 301		Pooled Studies	
SAE	APC-111 n= 302	Pen VK n= 306	APC-111 n= 248	Pen VK n = 259	APC-111 n= 550	Pen VK n= 565
Cellulitis (of the right foot)	1 (0.3)	-	-	-	1 (0.2)	-
Urethral obstruction	1 (0.3)	-		-	1 (0.2)	-
Infectious mononucleosis	-	1 (0.3)	-	-		1 (0.2)
Seizure			1 (0.3)	-	1 (0.2)	-
Total					3 (0.5)	1 (0.2)

MO Comments: *Considering the number of patients in the database, the reported number of patients who developed SAEs was small. The reviewer agrees with the Sponsor that, as reported, these SAEs did not appear to be treatment drug-related. The reviewer agrees with the Sponsor's adjudication of the patient whose S. pyogenes was apparently eradicated by study drug but subsequently diagnosed with infectious mononucleosis. The case was apparently confounded by a concurrent development of Epstein Barr viral infection and was appropriately considered an indeterminate case.*

SAEs in Phase 1 studies

There were no SAEs reported in Phase 1 studies.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Most patients had their study drugs discontinued when therapy was completed, in accordance with the protocol. The profile of dropouts is shown in Table S5. The distribution and proportions (or percentages) of patients in the various dropout categories in Phase 3 studies are displayed in the table. Most dropouts occurred in the "insufficient therapeutic effect" category. That is, in 38/550 (6.9 %) APC-111-treated patients, the therapeutic effect of APC was determined to be insufficient or inadequate. By comparison, 34/565 (6.0 %) patients who received Pen VK had insufficient therapeutic effect from the comparator drug. These rates were similar in both study arms. These patients were discontinued from the studies and generally had their treatments switched to alternative antibiotics.

One category of particular interest to the review concerns patients who dropped out because of treatment-emergent AEs (or TEAEs). In this group, 17/550 (3.1%) APC-111-treated patients dropped due to AEs compared to 23/565 (4.1%) who received Pen-VK. The dropout rates in this category were fairly similar in the two study arms.

Table S5- Modified Sponsor's Table 10-1: Reasons for Discontinuation

Table S5	Number (%) of Dropout Patients and Reasons for Dropping Out from Phase 3 studies					
	Study 302		Study 301		Pooled Studies	
Reasons for Dropping Out	**APC-111 n= 302**	**Pen VK n= 306**	**APC-111 n= 248**	**Pen VK n = 259**	**APC-111 n= 550**	**Pen VK n= 565**
Adverse event	10 (3.3)	14 (4.5)	7 (2.8)	9 (3.5)	17 (3.1)	23 (4.1)
Insufficient therapeutic effect	28 (9.3)	24 (7.8)	10 (4.0)	10 (3.9)	38 (6.9)	34 (6.0)
Lost to follow-up	14 (4.6)	11 (3.6)	6 (2.4)	5 (1.9)	20 (3.6)	16 (2.8)
Investigator's discretion	1 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)
Consent withdrawn	0 (0)	3 (1.0)	4 (1.6)	2 (0.8)	4 (0.7)	5 (0.9)
Protocol violations	0 (0)	1 (0.3)	1 (0.4)	2 (0.8)	1 (0.2)	3 (0.5)
Noncompliance	0 (0)	4 (1.3)	1 (0.4)	1 (0.4)	1 (0.2)	5 (0.9)
Other	2 (0.7)	4 (1.3)	10 (4.0)	8 (3.1)	12 (2.1)	12 (2.1)

MO comment: *The overall dropout rate in APC-111 arm was similar to that in the comparator arm (17.1 % versus 17.6%). The dropout rates in the "insufficient therapeutic effect" of study drug category were also comparable in the pooled studies (6.9% versus 6.0%) although slightly higher in the APC-111 arm in study 302. The rates of loss of study patients to follow-up were fairly similar across study arms (3.6% versus 2.8%) as were the rates of discontinuation due to AEs (3.1 versus 4.1).*

7.1.3.2 Adverse events associated with dropouts

According to the Sponsor, only two patients (0297-3007 and 0452-3003), both APC-111-treated, had their medications discontinued while the patients remained in the study (302) to the end.
The rest of the patients reported (study 301 or 302) had AEs leading to their discontinuation from their respective studies altogether.
As previously stated, a total of 17/550 (3.1%) APC-111-treated patients reported TEAEs leading to discontinuation from Phase 3 studies compared to 23/565 (4.1%) comparator-treated patients. The rates in both arms were similar.

Table S6 displays the types of AEs reported in study patients leading to discontinuation from Phase 3 studies. The relationship to study medication and severity of such AEs are also shown in the table. Some patients had more than one AE. Most AEs were considered mild to moderate and generally resolved in 2 to 4 days; only a few persisted for a longer period.

Among the AEs considered to be related to study drug, vomiting ranked the highest and occurred in 2/550 (0.4%) APC-111-treated patients versus 3/565 (0.5%) Pen VK-treated patients. The rates of these AEs were therefore similar in both study arms. The vomiting experienced by these patients was reported as mild in one patient who received APC-111 but moderate in the other patient. The vomiting experienced by all 3 patients who

received Pen VK-treatment was considered to be of moderate severity. This AE (vomiting) resolved in all patients within 2 to 4 days.

Abdominal pain in one of two patients who received APC-111 treatment was considered by the investigators to be unrelated to study drug, while the same AE reported in the other APC-111-treated patient and the one patient who received Pen VK were considered to be related to their study medications.

The most common AE necessitating patient discontinuation from the study was severity of streptococcal pharyngitis. Of these patients, 3/550 (0.6%) received APC-111 treatment; 7/565 (1.2%) received the comparator treatment. The rate of these AEs was higher in comparator-treated patients, but these AEs were not considered related to study drug.

The other AEs are as shown in the table (S6).

Table S6	Reported Adverse Events (%) Associated with Dropouts in the Phase 3 studies					
	APC-111 (n= 550)	**Related to Study Drug**	**Intensity**	**Pen VK (n= 565)**	**Related to Study Drug**	**Intensity**
Pharyngitis severity→ dropout	3 (0.6%)	No	Moderate	7 (1.2%)	No	Moderate
Urinary tract infection	4 (0.7%)	No	Moderate	1 (0.2%)	No	Severe
Pharyngeal pain	2 (0.4%)	No/	Moderate	3 (0.5%)	No	Moderate
Vomiting (± dehydration)	2 (0.4%)	Yes	Mild - Moderate	3 (0.5%)	Yes	Moderate
Abdominal pain	2 (0.4%)	1st: No; 2nd : Yes	Moderate	1 (0.2%)	Yes	Moderate
Nausea	2 (0.4%)	Yes	Moderate	1 (0.2%)	Yes	Moderate
Rash macular/pleuritic	2 (0.4%)	Yes	Moderate	1 (0.2%)	Yes	Moderate
Drug hypersensitivity	1 (0.2%)	Yes	Moderate	1 (0.2%)	Yes	Moderate
Pruritus	-			1 (0.2%)	Yes	Moderate
Dyspnea	1 (0.2%)	Yes	Mild	-		
Paraesthesia	-			1 (0.2%)	Yes	Mild
Disorientation	1 (0.2%)	Yes	Mild	-		
Dysphagia	-			1 (0.2%)	Yes	Moderate
Pyrexia	1 (0.2%)	Yes	Severe	1 (0.2%)	No	Moderate
Chest pain	1 (0.2%)	Yes		-		
Chills	1 (0.2%)	Yes	Severe	1 (0.2%)	No	Mild
Dizziness/Vertigo	1 (0.2%)	Possibly	Moderate	1 (0.2%)	yes	Mild
Headache	-			2 (0.4%)	Yes	Severe
Fatigue	-			1 (0.2%)	Possibly	Severe
Muscle Spasms	-			1 (0.2%)	Possibly	Severe
Migraine	1 (0.2%)	Possibly	Moderate	-		
Diarrhea (± Dehydration)	-			2 (0.4%)	Possibly	Severe
Infectious mononucleosis	1 (0.2%)	No	Moderate	2 (0.4%)	No	Moderate
Otitis media	1 (0.2%)	No	Mild	1 (0.2%)	No	Moderate
Sinusitis	1 (0.2%)	No	Mild	1 (0.2%)	No	Moderate
Viral Pharyngitis	1 (0.2%)	No	Moderate	-		
Peritonsillar abscess	1 (0.2%)	No	Moderate	-		
Helicobacter infection	1 (0.2%)	No	Moderate	-		
Back pain	-			1 (0.2%)	No	Moderate
Bronchitis	1 (0.2%)	No	Moderate	-		
Insomnia	-			1 (0.2%)	No	Moderate
Tooth infection	1 (0.2%)	No	Severe	-		
Lymph node pain/swelling	-			1 (0.2%)	No	Severe
Odynophagia	-			1 (0.2%)	No	Severe

ALA = At the last assessment; * including duration patient received provided outpatient medication; n/A = Non-applicable; ? = Information not provided.

MO comment: *Overall, the rates of reported AE-related dropouts in both treatment arms were similar in the pooled Phase 3 studies (i.e., 4% in the APC-111 arm versus 4.4% in the Pen VK arm). The issue of streptococcal pharyngitis being severe enough to lead to dropout from the study was more common in the comparator arm than the APC-111 arm (1.2% versus 0.6%). However, the numbers were small. The frequencies of the other AEs leading to discontinuation from study were not significant enough to merit further detailed discussion.*

Dropouts in Phase 1 studies

Table S7	**Number (%) of Dropout Patients and Reasons for Dropping Out in Phase 1 studies**					
Reasons for Dropping Out ⇓	**Study 109 n (%)**	**Study 110 n (%)**	**Study 111 n (%)**	**Study 112 n (%)**	**Study 115 n (%)**	**Group total n (%)**
	n = 2 0	n = 19	n = 24	n = 23	n = 26	N = 112
Adverse event	0 (0.0)	0.0	0.0	0.0	0.0	0 (0.0)
Insufficient therapeutic effect	0.0	0.0	0.0	1 (4.3)	0.0	1 (0.9)
Lost to follow-up	0.0	0.0	0.0	0.0	0.0	0 (0.0)
Investigator's discretion	0.0	*1 (5.3)	*1 (4.2)	*1 (4.3)	0.0	3 (4.2)
Consent withdrawn	0.0	0.0	0.0	0.0	^1 (3.8)	1 (0.9)
Protocol violations	0.0	0.0	0.0	0.0	0.0	0 (0.0)
Noncompliance	0.0	0.0	0.0	0.0	0.0	0 (0.0)
Other	0.0	§2 (10.5)	0.0	0.0	§1 (3.8)	3 (4.2)
*** Insufficient therapeutic effect; § Subject discontinuation for personal reasons; ^ This subject withdrew consent due to venipuncture difficulty.**						

MO comment: *As shown in table S7, no subject was discontinued from any study as a result of the development of an AE. In study 109, no event was reported whatsoever. Two subjects (Id #s 35 and 120) in study 110, and one (Id # 154) in study 115, asked to be discontinued from their studies for personal reasons. One subject each in study110 (Id # 78), study 111(Id # 136), and study 112 (Id # 90) was also discontinued by the investigator for "failed drug/alcohol", per the Sponsor. The term "failed drug/alcohol", probably had to do with ineligibility for study entry but was not further explained by the Sponsor. Lastly, one subject (Id # 120) withdrew consent for venipuncture difficulty.*

.

7.1.3.3 Other significant adverse events

No other significant AEs were reported.

7.1.4 Other Search Strategies

The following sources were explored for additional safety information directly or indirectly related to the product (APC-111) under review, particularly if new.

1. Literature Review

Literature materials were submitted by the Sponsor to support this application. Pertinent information related to Amoxicillin or APC-111 were summarized under section 7.2.2.3 of this review.

2. AERS Database

The reviewer has watched for any new AE reported about amoxicillin or related product throughout this review.

3. MedWatch

This is an additional source for reported AE related to amoxicillin products.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Per the Sponsor, safety assessments were based on: 1.) reports of AEs by patients, 2.) results of routine physical examinations and vital signs measurements; and 3.) laboratory determinations.
The Sponsor defined an AE as "... any untoward medical occurrence in a patient treated with a pharmaceutical product, not necessarily having a causal relationship with study treatment" and "could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product."

A serious AE (SAE) was defined as an AE that resulted in: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

AEs were collected from the time informed consent was obtained through the LPT visit. AEs occurring on or after the first day of study medication were considered treatment-emergent adverse events (TEAEs).
Patients with AEs that developed during the study and continued through the TOC visit (Days 14 to 18) were to be followed to resolution, or until no longer clinically significant or had not become a chronic condition, per the investigator's assessment.

All TEAEs were to be recorded in the source document and in the CRF. Whenever possible, diagnoses were to be reported when signs and symptoms were due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion were to be reported as "upper
respiratory infection").

Reporting AEs and SAEs
All AEs were to be reported thus: description of the event, date of onset and date event ended, severity, drug relationship to AE, countermeasure, and ultimate outcome. Patients withdrawn from the study due to any AE were to be observed until the AE became chronic, stabilized, had resolved or patient was lost to follow up.

If an AE led a patient to be withdrawn from the study or if a patient experienced a serious AE (SAE) the patient was to be followed until patient clinically recovered completely (including a return to baseline of laboratory values) or the event was no longer clinically significant, had stabilized, had become a chronic condition, or was lost to follow up.

All SAEs that were unexpected and potentially related to the study medication were to be reported to the investigator. The investigator was to have sent these reported events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol, unless otherwise required and documented by the IEC/IRB.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The investigators of the studies submitted seemed to have made their best efforts to document the AEs reported by the patients or observed by the investigator during patient physical or laboratory assessments. Patient self-reported verbatim terms of their AEs were translated into preferred terms. From the reviewer's standpoint, there were the following issues:

- Certain terms (though preferred terms) were used that were close in meaning, e.g. "diarrhea" and "loose stools". The term "diarrhea" is generally understood to mean stool that is watery in consistency and passed more frequently than what is usual for the patient. The practice of some study reports makes it unclear whether cases "diarrhea" and "loose stools" are 2 AEs or, indeed, the same qualitative event. The potential effect on data analysis is that a significant number of the same AE (if the 2 patient groups were summed up) could be reduced to two insignificant AEs (in terms of numbers). There was also "ear pain" versus "ear discomfort". The number was however small in each case, and did not make any significant impact on data analysis enough to alter the end result.

- Inappropriate characterization of an AE or non-specificity in reporting of an AE was also problematic; streptococcal pharyngitis was the disease under study. The AE of a patient who had "worsening streptococcal pharyngitis" was often described simply as "Streptococcal pharyngitis".

7.1.5.3 Incidence of common adverse events

Table S8 displays the most frequent TEAE (reported by $\geq$ 2% of Phase 3 patients), and tabulated in decreasing order of frequency in either treatment group. As the table

indicates, worsening streptococcal pharyngitis was the most frequent AE reported; it affected 37/550 (6.7%) APC-111-treated and 41/565 (7.3%) Pen VK-treated patients respectively. Other TEAE included headache (4.9% versus 6.0%), pharyngolaryngeal pain (4.5% versus 3.9%), upper respiratory tract infection (URI), etc.

There were no TEAEs in the APC-111 treatment group that exceeded the incidence rate in the penicillin VK treatment group by 2% or more.

