

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
50-813

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTIINFEKTIVE and OPHTHALMOLOGY PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW

NDA 50-813

Date review completed: 25 Oct 07

Date company submitted: 14 Dec 06
Reviewer: Fred Marsik, Ph.D.

Date received by CDER: 15 Dec 06
Date assigned: 15 Dec 06

NAME AND ADDRESS OF APPLICANT

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CONTACT PERSON

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DRUG PRODUCT NAME

Proprietary: None
Established name: Amoxicillin
Code Name/Number: Amoxicillin pulsatile
Chemical name: (2S,5R,6R)-6-[(R)-(-)-2-amino-2-(p-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate
Chemical formula: C₁₆H₁₉N₃O₃S•3H₂O

PROPOSED INDICATION

Tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes* in adolescents and adults

Currently amoxicillin is approved by the FDA to treat:

- Infections of the ear, nose, and throat – due to *Streptococcus* spp. (α and β-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 (α and β-hemolytic strains only), *Staphylococcus* spp., or *E. coli*
- Infections of the lower respiratory tract – due to *Streptococcus* spp. (α and β-hemolytic strains only), *S. pneumoniae*, *Staphylococcus* spp., or *H. influenzae*

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- Gonorrhoeae, acute uncomplicated (ano-genital and urethral infections) - due to *N. gonorrhoeae*
- Triple therapy: AMOXIL/clarithromycin/lansoprazole. *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence

PROPOSED DOSAGE FORM, ROUTE OF ADMINISTRATION, DOSAGE STRENGTH, DOSING INTERVAL, AND DURATION OF TREATMENT

Dosage form: Tablet (multiparticulate pulsatile-release)

Route of administration: Oral

Strength and dosing interval: 775 mg QD (once daily)

Duration of treatment: 10 days with food

DISPENSED

Rx

RELATED DOCUMENTS

IND 62,576, IND — NDA 62-118, NDA 50-755, NDA 50-749, NDA 50-542, NDA 21-222, NDA 50-785, NDA 50-460

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REMARKS

Middlebrook Pharmaceuticals (formerly Advancis Pharmaceutical) Corporation has developed a once-a-day pulsatile-release multiparticulate formulation of amoxicillin (APC-111 MP tablet, 775 mg) for a 10 day treatment regimen for tonsillitis and/or pharyngitis due to *Streptococcus pyogenes* in adolescents and adults.

A previous clinical trial involved the use of a 775 mg tablet given for a period of 5 to 7 days. The clinical trial failed to demonstrate statistical non-inferiority of APC-111 MP tablets administered QD for 7 days to penicillin VK QID for 10 days with a 95% CI [-20.0; -4.4]. The Applicant in this submission has provided data from a clinical trial where APC-111 MP 775 mg tablets were administered once a day for 10 days.

This review does not entail the establishment of interpretive criteria or quality control parameters. These laboratory test result interpretive criteria have been established previously. It is a review of the clinical and microbiological outcome data for the study drug and comparator.

CONCLUSION

From a "Clinical Microbiology" perspective the clinical microbiology information provided by the Applicant shows that the drug product, amoxicillin pulsatile was efficacious in eradicating *S. pyogenes* associated with pharyngitis/tonsillitis and that there

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was also clinical success with a 10 day course of treatment with the drug. The reader is referred to the statistical analysis reviews and medical officer reviews for additional information on the efficacy of amoxicillin pulsatile for the treatment of pharyngitis/tonsillitis — , *S. pyogenes*.

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The Applicant has provided in vitro susceptibility information from the literature on the susceptibility of better than 100 isolates of Group B and G streptococci to penicillin. Based on this information the inclusion of these two organisms in the PI is appropriate. While the Applicant provided in vitro susceptibility information on less than 100 isolates of Group C streptococcus from the literature it is appropriate to include this organism in the PI because its susceptibility to penicillin is similar to Group A and G streptococci and there have no major reports of penicillin failing to treat pharyngitis due to Group C streptococcus.

AGENCY'S PROPOSED SECTION OF THE "MICROBIOLOGY" PORTION OF THE
PACKAGE INSERT

SEE "EXECUTIVE SUMMARY" FOR PROPOSED "MICROBIOLOGY" PORTION
OF PACKAGE INSERT

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EXECUTIVE SUMMARY

INTRODUCTION

The Sponsor in previous submissions had provided information on a new formulation of the antimicrobial amoxicillin. This formulation allows for the release of amoxicillin from a tablet over a period of time. The tablet is designed to sequentially deliver an immediate release and two delayed release pulses of amoxicillin in the first six hours of the dosing interval. The Sponsor feels that a once-a-day product with a lower daily dose and shorter duration of therapy than conventional amoxicillin and penicillin therapies will increase convenience and likely improve compliance.

Streptococcus pyogenes is the primary bacterial cause of pharyngitis. The peak incidence of pharyngitis caused by *S. pyogenes* occurs between 5 to 15 years of age. While streptococcal pharyngitis is a self limiting disease it is critical to treat the disease early to prevent the occurrence of acute rheumatic fever, glomerulonephritis, suppurative complications, and reduce the transmission of the organisms to close contacts. Penicillin has long been and remains the drug of choice for the treatment of streptococcal pharyngitis due to its efficacy, safety, narrow spectrum of activity, and low cost. Amoxicillin is an accepted alternative to penicillin for eradication of *S. pyogenes* also because of its safety, efficacy, and narrow spectrum of activity. Despite the development of antimicrobial resistance among bacterial pathogens, *S. pyogenes* (e.g. erythromycin resistance) remains uniformly susceptible to the penicillin class of antimicrobials even when it is resistant to erythromycin. In fact, routine in vitro susceptibility testing of isolates of *S. pyogenes* is not recommended.

In Vitro Activity of Amoxicillin and Penicillin against *Streptococcus pyogenes*

As shown in Table 1 the amoxicillin MIC₉₀ is similar to the penicillin MIC₉₀ for *S. pyogenes* even when the *S. pyogenes* is resistant to erythromycin. To date there have been no reported instances of *S. pyogenes* being resistant to the penicillin class of antimicrobials. All susceptibility testing of the isolates in Table 1 were done by National Committee for Clinical Laboratory Standards [now Clinical and Laboratory Standards Institute (CLSI)] methods.

Table 1. In vitro susceptibility of *Streptococcus pyogenes* to penicillin and amoxicillin

Antimicrobial	Number of isolates	Mode	MIC $\mu\text{g/mL}$		Range	% susceptib
			MIC ₅₀	MIC ₉₀		
Penicillin (reference 6)	3918	≤ 0.06	≤ 0.06	≤ 0.06	$\leq 0.06 - 0.12$	100
Amoxicillin/clavulanate	3918	≤ 0.012	< 0.012	< 0.012	$\leq 0.012 - 0.5$	100*
Amoxicillin (reference 7)	40		≤ 0.015	≤ 0.015		100*
Amoxicillin/clavulanate	40		≤ 0.015	≤ 0.015		100*

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Penicillin (reference 8)	210	0.06	0.06	0.015 - 0.125	
Amoxicillin	210	0.03	0.06	0.015 - 0.125	100*
Amoxicillin/clavulanate	210	0.03	0.06	0.015 - 0.125	100*
Penicillin (reference 9)	34 erythromycin-resistant	0.008	0.008		
Penicillin (reference 4)	Erythromycin-susceptible = 3700		≤0.06		
	Erythromycin-resistant =214		≤0.06		

*Predicted on the basis of penicillin susceptibility

MECHANISM OF ACTION

Amoxicillin kills Gram