7.1.5.4 Common adverse event tables

TEAEs occurring in ≥ 2% of Phase 3 Patients [in decreasing order of frequency]

Table S8	Number (%) of TEAE occurring in ≥ 2% of Phase 3 Patients						
Adverse events	Study 302		Study 301			Pooled Studies	
	APC-111 n= 302	Pen VK n= 306	APC-111 n= 248	Pen VK n = 259		APC-111 n= 550	Pen VK n= 565
Strep Pharyngotonsillitis	32 (10.6)	31 (10.1)	5 (2.0)	10 (3.9)		37 (6.7)	41 (7.3)
Headache	8 (2.7)	16 (5.2)	19 (7.7)	20 (7.7)		27 (4.9)	36 (6.4)
Pharyngolaryngeal pain	9 (3.0)	12 (3.9)	16 (6.5)	10 (3.9)		25 (4.5)	22 (3.9)
URI	11 (3.6)	25 (8.2)	13 (5.2)	7 (2.7)		24 (4.4)	32 (5.7)
Nausea	8 (2.6)	8 (2.6)	10 (4.0)	11 (4.2)		18 (3.3)	19 (3.4)
Diarrhea	11 (3.6)	9 (2.9)	5 (2.0)	8 (3.1)		16 (2.9)	17 (3.0)
Nasal Congestion	6 (2.0)	11 (3.6)	8 (3.2)	5 (1.9)		14 (2.5)	16 (2.8)
Cough	6 (2.0)	16 (5.2)	6 (2.4)	16 (6.2)		12 (2.2)	32 (5.7)
Vomiting	5 (1.7)	9 (2.9)	7 (2.8)	9 (3.5)		12 (2.2)	18 (3.2)
Pain (Ear)	8 (2.6)	3 (1.0)	4 (1.6)	4 (1.5)		12 (2.2)	7 (1.2)
Vulvovaginal Candidiasis	8 (2.6)	8 (2.6)	1 (0.4)	3 (1.2)		9 (1.6)	11 (1.9)
URI = Upper Respiratory Tract Infection							

MO comments: *Table S8 details the TEAEs reported by ≥ 2% of Phase 3 study patients. The incidence of cough was reported with greater frequency in Pen VK-treated patients than in patients who received APC-111 (5.7% versus 2.2%). The incidence rates of the other AEs are fairly similar across study arms. Some patients had more than one TEAE. Those patients in whom "Streptococcal pharyngitis" was reported were patients whose disease worsened despite being on treatment with either study medication. These patients, with or without bacterial persistence, constituted most of the evaluable failures. As evident in an earlier table (table S6), only some of them were discontinued from the study altogether due to severity of this particular TEAE.*

Additional common adverse event tables are shown in sections 7.1.5.5, and 7.1.5.6.

7.1.5.5 Identifying common and drug-related adverse events

TEAE Related to Study Medication

Table S9 summarizes the incidence of drug-related TEAEs by preferred term. Using the pooled data from the Phase 3 studies, the most common drug-related adverse events (reported by ≥1% of the patients in either treatment group) were nausea (APC-111, 1.5 %; Pen VK, 1.4%), severe streptococcal pharyngotonsillitis (APC-111, 0.9%; Pen VK, 1.8%), vulvovaginal candidiasis (APC-111, 0.9%; Pen VK, 1.3%), headache (APC-111, 0.7%; Pen VK, 1.6 %), diarrhea (APC-111, 0.5 %; Pen VK, 1.2%), and abdominal pain (APC-111, 0.5 %; Pen VK, 1.2%).

Among study patients, 2/550 (0. 4%) APC-111-treated patients and 1/565 (0.2%) patients who received Pen VK reported drug hypersensitivity AEs. These AEs were reported by the Sponsor to be moderate in severity and resulted in permanent discontinuation of the study medication.

Drug-Related TEAE occurring in ≥ 1 % of Phase 3 Patients

Table S9	**Number (%) of Drug-related AEs occurring in ≥ 1% of Phase 3 Patients**						
Adverse events	**Study 302**		**Study 301**			**Pooled Studies**	
	APC-111 n= 302	**Pen VK n= 306**	**APC-111 n= 248**	**Pen VK n = 259**		**APC-111 n= 550**	**Pen VK n= 565**
Nausea	4 (1.3)	2 (0.7)	4 (1.6)	6 (2.3)		8 (1.5)	8 (1.4)
Strep Pharyngotonsillitis	6 (2.0)	10 (3.3)	-	-		6 (1.1)	10 (1.8)
Vulvovaginal Candidiasis	6 (2.0)	8 (2.6)	-	-		6 (1.1)	8 (1.4)
Headache	3 (1.0)	3 (1.0)	1 (0.4)	6 (2.3)		4 (0.7)	9 (1.6)
Diarrhea	5 (1.7)	6 (2.0)	2 (0.8)	6 (2.3)		7 (1.3)	12 (2.1)
Abdominal pain	1 (0.3)	3 (1.0)	2 (0.8)	4 (1.5)		3 (0.5)	7 (1.2)
Drug Hypersensitivity	1 (0.3)	1 (0.3)	1 (0.4)	-		2 (0.4)	1 (0.2)

MO comments: *Table S9 shows that the nausea was reported at a frequency rate similar in both study arms. The other study drug-related TEAEs were reported by more Pen VK–treated patients than APC-111-treated patients but not by a significantly higher rate and the numbers involved are relatively small.*

Treatment-Emergent Adverse Events by Severity

As shown in table S10, and per the Sponsor's report, most treatment-emergent adverse events were mild or moderate in intensity. A total of 27/550 (4.9%) patients who received APC-111 reported one or more adverse events that were considered severe in intensity in Phase 3 studies compared to 21/565 (3.7%) who received Pen VK. These rates were comparable. The severe AEs that were considered drug-related in the APC-111–treated patients were generalized rash and vulvovaginal candidiasis. In Pen VK- treated patients, headache and diarrhea were the severe AEs that were considered possibly drug-related.

Treatment-Emergent Adverse Events by Severity in Phase 3 Patients

Table S10	Number (%) of Patients with TEAE by severity in Phase 3 Patients						
Adverse event Severity	Study 302		Study 301			Pooled Studies	
	APC-111 n= 302	Pen VK n= 306	APC-111 n= 248	Pen VK n = 259		APC-111 n= 550	Pen VK n= 565
Missing	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)		0 (0.0)	1 (0.2)
Mild	89 (29.5)	106 (34.6)	89 (35.9)	101 (39.0)		178 (32.4)	207 (36.6)
Moderate	65 (21.5)	71 (23.2)	56 (22.6)	58 (22.4)		121 (22.0)	129 (22.8)
Severe	10 (3.3)	8 (2.6)	17 (6.9)	13 (5.0)		27 (4.9)	21 (3.7)

TEAEs occurring in Phase 1 Patients

Table S11 displays the TEAEs reported in Phase 1 study patients in descending order of frequency. All patients received at least one dose of APC-111. As shown in the table, the most frequently reported AE was headache and was reported by 17 (15.2%) of all Phase 1 study patients. Other TEAEs reported in study patients included dizziness (4.5%), rhinorrhea (3.6%), cough (2.7%), sore throat or pharyngolaryngeal pain (2.7%), nausea (1.8%), diarrhea (1.8%), and abdominal pain (1.8%). The types of AEs reported are, in general, similar to AEs reported by phase 3 study patients.

Relationship of TEAEs to Study Medication (Phase 1 Patients)

Of the Phase 1 study patients who experienced/reported TEAEs following the receipt of APC-111, 1/112 (2.7%) had three different TEAEs considered to be related to study drug; 21/112 (18.8%) had TEAEs that were considered to be possibly related to the drug. The TEAEs that were considered to be related to study drug included nausea, diarrhea, and abdominal pain.

Severity of TEAEs

Of the TEAEs experienced/reported by Phase 1 study patients, 18/112 (16.1%) considered to be of moderate severity; others were considered mild in severity. All TEAEs in these patients resolved prior to the end of studies.

Table S11	Treatment-Emergent Common Adverse Events (TEAE) occurring in Phase 1 Subjects					
Common TEAEs	**Study 109 n (%)**	**Study 110 n (%)**	**Study 111 n (%)**	**Study 112 n (%)**	**Study 115 n (%)**	**Group total n (%)**
	n = 2 0	**n = 19**	**n = 24**	**n = 23**	**n = 26**	**N = 112**
Headache	6 (30)	3 (16)	4 (17)	1 (4)	3 (12)	17 (15.2)
Dizziness	2 (10)	1 (5)	1 (4)	0.0	1 (4)	5 (4.5)
Rhinorrhea	2 (10)	0	1 (4)	1 (4)	0	4 (3.6)
Cough	1 (5)	0	1 (4)	1 (4)	0	3 (2.7)
Pharyngolaryngeal pain	2 (10)	0	0	1 (4)	0	3 (2.7)
Nausea	0	0	1 (4)	0	1 (4)	2 (1.8)
Loose stools/Diarrhea	0	0	1 (4)	0	1 (4)	2 (1.8)
Abdominal pain	0	0	0	1 (4)	1 (4)	2 (1.8)
Back pain	0	0	1 (4)	0	0	1 (0.9)
Pain	1 (5)	0	0	0	0	1 (0.9)
Musculoskeletal stiffness	1 (5)	0	0	0	0	1 (0.9)
Genital pruritus female	0	0	1 (4)	0	0	1 (0.9)
Feeling cold	0	0	1 (4)	0	0	1 (0.9)
Feeling hot	0	0	1 (4)	0	0	1 (0.9)
Night sweats	0	0	1 (4)	0	0	1 (0.9)
Pallor	0	0	1 (4)	0	0	1 (0.9)
Vomiting	0	0	1 (4)	0	0	1 (0.9)
Flatulence	0	0	1 (4)	0	0	1 (0.9)
Laryngitis	0	0	0	1 (4)	0	1 (0.9)
Nasal congestion			0	1 (4)	0	1 (0.9)
Venipuncture site bruise			0	1 (4)	0	1 (0.9)

MO comments: *Headache, nausea, and diarrhea, rank among the most frequent TEAEs experienced/reported by Phase 1 study subjects. The types of TEAEs experienced following the receipt of APC-111 were similar to those of Phase 3 APC-111-treated study patients despite the differences in duration of antibiotic use.*

7.1.5.6 Additional analyses and explorations

No additional data were submitted in this application that would require further analyses and exploration.

7.1.6 Less Common Adverse Events

In the periods that Phase 3 studies were being conducted, numerous TEAEs were reported. The more frequently reported ones (occurring in ≥ 1%, but < 2%, of Phase 3 study patients) are enumerated in descending order of frequency in table S12a. The less common TEAEs (reported by <1% of study patients) are further presented (but in

alphabetical order) in tables S12b through S12f. Tables S12a is shown below. Tables S12b –S12f are in Appendix 2

Among the other TEAEs, their rates of occurrence in the two treatment arms were fairly similar in both study arms. The one possible exception was the frequency of abdominal pain which was reported more in Pen VK-treated patients than in APC-111-treated patients (Pen VK, 3.2%; APC-111, 1.1%). The profile of the rest of the reported TEAEs is listed in Tables S12a as well as S12b through S12f (in Appendix 2).

Table S12a **Number (%) of Less common TEAEs reported by ≥ 1% of Phase 3 Patients in descending order of frequency**

Adverse events	Study 302		Study 301		Pooled Studies	
	APC-111 n= 302	Pen VK N= 306	APC-111 n= 248	Pen VK n = 259	APC-111 n= 550	Pen VK n= 565
Sinusitis	6 (2.0)	2 (0.7)	4 (1.6)	4 (1.5)	10 (1.8)	6 (1.1)
Vaginal candidiasis	8 (2.6)	8 (2.6)	1 (0.8)	3 (1.2)	9 (1.6)	11 (2.0)
Pyrexia	3 (1.0)	2 (0.7)	6 (2.4)	7 (2.7)	9 (1.6)	9 (1.6)
Lymphadenopathy	0 (0.0)	4 (1.3)	9 (3.6)	4 (1.5)	9 (1.6)	8 (1.4)
Rhinitis/ Rhinorrhea	2 (0.6)	5 (1.6)	6 (2.4)	2 (0.8)	8 (1.5)	7 (1.2)
Fatigue	0 (0.0)	5 (1.6)	7 (2.8)	2 (0.8)	7 (1.3)	7 (1.2)
Cellulitis	3 (1.0)	0 (0.0)	4 (1.6)	0 (0.0)	7 (1.3)	0 (0.0)
Abdominal Pain	2 (0.6)	10 (3.3)	4 (1.6)	8 (3.1)	6 (1.1)	18 (3.2)
Rash	3 (1.0)	3(1.0)	3 (1.2)	4 (1.5)	6 (1.1)	7 (1.2)
Sinus congestion/Drainage	1 (0.3)	1 (0.3)	5 (2.0)	3 (1.2)	6 (1.1)	4 (0.7)
Gastroenteritis	1 (0.3)	3 (1.0)	5 (1.6)	0 (0.0)	6 (1.1)	3 (0.5)
Pain (Back)	0 (0.0)	6 (2.0)	3 (1.2)	2 (0.8)	3 (0.5)	8 (1.4)
Pain (Body)	0 (0.0)	2 (0.7)	1 (0.4)	6 (2.3)	1 (0.2)	8 (1.4)
Dizziness	3 (1.0)	2 (0.7)	2 (0.8)	4 (1.5)	5 (0.9)	6 (1.1)
Tonsillitis/ ↑ Hypertrophy	2 (0.6)	4 (1.3)	2 (0.8)	2 (0.8)	4 (0.7)	6 (1.1)
UTI	3 (1.0)	3 (1.0)	1 (0.4)	3 (1.2)	4 (0.7)	6 (1.1)

UTI = Urinary Tract Infection;

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

According to the Sponsor, blood and urine samples were collected at baseline for screening purposes. They were sent to a central clinical laboratory for analysis and reporting of results. The central clinical laboratory (lab) provided each study site with kits for baseline urine pregnancy testing using the [redacted] and the [redacted] Strep A Test for detection of streptococcal A antigen. b(4)

Laboratory Tests by Category

The following hematology, chemistry, and urine laboratory tests were performed by the central clinical laboratory only at the screening/baseline visit:

- Hematology: complete blood count with differential.
- Serum chemistry: aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, albumin, bilirubin, total protein, blood urea nitrogen (BUN), creatinine, and glucose.

- Urinalysis:
  - Sediment, red blood cells, white blood cells, epithelial cells, crystals, casts, and bacteria;
  - Dipstick - specific gravity, pH, glucose, protein, blood, and ketones.

No post-dose blood or urine laboratory data were required, and this was pre-stated in the study protocol. However, additional chemistry, hematology or urine labs could be collected at the discretion of the investigator based on an abnormal baseline laboratory value. There were no subjects excluded from study entry based on baseline laboratory data.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

As allowed by the protocol, obtaining lab values from patients after being on medication was only at the investigator's discretion. Consequently, lab tests were not obtained regularly or routinely to monitor possible ill-effects of study drug on organ systems. In study 301, no post-dose laboratory data were collected.

The Sponsor reported the following clinical laboratory AEs in study 302, but not in study 301:
increased alanine aminotransferase (ALT), increased aspartate aminotransferase (APC-111, 1; penicillin VK, 0), increased blood alkaline phosphatase (APC-111, 1; penicillin VK, 0), increased hematocrit (APC-111, 1; penicillin VK, 0), increased platelet count (APC-111, 1; penicillin VK, 0), and increased red blood cell count (APC-111, 1; penicillin VK, 0).

The Sponsor reports that the three elevated liver function tests, shown in table 13 were adverse events of increased alanine aminotransferase (ALT) , increased aspartate aminotransferase, and increased blood alkaline phosphatase) were lab values obtained at baseline clinical laboratory and were all from one patient in study 302 (0388-3042) and should not have been reported as TEAEs.

The mistake arose from the specimen being wrongly dated. Rather than being labeled with the baseline date (prior to receipt of medication), the report date (after the patient had been on medication) was used to label the specimen. The reported adverse events were considered mild or moderate in severity.

The hematology events were considered not related to study medication by the Investigator and resolved prior to study completion.

Table S13	Number of patients with reported Abnormal Clinical Laboratory Values in Study 302						
Hematology	**Study 302**		**Study 301**			**Pooled studies**	
	APC-111	**Pen VK**	**APC-111**	**Pen VK**		**APC-111**	**Pen VK**
	N = 302	**N = 306**	**N = 248**	**N = 259**		**N = 550**	**N =565**
Increased WBC	1 (0.3)	0 (0.0)	-	-		1 (0.2)	0 (0.0)
Increased Hematocrit	1 (0.3)	0 (0.0)	-	-		1 (0.2)	0 (0.0)
Increased Platelet	1 (0.3)	0 (0.0)	-	-		1 (0.2)	0 (0.0)
Chemistry							
Increased ALT	1 (0.3)	0 (0.0)	-	-		1 (0.2)	0 (0.0)
Increased AST	1 (0.3)	0 (0.0)	-	-		1 (0.2)	0 (0.0)
Increased Blood Pressure	1 (0.3)	0 (0.0)	-	-		1 (0.2)	0 (0.0)
Increased Alk Phos	1 (0.3)	0 (0.0)	-	-		1 (0.2)	0 (0.0)
ALT = Alanine aminotransferase ; AST = aspartate aminotransferase; Alk Phos = Alkaline Phosphatase;							

MO comments: Above elevated hematology and liver enzyme results were reported as TEAEs and come from one patient. But they were baseline lab values, obtained before the patient took the first dose of study medication (APC-111). They were wrongly reported as TEAEs because they were labeled with a wrong date. How high the lab values rose above the upper limit of normal was not reported. Reporting it would probably have been a moot point, as the elevations occurred before study medications were received by study patients. If any of them were severe, it could have served, perhaps, as a reason for exclusion.

MO comments: *Above elevated hematology and liver enzyme results were reported as TEAEs and come from one patient. But they were baseline lab values, obtained before the patient took the first dose of study medication (APC-111). They were wrongly reported as TEAEs because they were labeled with a wrong date. How high the lab values rose above the upper limit of normal was not reported. Reporting it would probably have been a moot point, as the elevations occurred before study medications were received by study patients. If any of them were severe, it could have served, perhaps, as a reason for exclusion.*

Laboratory Testing in Phase 1 Studies

There were no clinically significant lab results reported in any of Phase 1 studies.

7.1.7.3 Standard analyses and explorations of laboratory data

Non-applicable

7.1.7. 4. Additional analyses and explorations

Non-applicable

7.1.7.3.2. Analyses focused on outliers or shifts from normal to abnormal

Non-applicable

7.1.7. 3.3 Marked outliers and dropouts for laboratory abnormalities

Non-applicable

7.1.7.4 Additional analyses and explorations

Non-applicable

7.1.7.5 Special assessments

Non-applicable

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs measurements included systolic and diastolic blood pressure (BP), pulse/ heart rate, respiration rate, and temperature (oral, ear canal, and axillary). These were measured at baseline (screening), and during subsequent visits.

The Sponsor does not provide margins for determining clinically significant values to enable delineation of patients 1.) who had normal baseline values but subsequently developed abnormal vital signs during the course of study or 2.) whose abnormal baseline value became worse during the course of study.

Based on experience from previous NDA reviews, literature figures, and knowing that the youngest study patient was 12 years of age, the MO made a decision to use the following vital signs parameters (Table 14) to identify potentially clinically significant vital sign values and to make comparison across treatment arms:

Table S14	**Criteria for Determining Potentially Clinically Significant Vital Sign Values**	
Variable	Criteria	
	Low Value	**High Value**
Heart rate	< 60 beats/min	≥ 110 beats/min
Supine systolic blood pressure	< 70 mm Hg	> 140 mm Hg
Supine diastolic blood pressure	< 50 mm Hg	> 90 mm Hg
Respiratory	< 8 breaths/min	> 30 breaths/min
Temperature	< 36 ^{0}C (96.8^{0}F)	≥ 38^{0}C (100.4^{0}F)
min = minute; mm Hg = millimeter of mercury		

MO Comments: *In their presentation of vital signs information, the Sponsor presented data about all patients (with normal and abnormal values) and calculated their mean and*

median values for all vital signs at baseline and other visits, i.e. During Therapy, early withdrawal, the TOC, and the LPT. While this approach can provide general information about differences between different treatment groups (i.e., APC-111-treated vs Pen VK-treated groups), it could obfuscate important details regarding subgroups, and individual patients, with regards to severity of specific abnormalities.
With respect to blood pressure information, the Sponsor tied systolic value to diastolic in the dataset provided for study 302, but provided information about systolic and diastolic values separately in study 301 dataset. In study 302, neither entity could be extracted independently, as in study 301. Although neither study drug is known for their propensity to cause blood pressure changes, aside from instances of hypersensitivity reaction, the development of hypertension or hypotension following the receipt of either study drug was ascertained from the dataset provided and compared across study arms.

7.1.8. 2 Selection of studies and analyses for overall drug-control comparison

In accordance with the foregoing pattern of analyses in this review, the Phase 3 data (from studies 302 and 301) were evaluated for vital sign values obtained from study patients across study arms for overall drug-control comparisons. Vital signs from non comparative Phase I subjects were evaluated only as an additional exploration for sub-section 7.1.8.4 ("Additional analyses and explorations"), the last sub-section under section 7.1.8).

7.1.8.3 Standard analyses and explorations of vital signs data

As shown in table S15, changes in the different vital sign parameters measured in study patents.
These vital sign values were obtained from patients who had normal baseline parameters but subsequently developed post-baseline abnormal values.

Cardiovascular
Based on the pooled studies, cardiovascular parameters (hypo- or hyper-tension and pulse rates) were comparable across study arms: hypertension, 1.8% in each study arm; hypotension, 0.4% for APC-treated versus 0.5% for Pen VK-treated patients. High pulse rates were recorded for 2/550 (0.4%) of APC-111-treated patients compared to 3/565 (0.5%) Pen VK-treated patients.

Respiratory rate
Only one case from each study arm had recorded high respiratory rate post-baseline. The tachypnea resolved before the end of treatment. No tachypnea was recorded as AE. No hypoventilation or respiratory depression was recorded.

Temperature
Most cases of fever were recorded at baseline. The patients in the table S15 were those who developed fever while on their study medications after normal baseline temperatures. That is, 2/550 (0.4%) APC-111-treated patients versus 4/565 (0.7%) Pen-

VK –treated patients had such post baseline fever. The rates are similar in both study arms.

Table S15	Number (%) of patients with Vital Signs Changes in Phase 3 Studies						
Parameter Measured	**Study 302**		**Study 301**			**Pooled Studies**	
Hypertension (mm Hg)	**N = 302**	N = **306**	**N = 248**	**N = 259**		**n = 550**	**n = 565**
Systolic BP > 140/ Diastolic BP > 90	7 (2.3)	3 (1.0)	3 (1.2)	7 (2.7)		10 (1.8)	10 (1.8)
Hypotension							
Systolic BP < 70/ Diastolic BP < 50	0 (0.0)	0 (0.0)	2 (0.8)	3 (1.2)		2 (0.4)	3 (0.5)
Pulse Rate (beats/min)							
Pulse >110	2 (0.7)	2 (0.7)	4 (1.6)	3 (1.2)		6 (1.1)	5 (0.9)
Pulse < 50	1 (0.3)	1 (0.3)	1 (0.4)	3 (1.2)		2 (0.4)	4 (0.7)
Respiratory Rate							
Respiratory Rate > 30	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)		1 (0.2)	1 (0.2)
Respiratory Rate < 8	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Temperature							
Oral Temperature ≥ 100.4 ^{0}F	1 (0.3)	2 (0.7)	1 (0.4)	2 (0.8)		2 (0.4)	4 (0.7)
BP = Blood Pressure							

MO comments: *Among patients with abnormal vital signs, most were recorded at baseline. Among the patients with abnormal post-baseline values, the incidence of hypertension, hypotension, high/low pulse rates, tachypnea and fever was similar across study arms, as shown in table S15.* 7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.1 Analyses focused on measures of central tendencies

The reviewer believes that for the antibiotic under review, amoxicillin (versus penicillin), with long history of use, as opposed to a new molecular entity (NME), it does not appear any additional insight is further gained by exploring measures of central tendencies.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were no dramatic outliers in the data submitted for review.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

Vital sign abnormalities were evaluated in the non-comparative Phase 1 study. This was an additional exploration to ascertain further vital signs abnormalities possibly associated with APC-111 use that may not have been evident in Phase 3 studies. As shown in table S16,

6 (5.4%) and 7 (6.1%) Phase 1 patients who had normal baseline vital sign values developed post baseline clinically significant high systolic and diastolic blood pressures respectively while receiving APC-111. One patient with normal baseline pulse rate developed lower pulse rate at a subsequent visit. These events per the Sponsor, resolved before the end of the studies and no causality attribution was attempted in each case by the investigator.

Table S16 | Number (%) of patients with Vital Signs Changes in Phase 1 Studies

Parameter Measured	Study 109 N (%)	Study 110 n (%)	Study 111 n (%)	Study 112 n (%)	Study 115 n (%)	Group total n (%)
	n = 20	n = 19	n = 24	n = 23	n = 26	N = 112
Blood Pressure						
Systolic BP > 140	*0	3 (15.8)	* 0.0	3 (13.0)	0	6 (5.4)
Diastolic BP > 90	0	4 (5.3)	2 (8.3)	1 (4.3)	* 0	7 (6.1)
Systolic BP < 70/	0	0	0	0	0	0
Diastolic BP < 50	0	0	0	0	0	0
Pulse						
Pulse >110	0	0	0	0	0	0
Pulse < 50	0	*0	*0	1 (4.3)	0	1 (0.9)
Respiratory Rate						
Respiratory Rate > 30	0	0	0	0	0	0
Respiratory Rate < 8	0	0	0	0	0	0
Temperature						
Oral Temperature ≥ 100.4 ^{0}F	0	0	0	0	0	0

*0.0 = Abnormal Vital Sign values in this group of patients were present at baseline (before receiving APC-111)

MO comments: *Most Phase 1 patients with abnormal vital sign values had such values before they received study medications. These were patients who had hypertension and those with low pulse.*

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

No ECG evaluation was done on any Phase 3 patient. Only Phase 1 subjects had ECG evaluation during their screening visits. None of the results obtained in these subject ECGs were considered
clinically significant by the Investigators.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Non-applicable

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Non-applicable

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Non-applicable

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Non-applicable

7.1.9.4 Additional analyses and explorations

Non-applicable

7. 1. 10 Immunogenicity

To the best of the reviewer's knowledge, the immunogenicity of Amoxicillin has not been reported in the literature.

7.1.11 Human Carcinogenicity

No human carcinogenicity study data are available. Even animal studies have not been performed. According to the amoxicillin product label, "Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to detect mutagenic potential of amoxicillin alone have not been conducted…" However, from amoxicillin clavulanate (Augmentin) data, "…tests on a 4:1 mixture of amoxicillin and potassium clavulanate …were non- mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay." In addition "Augmentin was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in

the Ames bacterial mutation assay and in the mouse micronucleus test, and was negative in each of these assays."

7.1.12 Special Safety Studies

Not applicable

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable

7.1.14 Human Reproduction and Pregnancy Data

No data derived from human studies were made available for this application. However, per the product label, "In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately [redacted] times the human dose in mg/m $^{2)}$." b(4)

Regarding **pregnancy**, the label reports that "Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to (b) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed."

And for nursing Mothers, the following: "Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman."

7.1.15 Assessment of Effect on Growth

Not applicable

7.1.16 Overdose Experience

7.1.16 Overdose Experience

The product label indicates that "Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin." In addition "Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adults and pediatric patients."

7.1.17 Postmarketing Experience

See section 2.4

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The clinical data sources used to evaluate safety are described in section 4.1 of this review, and individual studies are enumerated in tables G3 and G4.

7.2.1.1 Study type and design/patient enumeration

This NDA application is a 505 (b)(2) submission. The two Phase 3 studies submitted by the sponsor were both double-blind, double-dummy, randomized, parallel-group, multicenter studies. In these two studies, 550 patients received APC-111. There were no Phase 2 studies. There were five Phase 1 studies with a total of 112 subjects who received APC-111.

While the safety database was considered generally adequate, and may allow the detection of common AEs, a larger database would ordinarily be preferable, to allow the detection of rare AEs. Nevertheless, this reservation can be tempered with the long history of use of this product. Years of accumulation of postmarketing information about amoxicillin should provide the public comfort and reassurance about its safety.

7.2.1.2 Demographics

Information about the demographic characteristics of Phase 3 study patients and their comparisons in the two treatment arms was provided by the Sponsor. For study 302, the comparison of their characteristics is described in subsection 6.1.3, and patients enumerated in tables E2 and E3. Drug-demographic interaction in terms of efficacy is discussed in subsection 6.1.4, under "Efficacy Analyses in Subgroups..." With respect to drug-demographic interactions in relationship to the development of AEs in the studies, no significant differences were apparent between APC-111-treated patients and comparator treated patients.

MO comments: *Gender-related AE of vulvovaginitis occurred in 6/550 (1.1%) APC-111-treated patients compared to 8/565 (1.4%) Pen VK-treated patients. This gender-related AE of vulvovaginitis reported by these patients who participated in the Phase 3 studies is also known to occur with other antibiotics, e.g. the tetracyclines.*

One other potential demographic-related AE is ampicillin or amoxicillin rash associated with infectious mononucleosis. Although Epstein-Barr virus (EBV), the agent of this disease, is acquired from childhood, particularly in the lower socioeconomic group, the clinical disease is most often expressed in adolescents and young adults. According to the Red Book, "Endemic infectious mononucleosis is common in group settings of adolescents, such as educational institutions."[6] The EBV-related tonsillopharyngitis in this disease can mimic Streptococcal tonsillopharyngitis. Amoxicillin administered empirically or for false positive rapid antigen testing to a patient with EBV-related mononucleosis could result in a rash in the drug recipients. In the Phase 3 studies, 3/550 (0.5%) APC-111- treated patients, 16 to 20 years of age, had a diagnosis (and an AE) of infectious mononucleosis compared to 5/565 (0.9%) Pen VK-treated patients, 14 to 24 years of age. In the same studies, rash was reported in 6/550 (1.1%) patients who

received APC-111compared to 7/565 (1.2%) who received Pen VK. However, none of the patients who had an AE of infectious mononucleosis in either treatment arm reported rash.

7.2.1.3 Extent of exposure (dose/duration)

Overall, 662 subjects/patients received APC-III in all studies conducted by the sponsor. Of these, 550 patients were enrolled in the Phase 3 studies (302 in study 302, and 248 in study III-301). In Phase 1 studies, 112 subjects received APC-III. The highest dose of APC-III received by any study enrollee was 775 mg. All received the tablet formulation except two subjects who received sprinkles from research batches of pulsatile-release MP formulation during their biopharmaceutical studies.
In all these patients, no dose- or duration-related AEs were apparent.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Secondary clinical data were gathered from the 195 Amoxicillin-treated patients reported in various literature sources submitted by the Sponsor. The studies were all evaluated for safety signals. Three of these literature materials were particularly relevant. The AEs reported in the studies were incorporated in this review (see subsection7.2.2.3).

7.2.2.2 Postmarketing experience

See section 2.4

7.2.2.3 Literature

In addition to relying on FDA's findings of previous amoxicillin's safety (and effectiveness) from older submissions of other formulations of amoxicillin, the Sponsor provided selected literature articles to provide additional safety (and efficacy) information to support the use of APC-111 in patients.

Altogether, the Sponsor provided 195 literature articles. These articles presented results from studies of various designs. Some were prospective, others retrospective; still others were reports of anecdotal clinical experiences involving the use of amoxicillin. All were screened and those considered pertinent to the review were selected by the reviewer. These articles are presented in tables 7S17 and 7S18 and discussed under MO comments that follow the tables.

Table S17a

Literature Sources Submitted by the Sponsor for Additional Efficacy and Safety Information

Author/ Source (if known) /Study design	Amoxicillin-treated Patients: Age Range; Dose/Regimen/Duration	Efficacy			Safety Issues Reported in Studies
Shvartzman P et al : *BMJ* / May 1993 R/C/OL 1^0 endpoint = bacterial eradication	Eligible age Age : > 3years Dose: Children: 50 mg/kg /dose Adults: 750 mg once daily Duration: 10 days	Rx received →	Amox	Pen	The authors reported: "There were no rashes or other important side effects…"
		Throat cult (+)	75	82	
		Cured (D 14)	75	77	
		Failure (D 14)	0	5	
		Point est. diff	100 %	93.9 %	
		Point est. diff	6.1		
		(Exact CI required)	Sample size:small		
Feder HM Jr et al: *Pediatrics.* Jan. 1999 R/C/OL 1^0 endpoint = bacterial eradication at Visit 1 (Days 4-6) and Visit 2 /Test of cure (TOC) visit (= Days 14-21) following Rx initiation.	Age Range: 3- 18 years of age Dose: Adults: 750 mg once daily Duration: 10 days	Throat cult (+)	Amox	Pen	
		Received Rx →	84	77	
		No follow up visit	2	4	
		Discontinued med (AE)	3	0	
		Per Protocol Pop.	79	73	
		Cured (D 14-21)	75	65	
		Failure (D 14-21)	4	8	
		Point estimate in Per Protocol Population	94.9 %	89.0 %	
		Point est. difference	5.9%		
		Point estimate in ITT Population	89.3%	84.4%	

AEs	Amoxicillin	Penicillin
Urticaria -	1	1
Macular Rash	2	0
Pneumonia	1	0
Abd. Pain	3	3
Diarrhea	3	2

Amox = Amoxicillin (±clavulanate); BMJ = British Medical journal; CI= Confidence interval; C= Controlled; Cult = Culture; D = Day(s) (from start of Rx); IB = Investigator-Blinded; Med = medication; R = Randomized; OL = Open label; Point est. diff = Point Estimate Difference; Rx = Treatment;

Table S17b	Literature Sources Submitted by the Sponsor for Additional Efficacy and Safety Information						
#	Author/ Source (if known) /Study design	Amoxicillin-treated Patients: Age Range; Dose/Regimen/Duration	Efficacy			Safety Issues		
3	Clegg HW et al : *Pediatr Infect Dis J.* 2006 . R/C/IB/ NI 1^0 endpoint = bacterial eradication at visit 2 (Days 14 – 21) or visit 3 (Days 28 – 35) following Rx initiation.	Age Range: 3- 18 years of age Dose: < 40 Kg: 750 mg or 1000 mg once daily OR ≥ 40 kg: 375 mg or 500 mg BID Duration: 10 days	Throat cult (+)	Amox QD	Amox BID	Number of AEs reported in the Study		
			Rx received (ITT) →	326	326	AE	QD Reg Arm	BID Reg Arm
						Urticaria	1	
						GI AEs (NOS)	1	5 5
			Per Protocol Pop.	294	296			
			Cured (at the TOC visit)	235	250			
			Failure (at the TOC visit)	59	46			
			Point estimate in Per Protocol Population	79.9 %	84.5%			
			Point est. difference	- 4.52				
			95% CI	-10.7, 1.6				
			90 % CI	- 0.6, 9.7				
			Point estimate in ITT Population	72.1 %	76.7%			

Amox = Amoxicillin (±clavulanate); BMJ = British Medical journal; CI= Confidence interval; C= Controlled; Cult = Culture; D = Day(s) (from start of Rx); IB = Investigator-Blinded; Med = medication; NI= Noninferiority; R = Randomized; Reg. = regimen; OL = Open label; Point est. diff = Point Estimate Difference; Rx = Treatment; GI = Gastrointestinal ; NOS = not otherwise specified

MO Comments: *The Sponsor provided 195 literature publications to support the once-daily dosing of APC-111 as well as the safety of the product (in addition to FDA's previous findings of the product safety and efficacy) for the treatment of streptococcal pharyngotonsillitis. Of these 195 papers, only three studies (summarized in tables S17a and S17b) were designed to explore the use of daily amoxicillin for the treatment of patients with tonsillopharyngitis, similar to the studies submitted by the Sponsor. The three studies were then selected for closer evaluation by the reviewer.*

The appeal of ***a*** *once-daily dosing regimen for any medication is tied to the expected convenience it provides and the hope for increased compliance and, potentially, increased treatment effect of such drugs on the diseases for which they are administered. Since oral penicillin became available, it has been administered as a three or four-times-a-day regimen in clinical practice. The concept of a once-daily penicillin regimen for the treatment of streptococcal pharyngotonsillitis was initially explored in two comparative studies[8, 9]. The two studies failed. Each had too high bacteriologic failures at the test of cure (TOC) visits compared to the comparator arms in which study patients received multiple doses of penicillin. However, the promise of these studies, and the potential benefit of once daily dosing, if possible, needed to be further explored.*

Once Daily Amoxicillin Studies

1. The Study of Shvartzman et al: *The longer half-life of amoxicillin relative to penicillin, encouraged Shvartzman P et al (table S17a) to re-explore the use of once daily dosing, this time with amoxicillin, in their study[3] (published in 1993), using phenoxymethylpenicillin, administered 3 or 4 times a day (TID or QID,) as the comparator. The demographic characteristics of this open-label study were reported to be similar in both study arms. The study was small and had flaws; the performance of this regimen in the Intent-to-treat population could not be ascertained. The only population made available for analysis was the Bacterial Per Protocol (PPb) population. The efficacy of this regimen in this population at the TOC visit appeared excellent. No information was made available for late post-therapy (follow-up) visit. The value of this study, perhaps, was that it raised the hope that streptococcal pharyngotonsillitis could be successfully treated with once daily dosing of amoxicillin.*

Safety: *No AEs were reported in this study.*

2. The Study of Feder et al: *This study (published in 1999) came in the wake of the Shvartzman study and attempted to duplicate/ corroborate the older study. The main difference between the studies was the ascertainment of the S. pyogenes serotypes at baseline and at the TOC visit. This enabled S. pyogenes serotypes cultured from patients at the TOC visit and the baseline organisms to be compared. Like the Shvartzman study, this study was also too small (table S17a) for any meaningful analysis.*

Safety: *AEs reported in this study included diarrhea, macular rash, pneumonia, abdominal pain and urticaria. The last two AEs led to premature discontinuation of Amoxicillin in all four patients in the amoxicillin arm affected by these AEs. One other*

amoxicillin-treated patient developed pneumonia determined to be due to Mycoplasma pneumoniae. Accordingly, the patient's amoxicillin was switched to erythromycin therapy.

***3. The Study of Clegg HW et al**: This is the latest study (published in 2006) and was a noninferiority, investigator-blinded design which compared once daily amoxicillin with the BID dosing of the same amoxicillin, such that the daily dose (e.g. 1000 mg daily versus 500 mg BID daily) were equal for patients in different arms of the study (see table S17b). Patients were stratified according to weight (again, see table S17b). This study further probed into the question whether once daily amoxicillin is as efficacious (and safe) as the BID dosing. Unlike the previous two studies, sample size for this study was large. The TOC visit assessment was done between Days 14 and 21. S. pyogenes serotype comparison was part of the protocol, as was a late post therapy visit assessment. The authors chose a 10% noninferiority margin (delta) and 90% confidence limits.*

Efficacy-wise, using above parameters for analysis, the study demonstrated noninferiority of QD dose to BID dose. The point estimates were relatively low (again, table S17b). If 95% confidence intervals were employed, the noninferiority demonstrated would probably have been tenuous and subject to debate. The reviewer believes that the study would have provided more useful information by the addition of a third arm of patients who received penicillin, the standard of care for this disease. As the authors also acknowledge, the study was conducted in a single study center, which makes the generalizability of the study an important issue.

This and the previous two studies probably provided part of the information that spurred Advancis Pharmaceuticals (the Sponsor) to pursue the development of APC-111.

***Safety:** Although the authors reported that gastrointestinal (GI) symptoms were the most common AEs developed by study patients, they provided no specificity about the AEs. They provided no information regarding how many patients developed what GI symptoms/sign.*
They also reported occurrence of urticaria in six patients, one in the QD arm, and the other 5 in the BID arm.

7.2.3 Adequacy of Overall Clinical Experience

The Sponsor submitted Study 302 to FDA for the efficacy analysis of APC-111, while study 301 and all their Phase 1 studies were submitted for safety analysis. Ordinarily, a second study would be required by the Agency that would be expected to provide corroborative evidence for the product efficacy and safety. In this regard, and for this type of submission, the Sponsor is relying on FDA's knowledge of Amoxicillin's safety (and efficacy) in previous submissions to fill in that gap. Therefore, for this type of application, and for the indication of Streptococcal pharyngotonsillitis, the overall clinical experience can be considered adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This application relied on FDA knowledge of previous studies conducted for this product in earlier applications. Therefore, specific animal or in vitro testing for the purpose of this application was not required or necessary for this particular review.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing, on balance, was adequate. A relatively minor area of inadequacy involved the Sponsor omitting to stipulate appropriate lab value parameter limits for determining when high or low lab values would be considered clinically significant.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug

and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

No further study is recommended by this reviewer other than the PREA-mandated study in pediatric patients $\geq$ 2 years and $\leq$ 12 years of age using the company's APC-231 MP Sprinkle formulation (as stated in section 9.3.2).

7.2.8 Assessment of Quality and Completeness of Data

Overall, given the product's long history of clinical use, even in multiple daily treatment with other amoxicillin formulations for the indication the Sponsor is seeking claim, the database for this application is adequate.

7.2.9 Additional Submissions, Including Safety Update

During the review, the Sponsor submitted only some selected CRFs; that is not unusual. Additional CFRs were provided on request.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Based on the analyses of the data submitted by the Sponsor for review, the Medical Reviewer has reached the following safety conclusions:

1. The use of APC-111 by study patients caused no deaths or other serious adverse events in the studies submitted.

2. The SAEs reported in Phase 3 studies involved 3/550 (0.5%) and 1/ 565 (0.2%) APC-111- treated and Pen-VK- treated patients respectively. The number was small and the incidence rates were similar in both study arms and none of the events was considered related to study drug.

3. Overall, 22/550 (4.0%) APC-111-treated patients versus 25/565 (4.4%) who received Pen V had Treatment Emergent AEs (TEAE) leading to patient discontinuation from Phase 3 studies. The rates in both study arms were similar. Gastrointestinal symptoms/signs (vomiting, nausea and abdominal pain) and skin rash were the most common drug-related TEAEs leading to patient discontinuation from the studies. The rates of these TEAEs were similar across study arms.

4. Among commonly reported TEAEs in both APC-111- treated and comparator-treated patients, the four most common occurring in ≥ 2% of study patients in Phase 3 studies included severe streptococcal pharyngotonsillitis (6.7% versus 7.3%), headache (4.9% versus 6.4%), pharyngolaryngeal pain (4.5% versus 3.9%) and upper respiratory tract infection (4.4% versus 5.7%) respectively.

5. The four most common TEAEs considered to be study drug related occurring in ≥ 1% but < 2% of patients) APC-111-treated and Pen VK-treated patients included nausea (1.5% vs 1.4%), severe streptococcal pharyngotonsillitis (0.9% vs 1.8%), vulvovaginal candidiasis (0.9% vs 1.4%), and headache (0.7% vs 1.6%).

There was a slightly higher incidence rate among comparator-treated patients than in APC-treated patients for these AEs.

6. Most of the TEAEs reported by Phase 3 patients were considered mild to moderate in severity. Among TEAEs reported as severe, 27/550 (4.9%) patients received APC-111 compared to 21/565 (3.7%) patients who received Pen VK. These rates were comparable. The severe AEs that were considered drug-related in the APC-111-treated patients were generalized rash and vulvovaginal candidiasis. By comparison, headache and diarrhea were the AEs considered possibly drug-related among Pen VK- treated patients. All the reported TEAEs reported resolved before the end of the studies.

Laboratory Data

6. There were no clinically significant laboratory results reported in the studies submitted. Per the Sponsor, the abnormal liver function tests represented baseline values in one patient and were wrongly reported as abnormal post-baseline values.

7. Most abnormal vital signs were recorded at baseline, before patients received study medications. The rates of abnormal post-baseline vital signs were similar across study arms.

8. No ECGs were conducted in Phase 3 studies; in the ECG studies conducted in Phase 1 patients, per the Sponsor, no abnormality was reported or considered clinically significant.

Important Limitations of Data and the Review

The data submitted had the following limitations:

The targeted indication (streptococcal tonsillopharyngitis), for which treatment APC was evaluated, is not a rare disease. Therefore, the database submitted was limited, comprising 550 APC-treated Phase 3 patients and 112 Phase 1 patients.
This would generally limit detection of less common adverse events. However, the long history of use of amoxicillin makes this less of an issue.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

See Table S8

7.4.1.1 Pooled data vs. individual study data

Sponsor's Studies
Studies 301 and 302 were Phase 3 studies pooled to provide 550 APC-treated patients for AE analysis against 565 comparator-treated patients. All 112 patients were pooled from 5 Phase 1 subjects for safety analysis. In this process, each study was also evaluated individually.

Literature Reports
Among the 195 literature articles submitted by the Sponsor, three reports were most helpful and pertinent. Of these, 152 patients treated with QD regimen of amoxicillin were evaluated from the studies of Shvartzman P et al and Feder HP et al. The TEAEs in these studies were evaluated (see table S17a).
Lastly, a total of 652 patients received amoxicillin in the article by Clegg HW et al. This article focused more on efficacy than safety. Reports of AEs were scant and non-specific.

7.4.1.2 Combining data

Table S2 shows how the studies (and therefore data) were combined for analysis. The reviewer combined the comparative Phase 3 studies for analysis. The non-comparative Phase 1 studies PK studies, and subsequently, literature reports were analyzed for safety information.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

APC-111 dose used in study 301 was 775 mg QD for 7 days; for 302 was 775 mg QD for 10 days. Duration/time-dependent AEs were not apparent in the various explorations for safety signals. Literature by Shvartzman P et al. and Feder HM et al., each used 750 mg QD for 10 days. Table S2 shows how the studies (and therefore data) were combined for analysis. The reviewer combined the comparative Phase 3 studies for analysis. The non-comparative Phase 1 studies PK studies, and subsequently, literature reports were analyzed for safety information.
No difference in AE profile related to dose-difference was discernable. Nor was a dose-difference discernable with the 1000 mg QD for 10 days used in Clegg HW et al. Table S2 shows how the studies (and therefore data) were combined for analysis. The reviewer combined the comparative Phase 3 studies for analysis. The non-comparative Phase 1 studies PK studies, and subsequently, literature reports were analyzed for safety information.

7.4.2.2 Explorations for time dependency for adverse findings

The answer to section 7.4.2.1, in the preceding section, is applicable to this section as well.

7.4.2.2 Explorations for time dependency for adverse findings

The answer to section 7.4.2.1, in the preceding section, is applicable to this section as well.

7.4.2.3 Explorations for drug-demographic interactions

Refer to the discussion under Drug-Demographic (Section 7.2.1.2).

7.4.2.4 Explorations for drug-disease interactions

Amoxicillin has a long history of use in clinical practice. Therefore, AEs resulting from drug-disease interaction was not determined for this review. Like other penicillin products, the drug label does contain information for adults with renal insufficiency as a known drug-disease interaction.
There is no information available to address potential drug-disease interaction (and dosing) in pediatric patients with renal insufficiency.

As amoxicillin is often used in young infants with other conditions, e.g., otitis media in the very young, the label has the following to say regarding amoxicillin use in infants and neonates: (b) (4) [redacted]

7. 4.2.5 Explorations for drug-drug interactions

Although this was not evaluated for this application, as amoxicillin is an "old" drug, the label has information on drug-drug interaction:

"Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of amoxicillin and probenecid may result in increased and prolonged blood levels of amoxicillin.

Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin. This has been demonstrated in vitro; however, the clinical significance of this interaction is not well documented."

7.4.3 Causality Determination

There were no deaths reported in this application. But, serious adverse events, common adverse events and uncommon adverse events were assessed to ascertain the relationship

of these events to the receipt of APC. These were done by evaluating these AEs in subjects or patients in groups of pooled data/studies, or individually by CRF review.

During the review, and for the comparative Phase 3 studies, comparisons of APC-111-treated patients with comparator-treated patients were made to ascertain imbalance and significant asymmetry in AE frequencies across study arms. For this application, the comparisons were almost always similar.

Where there appeared to be an outlier, a narrative of the clinical course was sought, and as warranted, the CRF was scrutinized in great detail.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

All patients ≥ 12 years of age with documented streptococcal tonsillopharyngitis randomized to the APC-111 arm of Phase 3 studies received 775 mg of the product daily for 7 days (study 301) or 10 days (study 302) orally. The regimen for the indication the Sponsor is seeking to make claim is the 10-day regimen whose efficacy was evaluated in study 302. The 7-day regimen was inferior to 10 days of penicillin and is not recommended.
As the studies conducted for this NDA application did not include patients < 12 years of age, the dosing regimen for APC-111 in this group is not available at this time.

8.2 Drug-Drug Interactions

See section 7.4.2.5

8.3 Special Populations

Geriatric Use

Of the 550 study patients in Phase 3 clinical studies conducted for this NDA application, only 4 (0.7%) patients were 65 years of age or older. Consequently, per the Sponsor, this number was insufficient to determine whether they respond differently from younger patients. The Sponsor expresses caution that although differences in responses between elderly population with normal kidney function and younger patients have not be reported, a greater sensitivity of some older individuals cannot be ruled out. Current amoxicillin label reports that the "... drug is known to be substantially excreted by the kidney, and the risk of (b) reactions to this drug may be greater in patients with impaired renal function. As elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function."

8.4 Pediatrics

Sixty three (21%) pediatric patients 12-17 years of age received APC in study 302 and a total of 120 (21.8%) the same age range received APC in both Phase 3 studies. Amoxicillin has been used in clinical practice in pediatric population, and frequently, for the treatment of otitis media, streptococcal tonsillopharyngitis, etc. The only precaution for pediatric use involves the neonatal population and those up to 12 weeks of age (see section 7.4.2.4). .

8.5 Advisory Committee Meeting

Non-applicable.

8.6 Literature Review

See Section 7.2.2.3

8.7 Postmarketing Risk Management Plan

Postmarketing risk management activity has been on-going for amoxicillin. This must continue and must continue to include postmarketing reporting of adverse drug experiences as outlined in 21 CFR 314.80.
Prescribing clinicians should be informed through product labeling of the potential for gastrointestinal and skin-related AEs in APC-111-treated, and more generally, amoxicillin-treated patients. In this regard, prescribers also should be aware of the drug class-related potential for possible hypersensitivity reaction, like any other penicillin.

8.8 Other Relevant Materials

Non-applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sources of data for this review included two Phase 3 randomized, double-blind, double-dummy, multicenter studies; five Phase 1 studies; and literature publications that most closely addressed the topic of the review, i.e. the treatment of acute streptococcal tonsillopharyngitis using a once-daily dosing regimen of amoxicillin for 10 days. As this was a 505 (b) (2) application, the Sponsor also relied, in part, on FDA's previous finding of safety and/or efficacy of amoxicillin.

In sum, the data submitted for review have provided substantial evidence for safety and efficacy evaluation of APC-111 for use in patients similar to those in the clinical trials conducted and for the disease studied. The safety profile is adequate to support approval.

As indicated under efficacy conclusion, the efficacy of APC-111 administered as a 775 mg tablet daily, orally, and with meals, in the treatment of streptococcal pharyngitis in patients 12 years of age and older, compared to treatment with the comparator used (penicillin VK), has been demonstrated. Similarly, its safety in this regard is comparable to that of penicillin VK, the standard of care treatment at this time.

The value of this regimen of amoxicillin therapy for the treatment of acute streptococcal tonsillopharyngitis is to enhance compliance. The potential benefit is not only to relieve symptoms and signs more quickly but, perhaps more significantly to achieve a reduction of disease sequelae – be it suppurative or non-suppurative, and regardless of how uncommon. To be sure, alternative daily dosing of antibiotics from other antibiotic classes exist. Daily regimens of azithromycin, cefixime, cefadroxil, ceftibuten have been approved by the FDA. APC-111 represents a different drug class (penicillin class) that will be included in this group. It comes with a good safety profile and history. Resistance to macrolide class has been reported and is increasing. In this regard, as penicillin, despite its longer duration (10 days) recommended for its use in the treatment of acute streptococcal tonsillopharyngitis, APC-111 may offer some advantage. However, the 10-day duration recommended is probably crucial to assurance of cure, given the failure of a 7-day course in study 301.

9.2 Recommendation on Regulatory Action

The amount of data submitted by the Sponsor in the context of a 505 (b) (2) application was discussed above (section 9.1). Based on the evidence provided from the Phase 3 study (302), supportive evidence from literature sources, and the FDA (Reviewer's) previous finding of safety, there are adequate efficacy data to recommend approval. Similarly, from the safety standpoint, the reviewer also recommends APC-111 for approval for the treatment of (b) (4) tonsillopharyngitis (b) (4) to Streptococcus pyogenes in patients 12 years of age and older, with the disease, based on the risk/benefits assessment.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

As recommended for many other drug products, postmarketing risk management activity must include postmarketing reporting of adverse drug experiences as outlined in 21 CFR 314.80. Prescribing clinicians should be informed through product labeling of the abnormalities reported in this review, including gastrointestinal AEs (nausea, vomiting, diarrhea) and skin reactions (rash/urticaria) which have all been reported for adult patients in product labeling. Vigilance should be maintained with regard to development of in vitro resistance of clinical microbiology laboratory isolates to amoxicillin.

9.3.2 Required Phase 4 Commitments

Studies of an amoxicillin extended release formulation in pediatric patients 2-11 years of age are required under Pediatric Research Equity Act (PREA). The sponsor will conduct a phase 3 study of a (b) (4) formulation in this age group and submit the results by March 31, 2013 as a post-marketing commitment.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests related to APC-111.

Labeling Review

See labeling recommendations (section 10.2)

9.5 Comments to Applicant

A deferral has been granted to the Sponsor for conducting studies for the same indication in children 3-11 years of age using the sprinkle formulation of the approved product. This is in compliance with the Pediatric Research Equity Act (PREA). A partial waiver for children under years of age is recommended, because streptococcal pharyngitis is uncommon in this age group. Studies results are expected to be submitted by March 31, 2013. b(4)

10 APPENDICES

Appendix 1: Study Protocol

The primary objective of this study was to determine the efficacy of a once-daily, 775 mg, pulsatile-release, multi-particulate oral formulation of amoxicillin (APC-111 MP Tablet or APC-111) administered for 10 days compared with the 4-times daily, 250 mg oral dose of penicillin VK administered for 10 days in the treatment of tonsillitis and/or pharyngitis secondary to S. pyogenes in adolescents and adults. The non-inferiority of the APC-111 treatment to the penicillin VK treatment was to be demonstrated in terms of the rate of satisfactory bacteriological outcome at the TOC visit (Day 14-18) in the PPb and the mITT
[b] populations, as co-primary populations.

Secondary Objectives
Secondary objectives included the following:

This was a double-blind, double-dummy, randomized, parallel-group, multicenter, clinical study involving outpatients presenting with protocol-defined acute streptococcal tonsillitis and/or pharyngitis suitable for treatment with oral antibiotics.

A minimum of 600 subjects (approximately 300 subjects per treatment group) up to a maximum of 800 subjects (approximately 400 subjects per treatment group) were to be enrolled in the study at approximately 50 sites in the USA and Canada. Enrollment was considered complete when either 800 subjects were enrolled OR the end of the tonsillitis/pharyngitis season was reached (which was estimated as early May 2006).

There were four (4) study visits for bacteriological and/or clinical assessments: Visit 1 (Day 1) was the screening/baseline visit, Visit 2 (Day 3-5) was the During Therapy visit, Visit 3 (Day 14-18) was the TOC visit, and Visit 4 (Day 38-45) was the LPT visit. The study design is summarized in Figure 9-1.

Schedule of Study visits

	Study Design		
Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
Baseline/screening visit (Day 1)	During therapy visit (Day 3-5)	TOC visit (Day 14-18)	LPT visit (Day 38-45)
Assessment of subject eligibility, including clinical signs and bacteriology	Assessment of clinical signs and symptoms	Assessment of bacteriological and clinical outcome	Assessment of bacteriological and clinical outcome
LPT visit = Last Post-Therapy visit, TOC visit = Test-of-Cure visit.			

At the baseline/screening visit, subjects who met the eligibility criteria were to be randomized in a 1:1 ratio to APC-111 (775 mg QD for 10 days) or penicillin VK (250 mg QID for 10 days). Due to the double-blind, double-dummy design of the study, the commercially-obtained penicillin VK tablets were over-encapsulated. Furthermore, matching penicillin VK placebo capsules were manufactured, as were APC-111 placebo tablets. Subjects randomized to APC-111 received penicillin VK placebo capsules for 10 days, in addition to active APC-111 tablets, and subjects randomized to penicillin VK received APC-111 placebo tablets QD for 10 days, in addition to the active penicillin VK QID treatment for 10 days.

Discussion of Study Design

Amoxicillin, the active ingredient in the APC-111 tablet, has been approved since 1974 in the USA for the treatment of adults with mild/moderate, susceptible Gram-positive and Gram-negative bacterial infections of the ear, nose, and throat. This study was a non-inferiority trial designed to investigate the efficacy of the new pulsatile-release multi-particulate oral formulation of amoxicillin (775 mg), APC-111, administered QD for 10 days compared with penicillin VK (250 mg) administered QID for 10 days, in the treatment of tonsillitis and/or pharyngitis secondary to S. pyogenes. If, and only if, the lower limit of the 95% confidence interval was greater than –10.0% would APC-111 for

10 days be considered at least as effective as penicillin for 10 days, in the treatment of tonsillitis and/or pharyngitis due to S. pyogenes. As stated in the International Conference on Harmonization (ICH) guidance documents 'E9 – Statistical Principles for Clinical Trials' and 'E10 – Choice of Control Group and Related Issues in Clinical Trials', a non-inferiority margin should be defined as the 'largest difference that can be judged clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator'. Furthermore, 'the non-inferiority margin cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo'. The non-inferiority margin of 10% is clinically acceptable in this indication and significantly smaller than the difference expected to be obtained in a superiority trial of the active comparator, penicillin, to placebo. The penicillin treatment effect compared to placebo has been demonstrated in a randomized, double-blind, placebo-controlled trial. The bacteriological eradication rate was 7% following placebo treatment, 41% following treatment with penicillin 500 mg TID for 3 days, and 72% following treatment with penicillin 500 mg TID for 7 days. For the present trial, the expected response rate (proportion of 'satisfactory' bacteriological outcomes ['eradication']) of at least 85% for the test treatment (APC-111 750 mg QD for 10 days) is significantly greater than the spontaneous response rate (placebo) estimated to be 7%. Based on literature, a similar response rate is expected for the active comparator (penicillin VK 250 mg QID for 10 days).

The active comparator chosen, penicillin, is considered the drug of choice for the treatment of streptococcal pharyngitis and/or tonsillitis and has been used in a number of registrational studies.

The daily dose of APC-111 was 775 mg compared with a daily dose of penicillin VK of 1000 mg. Based on previous Phase 1 pharmacokinetic studies, a single dose of APC-111, given with food, achieves a daily T>MIC of >40% of the 24-hour dosing interval for S. pyogenes (MIC90 of 0.06 μg/mL for amoxicillin), traditionally considered adequate to confer efficacy against S. pyogenes.

The ultimate goal of therapy for the treatment of tonsillitis and/or pharyngitis is the eradication of the infecting bacteria and, consequently, the primary endpoint of the study was
a test for eradication of S. pyogenes via throat cultures taken 14-18 days after treatment began (i.e., the TOC visit) in accordance with the Food and Drug Administration (FDA) draft guidance document for the development of antimicrobial drug products for the treatment of tonsillitis and/or pharyngitis secondary to S. pyogenes.
This was a double-blind, double-dummy study. The blind was maintained throughout the study by the use of over-encapsulated penicillin VK tablets with matching penicillin VK placebo capsules, and APC-111 placebo tablets identical in appearance to APC-111.

Selection of Study Population
Exceptions to the protocol inclusion/exclusion criteria were to be infrequent and discussed in advance with the medical monitor. Any exceptions to the protocol were to be documented in the case report form (CRF) and source document(s). A waiver was to be obtained from the medical monitor prior to any deviation from the protocol inclusion and exclusion criteria. If the waiver was initially verbal, written documentation was to be provided in the source documents for inclusion of the subject.

Inclusion Criteria

Subjects meeting all of the following criteria were to be considered for enrollment in the study:

• Gave informed consent, assent, and subject's authorization for disclosure of study results
as evident by the signing of the written documentation.

– By signing the informed consent and subject authorization, the subject agreed to release medical records for review by the sponsor or its designee or the FDA. The subject, and when necessary parent/guardian, voluntarily signed a written informed consent after the nature of the study was explained. For subjects below the legal age of consent, assent from the subject was obtained and written informed consent obtained from the parent or legal guardian.
• Age ≥12 years.
• A clinical diagnosis of acute tonsillitis and/or pharyngitis defined as having the clinical signs and symptoms compatible with tonsillitis and/or pharyngitis including sore throat and pharyngeal erythema with at least one of the following:

– Odynophagia

– Tonsillar or pharyngeal exudate
– Tender cervical lymph nodes
– Fever or history of fever treated with antipyretics (within 24-48 hours from onset of symptoms)
– Chills
– Uvular edema
– Elevated white blood cell (WBC) >12,000/mm3 or ≥10% bands
– Red tongue and prominent papillae (strawberry tongue).
• A positive rapid screening test for S. pyogenes (enzyme immunoassay, (b) (4) Strep
A Test).
• Subject was an appropriate candidate for oral antibiotic therapy and could swallow the study dosage forms.

Females must have been non-lactating and:

– At no risk of pregnancy for one of the following reasons: post-menopausal for at least one year, hysterectomy, or tubal ligation, or abstinent from sexual activity that could result in pregnancy, OR
– If of childbearing potential and sexually active, the subject must have had a negative baseline urine pregnancy test and have been utilizing acceptable contraceptives throughout the study.
– If of child bearing potential and not currently sexually active, the subject must have had a negative baseline urine pregnancy test and must have agreed to remain abstinent for the duration of the study. If the subject decided to become sexually active during the period of the study, they must have agreed to use acceptable contraceptives.
• Subjects and (if applicable) parents/legally authorized guardians who were able to comply with the requirements of the protocol (i.e., ability to return for follow-up visits, accessibility by telephone).

Exclusion Criteria

Subjects meeting any of the following criteria were not to be included in the study:

• Chronic or recurrent odynophagia or enlarged tonsils of obscure etiology (two weeks duration a minimum of two times per year or longer duration occurring less frequently).
• More than one episode of acute tonsillitis and/or pharyngitis in the 6 months prior to baseline.
• Pharyngitis known or suspected to be due to a pathogen resistant to beta-lactam antimicrobials
• Subjects who were known carriers of S. pyogenes.
• Previous allergies, serious adverse reaction to, or intolerance to penicillin or any other member of the beta-lactam class of antimicrobials including cephalosporins.
• Any serious illness or concomitant condition that the investigator judged would have precluded the study evaluations or made it unlikely that the course of study therapy and follow-up could be completed. This would also include:

– Any rapidly progressive underlying disease with a shortened life expectancy.
– The inability to swallow the study dosage form.
– Unable to understand the requirements of the study.
– Neutropenia (<1000 polymorph nuclear leukocytes/mm3) or other immunocompromised state.
• Concurrent condition of upper/lower respiratory track infections (e.g., sinusitis, bronchitis, and acute otitis media).
• Concurrent symptoms of viral etiology including:
– Conjunctivitis, coryza and cough
– Diffuse adenopathy or rash suggestive of mononucleosis
– Rash or arthropathy suggestive of scarlet fever.
• Seizure disorder, lowered seizure threshold, or psychiatric condition requiring use of major tranquilizers.
• Pregnancy or nursing.

- Expectation that additional effective systemic antibacterials would be required for any condition during the duration of the study.
- Current drug or alcohol abuse.
- Receipt of any experimental drug or medical device within the previous 30 days (or was scheduled to receive any other experimental procedures during the study period or current involvement in another clinical study).
- Previous treatment under this protocol.
- The need for hospitalization or intravenous antimicrobial therapy.
- Previous systemic antimicrobial therapy within 30 days.
- The presence of clinically significant hematologic conditions (especially neutropenia).
- History of cardiac disease, renal disease, or neurological disease secondary to previous infection with S. pyogenes or previous rheumatic fever.
- Probenecid treatment or systemic steroids for 7 days prior to baseline visit and throughout the duration of the study.

Removal of Patients from Therapy or Assessment

A subject was free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor could also withdraw the subject at any time in the interest of their safety, for administrative, regulatory, or other issues. The sponsor reserved the right to terminate the study at any time. The primary reason for withdrawal was to be recorded in the subject's medical record and on the withdrawal form in the CRF. If a subject was withdrawn for more than one reason, each reason was to be documented in the source document and the most medically significant reason was to be entered in the CRF.

The withdrawal of a subject from the study was to be discussed, where possible, with the medical monitor before the subject stopped medication, if applicable. If the subject withdrew, the final evaluations were to be performed as completely as possible. Subjects who discontinued were not replaced. Any comments (spontaneous or elicited) or complaints made by the subject and the reason for termination, date of stopping the study medication, and the total amount of study medication taken were to be recorded in the CRF and source documents.

If a subject was lost to follow-up, at least 3 documented attempts were to be made to contact the subject, one of which was to include sending a certified letter to the subject's last known address, requesting that they return any unused study medication and return to the investigational site for final safety evaluations.

Reasons for Withdrawal

A subject was to be removed from the study for the following medical or administrative reasons:

- If consent was withdrawn or the subject refused to continue treatment and/or procedures/observations.
- Subject was lost to follow-up.
- Occurrence of unmanageable adverse events or subject required concomitant medication not allowed per protocol.

• Subjects that have taken any other non-protocol specified systemic antimicrobial therapy for another indication or for the treatment of the current indication of tonsillitis and/or pharyngitis at any time during the study.
• For other reasons (e.g., significant protocol violation, non-compliance, or if the blind was broken, or Investigator's discretion to withdraw subject due to negative baseline culture).

Treatments Administered
Study medications, APC-111 and penicillin VK, was supplied to the investigator by the sponsor, details are provided in Table 9-1. The study medications provided were the 775 mg
APC-111 tablet and the 250 mg penicillin VK over-encapsulated tablet. Matching placebo tablets and capsules were provided to maintain the blinding of the study medications.

The study medication was packaged in daily blister cards (Days 1-10) and placed in treatment kit boxes by (b) (4) [redacted]. Each subject was dispensed 1 treatment kit box. The entire amount of study medication required for each subject was included in the subject-specific treatment box.

Table 9-1 Identity of Investigational Products

StudyMedication	APC-111	Placebo	Penicillin VK	Placebo
INN:	Amoxicillin –		Penicillin VK –	
Formulation:	775 mg MP tablet	Matching tablet	250 mg tablet over-encapsulated	Matching capsule
Manufacturer:	(b) (4) [redacted]			
Batch Number a:	H9999	5G09/07	4MT202c/ 14697.2,	14697.1
Date of manufacture:	31 Aug 2004	08 July 2005	27 July 2005	27 July 2005
Expiry dateb:	–	–	–	–

a Refers to the manufacturing product batch number and not the batch number associated with packaging of products.

b No expiration date was assigned; product ongoing stability was sufficient to cover the duration of the study.

c Penicillin VK tablet from (b) [redacted] has expiration date October 2007.
INN = International Nonproprietary Name, MP = multi-particulate.

9.4.3 Method of Assigning Subjects to Treatment Groups
Study medication was assigned and administered to subjects following the procedures

described in the clinical study protocol. After informed consent was obtained and documented, and a subject met all the inclusion criteria and none of the exclusion criteria, the investigator or designee used a web-based interactive response system to obtain a randomization kit number that corresponded to a blinded treatment group assignment. Subjects were randomized to receive either APC-111 or penicillin VK, the randomization was 1:1 in blocks of 4 by site.

9.4.4 Selection of Doses in the Study

The 775 mg dose of APC-111 employed in this study was selected based on well-established antibacterial pharmacotherapy principles. It is widely accepted that the efficacy of β-lactam antibiotics, such as amoxicillin, correlates directly with the T>MIC of a target organism. Amoxicillin T>MIC values of 40% of a 24-hour dosing interval are traditionally considered adequate to provide efficacious drug exposure against most relevant respiratory pathogens, particularly those strains that are drug sensitive. The APC-111 dose used in this study was designed to provide amoxicillin concentrations that exceed the target MIC of S. pyogenes for 40% of the dosing interval after a single dose as confirmed in previously conducted Advancis Phase I studies. The T>MIC was calculated based on free amoxicillin plasma concentrations in healthy volunteers given a single dose of APC-111 using MICs of 0.06 μg/mL (approximate MIC90 for S. pyogenes reported for amoxicillin) and 0.015 μg/mL (MIC90 from a recently conducted Advancis Phase III study [Protocol 111.301]). Mean (± SD) T>MIC values from these Phase I studies are summarized in Table 9-2.

Table 9-2: Mean (±SD) % T>MIC Values against S. *pyogenes* post receipt of APC-111 Under Various Conditions

Protocol	Food Administered	T>MIC (% of 24-hr Interval)[a]	
		MIC 0.06 μg/mL	MIC 0.015 μg/mL
111.109 (Day 1)	Low-Calorie Meal	55.4±11.3	67.5±11.3
111.109 (Day 7)	Low-Calorie Meal	56.6±11.1	70.7±10.6
111.111	Low-Calorie Meal	51.9±11.6	64.2±11.7
111.111	High-Fat Meal	62.3±15.3	75.4±15.2
111.110	High-Fat Meal	66.2±17.0	76.5±13.1

[a] **T>MIC determined using free, unbound plasma concentrations.**

a T>MIC determined using free, unbound plasma concentrations.

Thus, when administered with food, a single dose of APC-111 provides T>MIC coverage of at least 40% of a 24-hour dosing interval.

In addition to daily T>MIC, however, the duration of dosing is also of critical importance to the success of β-lactam treatment in tonsillitis and/or pharyngitis secondary to S. pyogenes.

As shown in Figure 9-2, a direct relationship between length of treatment and efficacy of penicillin VK against group-A streptococcal tonsillitis and/or pharyngitis is evident when data from several literature reports are consolidated. In the previously conducted Advancis Phase III study (Protocol 111.301) assessing APC-111 once-daily for 7 days, the lower (<80%) bacterial eradication rate observed is consistent with that of a comparable 7-day penicillin VK treatment course (see Figure 9-2). This observation implies that a satisfactory antibacterial outcome might not have been achieved study

Protocol 111.301 because the 7-day treatment duration was insufficient, in spite of the fact that these regimens exceeded the 40% target daily T>MIC coverage considered adequate to confer efficacy against S. pyogenes. The data also imply that antibacterial outcome would have likely improved had these regimens been continued for a longer course of treatment (e.g., 10 days).

9.4.5 Selection and Timing of Dose for Each Subject

The first dose (one tablet and one capsule) on Day 1 was to be administered in the clinic and the subject was to remain in the clinic for 30 to 60 minutes to monitor for any untoward reactions. If Day 1 treatment was begun late in the day, such that not all of the Day 1treatment doses (remaining capsules) could be taken on Day 1, any remaining doses from Day 1 were to be administered on Day 11 to complete treatment. Day 2 treatment was to begin with the first dose of Day 2 and not with the remaining doses of the previous day.
The subject was instructed not to break, crush, or chew any study medication to maintain the integrity of the dosage form. The tablet was to be taken once daily shortly after a meal (optimally within one hour and after the same meal each day if possible). The capsules were to be taken without regard to food and four times a day.

9.4.6 Blinding
The double-blind, double-dummy blinding was achieved using the appropriate active or placebo for each dose for each daily blister card.

For subjects randomized to APC-111, the unit dose blister cards contained the following:
• Study Days 1 to 10, the first dose of each treatment day consisted of one 775 mg APC-111 tablet and one placebo penicillin capsule. The remaining three doses of each treatment day consisted of one placebo penicillin capsule per dose.

For subjects randomized to penicillin VK, the unit dose blister cards contained the following:
• Study Days 1 to 10, the first dose of each treatment day consisted of one 250 mg penicillin VK tablet over-encapsulated and one placebo APC-111 tablet. The remaining three doses of each treatment day consisted of one over-encapsulated penicillin VK tablet per dose.

9.4.7 Prior and Concomitant Therapy
Therapies intended for other indications, with the exception of systemic antimicrobials, were to be administered as usual. Adjunctive medications for treatment of pain or fever were allowed (i.e. Acetaminophen [Tylenol®], ibuprofen, etc.).

Due to their anti-inflammatory nature and potential for significant pharmacokinetic interaction, systemic steroids or probenecid were not allowed for 7 days prior to the baseline
visit and during the time period extending from the first day of the study to the LPT visit. Intranasal or aerosolized steroids for oral inhalation were acceptable.

Subjects were also not to receive any other systemic antibiotic for 30 days prior to the baseline visit and during the time period from the first day of study therapy to the LPT visit evaluation. If any systemic antimicrobial agent other than the study medication was initiated for any reason, the subject was to be withdrawn and undergo a complete assessment, which included all of the LPT visit procedures except collection of the throat culture.

All concomitant medication(s) (including any antibacterial agents) taken during the study up to and including the LPT visit (Day 38 - 45), were to be recorded in the CRF.

9.4.8 Treatment Compliance

Compliance was to have been verified by a physical count of dosage forms (tablets and capsules) and recorded in the CRF. For the initial assessment of compliance prior to unblinding, subjects were required to have been 100% compliant with taking study medication (tablets and capsules) during the first 3 days of the study and must have had an
overall compliance of at least 80% with taking study medication (tablets and capsules) during
the study. To be included in the per-protocol population analyses (PPc2 and PPb2, defined in
Section 9.6.2, (page 58), subjects were required to have been 100% compliant with taking active study medication during the first 3 days of the study and must have had an overall compliance of at least 80% with taking the active study medication during the 10-day study
period.

9.5 Study Procedures - Subjects were evaluated at scheduled intervals as presented in Table 9-3.

Table 9-3 Schedule of Events

Procedures	Screening/ Baseline Visit 1	During-Therapy Visit 2a,b	Test-of-Cure Visit 3a	Late Post Therapy Visit 4a
Study Day	Day 1	3 to 5	14 to 18	38 to 45
Inclusion/exclusion criteria	X			
Written informed consent/assent	X			
Medical history	X			
Physical examination	X			
HEENT examination	X	X	X	X
Vital signs	X	X	X	X
Height	X			
Weight				
Urine pregnancy test c	X			X

Hematology X
Blood chemistry
Urinalysis d X
X
Clinical signs and symptoms X X X X
Swab for enzyme immunoassay X
Swab for bacteriology X X X
Administer first dose study medication X
Dispense food diary X
Continue daily dosing X X
Subject activity X X X
Telephone Call for Dose Compliance e X X
Review Compliance and Return Drug/Food Diary X X
Clinical response determination Adverse event reportingf
Prior/Concomitant medications g,h X X X
X
X X
X
X X
X
X

a If the subject withdrew from study prior to a scheduled visit due to failure (including use of additional systemic antibiotic) or other reason for early withdrawal, appropriate procedures were to be completed. Serious adverse events and non- serious adverse events were to be collected through 30 days after the last dose of study medication by telephone/in-clinic visit at 30 days post last dose.
b It was recommended that this visit be completed as an in-clinic visit for all subjects; however, if a subject was unable to complete this visit it was allowed to be completed by telephone visit to review compliance and assess adverse events.
c If subject was female and fit criteria for testing.
d Urinalysis was required, unless subject was unable to provide a urine specimen during the visit.
e Site was to contact subject with one phone call prior to During Therapy Visit in order to confirm dosing compliance (e.g., Day 2 or Day 3) and three phone calls at regular intervals prior to TOC Visit in order to confirm dosing compliance (e.g., Day 5, Day 7, Day 9).
f All serious adverse events and non-serious adverse events were to be collected from the first study-related procedure through the late post-therapy (LPT) visit. If a subject withdrew early, all serious adverse events and non-serious adverse events were to be collected through 30 days after the last dose of studyn medication by telephone/in-clinic visit at 30 days post last dose.
g Prior medications recorded in source documents were to be recorded on the case report form (CRF) for all medications taken from 30 days prior to baseline.

h Concomitant medications recorded in source documents were to be recorded on the CRF for all medications taken from baseline through LPT, including those for the treatment of an adverse event or serious adverse event.

9.5.1 Schedule of Events

9.5.1.1 Screening/Baseline Visit (Visit 1, Day 1)

The subject was to have the following procedures performed prior to the start of study-related
treatment. Subjects were assessed for eligibility for inclusion into the study. Written informed consent/assent (depended on state regulations) and subject authorization was obtained. Medical history was taken and a physical examination was performed including head, eyes, ears, nose, and throat (HEENT) examination. Vital signs, height, and weight were measured and recorded. Previous and concomitant medications were recorded. Blood and urine samples were taken for clinical laboratory assessments and pregnancy testing (females of childbearing potential only). Infection-related signs and symptoms were assessed and recorded. Two throat swabs were obtained (recommended to collect samples simultaneously); one for the rapid screen test [redacted] Strep A Test) and the second specimen for culture to confirm the presence of S. pyogenes. Subjects who met eligibility requirements were randomized and dispensed study medication. The first dose of study medication was administered in the clinic. Food diary was dispensed and completion was explained to the subject (or subject and parent or legal guardian). Subject level of activity was recorded. Any adverse events that occurred after signing the informed consent form were recorded.

b(4)

9.5.1.2 During Therapy Visit (Visit 2, Day 3 - 5)

Subjects were to have been observed in clinic for efficacy and safety during the interval Day 3 to 5 by the investigator or their designee to evaluate their clinical status, check compliance, and document any adverse events. The following assessments/procedures were to have been completed at visit 2. The HEENT examination was performed. Vital signs and weight were measured and recorded. Infection-related signs and symptoms were assessed and recorded. If the subject was prematurely withdrawing from the study, a throat swab specimen was obtained for culture to confirm the presence or absence of S. pyogenes. Food diary was reviewed. Subject level of activity was recorded. Compliance with study medication was reviewed. Adverse events and concomitant medications were recorded.
If the subject could not come to the office for the visit at Day 3 - 5, the visit must have been completed via telephone to review compliance and to assess signs and symptoms related to sore throat, odynophagia, fever and chills.

9.5.1.3 Early Withdrawal Visit

If a subject was prematurely withdrawn from the study therapy for any reason, the early withdrawal procedures were to follow the same as those required for the TOC visit (Day 14 - 18) with the exception of those subjects that started a new antimicrobial therapy

prior to the visit in which case no culture was to be obtained. All adverse events, serious and non-serious, were to have been collected for 30 days after the last dose of study medication
was received.
If a subject was treated with a new antimicrobial for tonsillitis and/or pharyngitis, the subject was considered evaluable for efficacy at the TOC visit and was considered a clinical treatment failure.
If a subject was treated with a new antimicrobial for reasons other than tonsillitis and/or pharyngitis, the subject was considered non-evaluable for the bacteriological and clinical outcome at the TOC visit.

9.5.1.4 Test-of-Cure Visit (Visit 3, Day 14 - 18)
Subjects were scheduled for the TOC visit during the interval of Day 14 to 18 and after the completion of study medication therapy. The following assessments/procedures were to have been competed. The HEENT examination was performed. Vital signs were measured and recorded. Infection-related signs and symptoms were assessed and recorded and the clinical response was determined. A throat swab specimen was obtained for culture to confirm the presence or absence of S. pyogenes. Food diary was reviewed and collected. Subject level of activity was recorded. Compliance with study medication was reviewed and all unused study medication was returned. Adverse events and concomitant medications were recorded. antimicrobial therapy for the subject was recommended.

9.5.1.5 Late Post-Therapy Visit (Visit 4, Day 38 - 45)
All subjects who completed the TOC visit on Day 14 to 18 were to have been scheduled for the LPT visit on Day 38 to 45. The following assessments/procedures were to be performed at the LPT visit. The HEENT examination was performed. Vital signs were measured and recorded. Infection-related signs and symptoms were assessed and recorded and the clinical response was determined. A throat swab specimen was obtained for culture to confirm the presence or absence of S. pyogenes. Adverse events and concomitant medications were recorded.
If the subject withdrew from the study between the TOC and the LPT visits, and if the subject had not taken any additional systemic antimicrobials, then the procedures listed at the LPT visit were to have been completed. If any additional systemic antimicrobials were taken between the TOC and LPT visits, then all procedures except the throat culture were to have been completed. In all cases, serious adverse events were to have been collected for 30 days after the last dose of study medication.

A subject who was treated with a new antimicrobial for reasons other than tonsillitis and/or pharyngitis between the TOC and LPT visits was non-evaluable for the bacteriological and clinical outcome at the LPT visit.
A subject who was treated with a new antimicrobial for tonsillitis and/or pharyngitis between the TOC and LPT visits were evaluable for efficacy at the LPT visit and was considered a clinical treatment failure.
The schedule of events, presented in Text Table 9-3, summarizes the efficacy and safety measurements/assessments performed during each study visit.

9.5.2. Efficacy Assessments

Efficacy assessments included bacteriological and clinical response determinations at the TOC and LPT visits. At the During Therapy visit, only clinical response assessments were made. In addition, subject activity levels were assessed at the During Therapy and TOC visits. Baseline MIC levels were evaluated and further assessed at any time post baseline upon isolation of S. pyogenes. For those subjects with a positive culture at baseline and a negative culture at TOC (that is, a bacteriological eradication) or a bacteriological presumed eradication, but a positive culture at LPT for S. pyogenes, concordance/discordance of the baseline and the LPT isolates were determined.

9.5.2.1 Bacteriological Response and Outcome

9.5.2.1.1 Bacteriological Response at the TOC Visit

The bacteriological response at the TOC visit was assessed using the following categories:

- Eradication: Positive throat culture for S.pyogenes at baseline and confirmed as negative in the throat culture obtained at the TOC visit, irrespective of the clinical response at TOC. No new systemic antimicrobial therapy was started before the culture was obtained at the TOC visit.

- Presumed eradication: Positive throat culture for S.pyogenes at baseline and no culture results available at the TOC visit. Clinical response at TOC was assessed as clinical cure. No new systemic antimicrobial therapy was started before the clinical assessment at the TOC visit.

- Persistence: Positive throat culture for S. pyogenes at baseline and confirmed as positive in the culture obtained at TOC, irrespective of the clinical response.

- Presumed persistence: Positive throat culture for S. pyogenes at baseline and no culture results available at the TOC Visit. Clinical response at TOC was assessed as clinical failure. Subjects who prematurely withdrew and started a new systemic antimicrobial for he treatment of tonsillitis and/or pharyngitis and no culture result was available postbaseline, were presumed to have a persistence of S. pyogenes.

- Indeterminate: Positive throat culture for S. pyogenes at baseline and no culture results available at TOC. The clinical response was assessed as unable to evaluate: In addition the subject met one or more of the following:
- New antimicrobial therapy for an indication other than tonsillitis and/or pharyngitis was started before TOC.

- The subject discontinued the use of the study medication but did not start a new antimicrobial therapy for the treatment of tonsillitis and/or pharyngitis.

• Death not due to tonsillitis and/or pharyngitis before TOC.

• Subject was lost to follow-up prior to TOC.

9.5.2.1.2 Bacteriological Outcome at the TOC Visit
Based on the bacteriologic responses at the TOC visit, subjects were assigned to 1 of 3 bacteriological outcomes of satisfactory, unsatisfactory, or indeterminate as follows:

The bacteriological outcome at TOC was categorized as defined below based on the resultsof the culture at TOC. The acceptable time window for the repeat culture to be conducted at TOC Visit was Day 14 to 18 from the first dose of study medication (Day 1).

• Satisfactory: Bacteriological response of eradication or presumed eradication (excluded from PPb) at the TOC visit.

• Unsatisfactory: Bacteriological response of persistence or presumed persistence (excluded from PPb*) at the TOC visit.

• Indeterminate: Bacteriological response of indeterminate at the TOC visit.

9.5.2.1.3 Bacteriological Response at the LPT Visit

The bacteriological response at the LPT visit was assessed using the following categories:

• Eradication: Positive throat culture for S. pyogenes at baseline and confirmed as negative in a throat culture obtained at the LPT Visit, irrespective of the clinical response at LPT. No new systemic antimicrobial therapy was started between the TOC and LPT Visits.

• Presumed Eradication: Positive throat culture for S. pyogenes at baseline and no culture results available at the LPT Visit, with a clinical response of 'Clinical Cure' at LPT. No new systemic antimicrobial therapy was started between the TOC and LPT Visits.

• Persistence: Positive throat culture for S. pyogenes at baseline, a bacteriological response of 'Persistence', 'Presumed Persistence' or 'Indeterminate' at TOC and confirmed as positive in the culture obtained at LPT, irrespective of the clinical response.

• Presumed Persistence: Positive throat culture for S. pyogenes at baseline, a bacteriological response of 'Persistence', 'Presumed Persistence' or 'Indeterminate' at TOC and no culture results available at the LPT Visit. Clinical response at LPT was assessed as 'Clinical Failure' or 'Unable to Evaluate'. Subjects who prematurely withdrew and started a new systemic antimicrobial for the treatment of tonsillitis and/or pharyngitis, or subject who died due to the indication and no culture result was available post-baseline, were presumed to have a persistence of S. pyogenes.

• Carrier/Re-colonization: A positive culture for S. pyogenes (identical to the baseline strain, as confirmed by PFGE) at the LPT Visit (Day 38-45) in a subject with a negative culture at the TOC Visit (Day14-18) and a clinical response at LPT of "Clinical Cure" whose signs and symptoms of pharyngitis resolved with treatment and did not reappear.

• Recurrence: Positive throat culture for S. pyogenes at baseline, a bacteriological response of 'Eradication' or 'Presumed Eradication' at TOC, culture positive for S. pyogenes (identical strain to baseline strain, as confirmed by PFGE) at LPT and a clinical response assessed as 'Clinical Failure' or 'Unable to Evaluate' at LPT.

• Presumed Recurrence: Positive throat culture for S. pyogenes at baseline, a bacteriological response of 'Eradication' or 'Presumed Eradication' at TOC, no culture results at LPT and a clinical response assessed as 'Clinical Failure' at LPT.

• Reinfection: Positive throat culture for S. pyogenes at baseline, a bacteriological response of 'Eradication' or 'Presumed Eradication' at TOC, culture positive for S. pyogenes (discordant strain to baseline strain, as confirmed by PFGE) at LPT and a clinical response assessed as 'Clinical Failure' or 'Unable to Evaluate' at LPT.

• Indeterminate: Positive throat culture for S. pyogenes at baseline and no culture results available at LPT. The clinical response was assessed as 'Unable to Evaluate'.

9.5.2.1.4 Bacteriological Outcome at the LPT Visit

The bacteriological outcome at LPT was categorized as defined below based on the bacteriological outcome at TOC and results of the repeat culture at LPT Visit. The acceptable time window for the repeat culture to be conducted at LPT Visit was Day 38-45 from the first dose of study medication (Day 1).

• Satisfactory: Bacteriological response was eradication or presumed eradication at both the TOC and LPT visits.
• Unsatisfactory: The patient had a bacteriological outcome at the TOC visit of:

- Unsatisfactory:

. Bacteriological response was persistence or presumed persistence (excluded from PPb*) at the TOC visit, or

O The bacteriological response was indeterminate at the TOC visit with persistence t the LPT visit.

- Satisfactory with secondary failure:

O The bacteriological response was eradication or presumed eradication at the TOC visit, but carrier / re-colonization at the LPT visit.

o The bacteriological response was eradication or presumed eradication at the TOC visit, but recurrence at the LPT visit.

o The bacteriological response was eradication or presumed eradication at the TOC visit, but presumed recurrence (excluded from PPb*) at LPT.-Indeterminate when it was not possible to categorize the bacteriological outcome because of:

o Withdrawal of the subject from the study before follow-up cultures can be obtained for reasons other than treatment failure OR

o Incomplete microbiological data OR

o Concurrent treatment of the subject with a potentially effective anti-infective agent that is not provided for the infection under this treatment protocol.

*Subjects with a bacteriological outcome of Indeterminate were excluded from the PPb and the mITT [a] analyses, except in the case where subjects evaluated as treatment failures and who started a new systemic antimicrobial therapy for the indication under investigation following the TOC Visit but prior to the LPT Visit withdrew from the study before obtaining follow-up cultures at LPT. The bacteriological outcome at LPT for such subjects was categorized as unsatisfactory.

9.5.2.2 Clinical Response and Outcome

9.5.2.2.1 Evaluation of Signs and Symptoms of Tonsillitis and/or Pharyngitis

At each study visit, the investigator (or sub-investigator) was to document in the CRF the presence or absence of the following signs and symptoms of tonsillitis and/or pharyngitis.

•Sore throat, odynophagia, history of fever (baseline only) or fever, chills, strawberry tongue, uvular edema, pharyngeal erythema, tonsillar/pharyngeal exudate, adenopathy of head and neck and tenderness of lymph nodes.

•In addition, if the sign/symptom was present, the investigator assessed the intensity as mild, moderate, or severe with the exception of sore throat, strawberry tongue, and tonsillar/pharyngeal exudate, which were assessed as either present or absent according to the definitions provided.

9.5.2.2.2 Clinical Response at the TOC and LPT Visits

Based on the evaluation of the signs and symptoms of tonsillitis and/or pharyngitis, the clinical response at the TOC and LPT visits was assessed using the following categories:

• Cure:

• At TOC defined as the resolution of baseline abnormal clinical signs/symptoms or sufficient improvement that no further antimicrobial therapy (ies) required for tonsillitis and/or pharyngitis.
• At LPT required a cure at TOC, continued resolution of baseline clinical signs/symptoms and no appearance of new clinical signs/symptoms, or sufficient improvement at LPT visit, and no further antimicrobial therapy required for tonsillitis and/or pharyngitis.
• Failure:
• At TOC, defined as a persistence of baseline clinical signs/symptoms including the appearance of new infection in that there was no apparent response to therapy or an inadequate response requiring additional antimicrobial therapy for tonsillitis and/or pharyngitis.
• At LPT, defined as a failure at TOC OR the occurrence of signs/symptoms of a new infection that required the initiation of new antimicrobial therapy for the indication between the TOC and LPT visits.
• Unable to Evaluate:
• Circumstances precluded classification as clinical cure or failure such as missing post-treatment information, use of non-protocol specified systemic antibacterial therapy for another indication, or early discontinuation of treatment for reasons that were not study medication related. (Note for Protocol 111.301, this response was termed 'Indeterminate' rather than 'Unable to Evaluate'. However, the same definition was applied.)

9.5.2.2.3 Clinical Outcome at the TOC and LPT Visits

Based on the clinical responses at the TOC and LPT visits, PPc and PPb subjects were assigned to 1 of 2 clinical outcomes success or non-success as follows:

• success: A clinical response of cure.

• Non-success: A clinical response of failure or unable to evaluate.

Assignment of clinical outcome as success or non-success was made for the ITT/Safety and mITT [a] populations as for the PPc and PPb populations at TOC, with the exception that subjects with missing clinical evaluations were included as an outcome of non-success.

2.7.3.1.2.8 Statistical Methods

A statistical analysis plan was prepared for both Protocol 111.302 and Protocol 111.301 and finalized before breaking the randomization code. Complete details regarding the analyses can be found in this plan.
Continuous (quantitative) variables such as age and weight were summarized using mean, standard deviation, median, minimum, and maximum, and the treatment groups were compared with respect to mean age and weight using analysis of variance (ANOVA) with treatment group and region as main effects. Categorical (qualitative) variables such as gender, race, ethnicity, age group, weight, physical examination findings, clinical

assessment of signs and symptoms of tonsillitis and/or pharyngitis, and number of previous episodes of tonsillitis and/or pharyngitis in the previous 36 months were summarized using frequencies and percentages, and the treatment groups were compared (if appropriate) using a Cochran Mantel-Haenszel test stratified by region.

2.7.3.1.2.8.1 Analysis Populations

Analysis Populations are discussed in the body of the review.

9.5.2.3 Pulse Field Gel Electrophoresis
Pulse field gel electrophoresis (PFGE) testing was to be performed on both the baseline and LPT visit isolates for all subjects who had a positive culture at baseline, a negative culture at TOC, and a positive culture at LPT for S. pyogenes. The PFGE testing was performed to determine if the culture isolates from the baseline and LPT visits were of the same biotype (i.e., concordant strains of S. pyogenes) or a different biotype (i.e., discordant strains of S. pyogenes). Subjects with concordant strains of S. pyogenes were determined to have persistent colonization or recurrence of the baseline organism, whereas those subjects with discordant strains of S. pyogenes were determined to have a new infection with a new strain of S. pyogenes. These determinations did not affect the assignment of bacteriological outcome at the LPT visit. All such cases were considered unsatisfactory.

9.5.2.4 Subject Activity Level
The subject's current level of activity in relation to their normal level of activity was recorded at the baseline visit, early withdrawal visit (if applicable), During Therapy visit, and the TOC visit.

9.5.2.5 Minimum Inhibitory Concentration
Susceptibility testing and antimicrobial MIC determinations were performed on all baseline S. pyogenes isolates in accordance with Clinical and Laboratory Standards Institute (CLSI) standardized procedures.

9.5.3 Safety Assessments
Safety measurements included the collection of adverse events and changes in vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and temperature) from baseline through the LPT visit. Clinical laboratory evaluations (hematology, chemistry, and urinalysis) were performed at baseline for screening purposes; no post-baseline laboratory evaluations were performed.31,32

Pulse Field Gel Electrophoresis (PFGE) Testing:
For all subjects who have a positive culture at baseline, a negative culture result at TOC (that is, a bacteriological response of 'Eradication') or a bacteriological response of 'Presumed Eradication' and a positive culture at LPT, for S. pyogenes, PFGE testing was performed to document concordance or discordance of the baseline S. pyogenes isolate and the S. pyogenes isolated at LPT. PFGE testing was performed to establish whether:

• The organism isolated at baseline and the organism isolated at LPT were identical (concordant with the primary strain, where the primary strain was regarded as the strain isolated at baseline), hence persistent colonization ('Carrier/Re Colonization') or recurrence f the baseline organism has occurred ('Recurrence'), or

• The organism isolated at baseline and the organism isolated at LPT were not identical 9 discordant with the primary strain), hence persistent colonization or recurrence of the baseline organism had not occurred, but rather a reinfection with a new strain of S. pyogenes occurred ('Reinfection').

These determinations were performed to allow for assignment of bacteriological response at LPT and did not affect the final bacteriological outcome at LPT. All such cases were considered to have an unsatisfactory bacteriological outcome.

2.7.3.1.2.8.6 Subgroup Analyses

Protocol 111.302

In addition to the efficacy analyses outlined above for Protocol 111.302, bacteriological outcome rates (satisfactory or unsatisfactory) at the TOC visit were summarized across the following subgroups of the PPb and mITT [b] populations: gender, age subgroups, race, ethnicity, weight subgroups, characteristics of current infection and key factors of interest, and percentage of times APC-111 was taken with food. The satisfactory bacteriological outcome rates were compared in
each of the subgroups by calculating the asymptotic point estimate and two-sided 95% confidence interval for the difference in satisfactory bacteriological outcome rates.

Protocol 111.301

For Protocol 111.301, bacteriological outcome rates (satisfactory or unsatisfactory) at the TOC visit were also summarized across the following subgroups of the PPb population: gender, age subgroups, race, ethnicity, weight subgroups, characteristics of current infection and key factors of interest, and percentage of times APC-111 was taken with food. No statistical comparisons were made.

Major Protocol Violations
Protocol violations were evaluated on a case-by-case basis. Subjects who met any of the following criteria were classified as subjects with major protocol violations and were not eligible for the PPc or PPb populations.

• Signs and symptoms at baseline insufficient to meet inclusion criteria:

– A clinical diagnosis of acute tonsillitis and/or pharyngitis due to S. pyogenes was

defined as having the clinical signs/symptoms compatible with tonsillitis and/or pharyngitis including a sore throat and pharyngeal erythema and at least one of the following: Odynophagia, tonsillar or pharyngeal exudate, adenopathy of head and neck, tenderness of lymph nodes, fever or history of fever treated with antipyretics within 24-48 hours from onset of symptoms), chills, uvular edema, elevated WBC count >12,000/mm3 or ≥10% bands, and red tongue and prominent papillae (strawberry tongue). Three subjects (0318/3017; 0324/3014; 0461/3005) did not present with pharyngeal erythema. In all three cases the absence of pharyngeal erythema was considered a minor violation and subjects were subsequently included in the appropriate analysis populations.

• Previous antimicrobial therapy (e.g., antivirals, antifungals, or antibacterials):

– Antimicrobial therapy received within 30 days prior to inclusion in the study was evaluated on a case by case basis to determine whether such use was considered a minor or major violation. Any systemic antibacterial therapy within 7 days prior to inclusion in the study was considered a major violation.

• Use of non-study systemic (oral or intravenous) antibiotics between baseline and the TOC evaluation (e.g., for the treatment of urinary tract infection, ear infection, etc.), with the exception of clinical failures occurring before the end of Day 23 (upper limit of visit window for analysis purposes) were considered major violations. Use of non-study systemic antibiotics between TOC and LPT was also considered a major violation.

• Insufficient treatment compliance:

– <100% compliance (with tablet and capsule utilization for PPc1/PPb1 assignment or with active study medication for PPc2/PPb2 assignment) during the first 3 days of the study.
– Overall compliance <80% (with tablet and capsule utilization for PPc1/PPb1 assignment or with active study medication for PPc2/PPb2 assignment) (except for subject withdrawal prior to the completion of all active study medication due to treatment failure).

• Concurrent symptoms of viral etiology including:
– Conjunctivitis, coryza and cough
– Diffuse adenopathy or rash of suggestive mononucleosis
– Rash or arthropathy suggestive of scarlet fever

• Concurrent conditions of the upper/lower respiratory tract including:
– Epiglottis, glossitis, retropharyngeal or buccal cellulitis, retropharyngeal, tonsillar or peritonsillar abscess, sinusitis, bronchitis, otitis media, and/or orbital or periorbital cellulitis

• Subjects with head and neck cancer, or any rapidly progressive underlying disease with a shortened life expectancy

• Subjects with clinically significant neutropenia defined as <1000 polymorphonuclear cells/mm3 or other immunocompromised state

• Subjects previously enrolled and randomized in this study

• Baseline enzyme immunoassay (b) (4) Strep A Test) was negative or the test result was not available and the baseline throat swab culture for S. pyogenes was negative or not available.

• Missing clinical assessment at the TOC visit or the TOC visit occurred outside of the Day 14 to Day 23, inclusive, visit window with the exception of clinical failures occurring before the end of Day 23. Efficacy results for clinical failures who were not withdrawn from the study due to an adverse event were carried forward.

• Randomized, double-blind treatment assignment unblinded prior to TOC

• No written informed consent and/or assent, if applicable

Subjects who met any of the major protocol violations described above and/or the violations/deviations listed below were excluded from the PPb population.

• Baseline throat swab culture result was negative for S. pyogenes or baseline culture result was not available.
• Baseline throat swab specimen for culture was obtained more than 3 days before the first dose of study medication.

• No throat swab culture results were available at the TOC visit except clinical failures who withdrew early from the study and started a new antimicrobial for tonsillitis and/or pharyngitis or who died due to tonsillitis and/or pharyngitis.

• The TOC throat swab culture sample was collected before the TOC window (i.e., before Day 14) except clinical failures occurring before the end of Day 23 who withdrew early from the study and started a new antimicrobial for tonsillitis and/or pharyngitis or who died due to tonsillitis and/or pharyngitis.

• The TOC throat swab culture sample was collected after the TOC window (i.e., major protocol violation if after Day 23). If the sample was collected on Day 19, 20, 21, 22 or 23, it was regarded as a minor violation.

Summary of Protocol Violations

A. Signs and symptoms at baseline insufficient to meet inclusion criteria;
B. Previous antimicrobial therapy received within 7 days prior to inclusion in the study;

C. Use of non-study systemic (oral or i.v.) antibiotics between baseline and the TOC evaluation, with the exception of clinical failures occurring before the end of Day 23 (upper limit of visit window for analysis purposes);
D. Insufficient treatment compliance:
   - If patient was <100% compliant with treatment during the first 3 days of the study;
   - Overall compliance <80% (tablet or capsule) except for patient who withdrew due to treatment failure prior to the completion of all active study medication.
E. Concurrent symptoms of viral etiology, including:
   - Conjunctivitis, coryza and cough,
   - Diffuse adenopathy or rash of suggestive mononucleosis,
   - Rash or arthropathy suggestive of scarlet fever;
F. Concurrent conditions of the upper/lower respiratory tract including:
   - Epiglottis, glossitis, retropharyngeal or buccal cellulitis, retropharyngeal, tonsillar or peritonsillar abscess, sinusitis, bronchitis, otitis media, and/or orbital
     or periorbital cellulitis;

G. Patients with head and neck cancer, or any rapidly progressive underlying disease with a
   shortened life expectancy;
H. Patients with clinically significant neutropenia (defined as <1000 polymorphonuclear
   Cells/mm^3) or other immunocompromised state;
I. Patients previously enrolled and randomized in this study;
J. Baseline enzyme immunoassay (b) (4) Strep A Test) was negative or the test result
   was not available and the baseline throat swab culture for GAS was negative or not
   available;
K. Missing clinical assessment at the TOC visit or the TOC visit occurred outside of the
   Day 14 to Day 23 visit window, inclusive, with the exception of clinical
   failures occurring before the end of Day 23. Efficacy results for clinical failure
   patients who were not withdrawn from the study due to an adverse event that were carried
   forward.
L. Randomized, double-blind treatment assignment unblinded prior to TOC
M. No written informed consent and/or assent, if applicable

[Subjects who met any of the major protocol violations described above and/or the violations/ deviations listed below were excluded from the PPb population].

N. Baseline throat swab culture result was negative for GAS or baseline culture result
was not available.

O. Baseline throat swab specimen for culture was obtained more than 3 days before the first
dose of study medication.

P. No throat swab culture results were available at the TOC visit except clinical failures who
withdrew early from the study and started a new antimicrobial for PT or who died due to
PT.

Q. The TOC throat swab culture sample was collected before the TOC window (i.e., before
Day 14) except clinical failures occurring before the end of Day 23 who withdrew early
from the study and started a new antimicrobial for PT or who died due to PT;

R. The TOC throat swab culture sample was collected after the TOC window (i.e., major
protocol violation if after Day 23). If the sample was collected on Day 19, 20, 21, 22
or 23, it was regarded as a minor violation

Appendix 2:
[Tables S12b, S12c, S12d, S12e, and S12f]

Tables of Less Common TEAEs (in alphabetical Order)

Table S12b	Number (%) of less common TEAEs reported by < 1% of Phase 3 Patients (Continued - in alphabetical order)					
	Study 302		Study 301		Pooled Studies	
	APC-111 n= 302	Pen VK n= 306	APC-111 n= 248	Pen VK n = 259	APC-111 n= 550	Pen VK n= 565
Alopecia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Allergic (Drug/chemical reaction)	1 (0.3)	1 (0.3)	1 (0.4)	2 (0.8)	2 (0.4)	3 (0.5)
Anemia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Ankle swelling (right)	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
Anorexia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Anxiety	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)
Arthralgia/ Arthritis	0 (0.0)	0 (0.0)	1 (0.4)	4 (1.5)	1 (0.2)	4 (0.7)
Aphthous ulcer (Canker sore)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
Blepharitis	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Blister (Upper lip)/ or chapped lip	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Blurred vision	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Breast discharge/ disorder	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)
Bronchitis	1 (0.3)	2 (0.7)	4 (1.6)	2 (0.8)	5 (0.9)	4 (0.7)
Bronchospasm	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Cheilitis	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)
Chest pain/congestion	2 (0.6)	0 (0.0)	0 (0.0)	3 (1.2)	2 (0.4)	3 (0.5)
Chills	0 (0.0)	1 (0.3)	1 (0.4)	2 (0.8)	1 (0.2)	3 (0.5)
Clostridium Colitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Confusional state	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Conjunctivitis	2 (0.6)	1 (0.3)	2 (0.8)	1 (0.4)	4 (0.7)	2 (0.4)
Constipation	2 (0.7)	0 (0.0)	1 (0.4)	2 (0.8)	3 (0.5)	2 (0.4)
Costochondritis	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Contusion (Head)	2 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	3 (0.5)	0 (0.0)
Contusion (Jaw)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Convulsion	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
COPD	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Cyst (right ear canal)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Cystitis (Acute)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

Table S12c:	Number (%) of less common TEAEs reported by < 1% of Phase 3 Patients (Continued - in alphabetical order)					
	Study 302		Study 301		Pooled Studies	
Dehydration	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Depression	1 (0.3)	1 (0.3)	1 (0.4)	0 (0.0)	2 (0.4)	1 (0.2)
Dermatitis	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Diabetes	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Dry mouth	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)
Dry skin	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Dry Throat	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Dysgeusia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Dysmenorrhea	1 (0.3)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)
Dyspepsia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Dysphagia (acute)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Dyspnea	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)
Dysuria	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Edema (Localized)	0 (0.0)	2 (0.7)	2 (4.0)	1 (0.4)	2 (0.4)	3 (0.5)
Effusion (middle ear)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.8)	0 (0.0)	3 (0.5)
Epistaxis	0 (0.0)	3 (1.0)	1 (0.4)	0 (0.0)	1 (0.2)	3 (0.5)
Excoriation	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Eye discharge/ irritation	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)
Fever	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Flatulence	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)
Flushing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Folliculitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
Foot Injury	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Foreign body in eye /Trauma	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Gastrointestinal Reflux	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Gum bleeding	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Table S12d	Number (%) of less common TEAEs reported by < 1% of Phase 3 Patients (Continued - in alphabetical order)					
	Study 302		Study 301		Pooled Studies	
Heat flush	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hot Flashes (Menopausal)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hematoma (abdominal or left arm)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	1 (0.2)
Herpes simplex	3 (1.0)	4 (1.3)	2 (0.7)	1 (0.4)	5 (0.9)	5 (0.9)
Hoarseness	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
H. pylori infection	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hyperacousia –ear sensation blocked	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hypersensitivity	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hypertension	0 (0.0)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.2)	2 (0.4)
Hypoacusis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
Hypoesthesia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Impetigo	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Infectious Mononucleosis	2 (0.7)	5 (1.6)	1 (0.4)	0 (0.0)	3 (0.5)	5 (0.9)
Influenza	0 (0.0)	2 (0.7)	1 (0.4)	1 (0.4)	1 (0.2)	3 (0.5)
Injury ((Limb/joint)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)
Insomnia	2 (0.7)	1 (0.3)	0 (0.0)	1 (0.4)	2 (0.4)	2 (0.4)
Joint sprain	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)
Labyrinthitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Laceration (skin)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)
Laryngitis	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.2)	2 (0.4)
Migraine	2 (0.7)	2 (0.7)	2 (0.8)	2 (0.8)	4 (0.7)	4 (0.7)
Molluscum contagiosum	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Motor vehicle accident	1 (0.3)	1 (0.3)	4 (1.6)	0 (0.0)	5 (0.9)	1 (0.2)
Mucus in throat	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)
Musculo-skeletal stiffness/ spasm	0 (0.0)	2 (0.7)	2 (0.7)	0 (0.0)	2 (0.4)	2 (0.4)
Myalgia	1 (0.3)	3 (1.0)	4 (1.6)	0 (0.0)	5 (0.9)	3 (0.5)
Nasal mucosa erythema/edema/drainage	1 (0.3)	2 (0.7)	0 (0.0)	2 (0.8)	1 (0.2)	4 (0.7)
Nasopharyngitis	5 (1.7)	3 (1.0)	7 (2.8)	3 (1.2)	12 (2.2)	6 (1.1)
Night sweat	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Table S12e	Number (%) of less common TEAEs reported by < 1% of Phase 3 Patients (in alphabetical order)					
Less Common (< 1%) Adverse Events [In alphabetical order]	**Study 302**		**Study 301**		**Pooled Studies**	
Odynophagia	0 (0.0)	1 (0.3)	4 (1.6)	2 (0.8)	4 (0.7)	3 (0.5)
Oral mucosal blister	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Otitis media	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.4)
Pain (Arm)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pain (Axillary)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Pain (Bone)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Pain (Breast)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Pain (chest)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)	0 (0.0)
Pain (Extremity)	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.4	1 (0.2)	2 (0.4)
Pain (Jaw)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Pain (Lymph node)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)
Pain (Neck)	0 (0.0)	2 (0.7)	2 (0.8)	1 (0.4)	2 (0.4)	3 (0.5)
Pain (pelvic)	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)	3 (0.5)	0 (0.0)
Pain (sinus)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Paraesthesia (tongue)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	1 (0.2)
Periodontitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Peritonsillar abscess	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.4)	1 (0.2)	1 (0.2)
Paronychia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Petechial lesion – Palate	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pharyngeal ulceration	1 (0.3)	1 (0.3)	1 (0.4)	0 (0.0)	2 (0.4)	1 (0.2)
Pharyngeal erythema/ edema	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	3 (0.5)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)	3 (0.5)
Pneumonia	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Proteinuria	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Post nasal Drip	1 (0.3)	0 (0.0)	1 (0.4)	5 (1.9)	2 (0.4)	5 (0.9)
Pregnancy	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)
Pruritus	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
Psoriasis	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	1 (0.2)
Pulmonary congestion	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)

Table S12 f	Number (%) of less common TEAEs reported by < 1% of Phase 3 Patients (in alphabetical order)					
Less Common (< 1%) Adverse Events [In alphabetical order]	**Study 302**		**Study 301**		Pooled Studies	
	APC-111 n= 302	**Pen VK n= 306**	**APC-111 n= 248**	**Pen VK n = 259**	**APC-111 n= 550**	**Pen VK n= 565**
Renal Calculi	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Respiratory Tract congestion	2 (0.6)	0 (0.0)	2 (0.8)	0 (0.0)	4 (0.7)	0 (0.0)
Rhonchi	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Seasonal Allergy	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Severe spasmodic torticollis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Shin splints (Bilateral)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Skin Desquamation	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.4)	0 (0.0)
Stomach discomfort	0 (0.0)	1 (0.3)	2 (0.8)	3 (1.2)	2 (0.4)	4 (0.7)
Sore throat/seasonal allergy	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Stress disorder (acute)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Supraventricular tachycardia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Increased sweating	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Tendonitis	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Throat irritation	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Thrush (candidiasis)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	1 (0.2)
Tinea corporis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Tonsillar ulceration/ Tonsillectomy	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
Toothache	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Tooth infection	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)
Tracheitis	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Tympanic membrane perforation	0 (0.0)	3 (1.0)	0 (0.0)	1 (0.4)	0 (0.0)	4 (0.7)
Ureteral obstruction	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Upper airway secretion (↑)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Vertigo	0 (0.0)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.2)	2 (0.4)
Viral infection	2 (0.6)	2 (0.7)	3 (1.2)	2 (0.8)	5 (0.9)	4 (0.7)
Viral Pharyngitis	1 (0.3)	3 (1.0)	2 (0.8)	0 (0.0)	3 (0.5)	3 (0.5)
Weight loss	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Wheezing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Wound (Puncture)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

UTI = Urinary Tract Infection; URI = Upper Respiratory Tract Infection; COPD = chronic obstructive pulmonary disease

10.1 Review of Individual Study Reports

Not applicable.

10.2 Labeling Line-by-Line Labeling Review

After looking over the Sponsor's proposed label, including the Agency's recommended changes involving the clinical study results, the reviewer is in agreement with the content.

REFERENCES

1. Suarez-Kurtz G, Ribeiro FM, Vicente FL, and Struchiner CJ. Development and Validation of Limited-Sampling Strategies for Predicting Amoxicillin Pharmacokinetic and Pharmacodynamic Parameters. *Antimicrobial Agents and Chemotherapy*, November 2001, p. 3029-3036, Vol. 45, No. 11

2. Brook I. Overcoming penicillin failures in the treatment of Group A streptococcal pharyngo-tonsillitis.Int *J Pediatr Otorhinolaryngol.* 2007 Jul 16

3. Shvartzman P, Tabenkin H, Rosentzwaig A, Dolginov F. Treatment of streptococcal pharyngitis with amoxycillin once a day. *BMJ.* 1993 May 1;306 (6886):1170-2.

4. Feder HM Jr, Gerber MA , Randolph MF, Stelmach PS, Kaplan EL. Once-daily therapy for streptococcal pharyngitis with amoxicillin. *Pediatrics.* 1999 Jan;103 (1):47-51.

5. Clegg HW, Ryan AG, Dallas SD, Kaplan EL, Johnson DR, Norton HJ, Roddey OF, Martin ES, Swetenburg RL, Koonce EW, Felkner MM, Giftos PM. Treatment of streptococcal pharyngitis with once-daily compared with twice-daily amoxicillin: a noninferiority trial. *Pediatr Infect Dis J.* 2006 Sep;25 (9):761-7.

6. American Academy of Pediatrics. Group Streptococcal Infections. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. 2006 Report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: *Academy of* Pediatrics; 2006:610-620.

7. Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL and Schwartz RH. Practice guidelines for diagnosis and management of group A streptococcal pharyngitis. *Clin. Infect. Dis.* **35** (2002), pp. 113–125

8. Breese BB, Disney FA, Talpey WB. Penicillin in Streptococcal Infections; Total Dose
and Frequency of Administration. *Am J Dis Child.* 1965 Aug;110:125-30.

9. Gerber MA, Randolph MF, DeMeo K, Feder HM Jr, Kaplan EL Failure of once-daily penicillin V therapy for streptococcal pharyngitis. *Am J Dis Child.* 1989 Feb;143(2):153-5.

10. Dagnelie CF, van der Graaf Y, De Melker RA. Do patients with sore throat benefit from penicillin? A randomized double-blind placebo-controlled clinical trial with penicillin V in general practice. Br J Gen Pract. 1996 Oct;46(411):589-93.

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

/s/

Menfo Imoisili
1/17/2008 06:08:21 PM
MEDICAL OFFICER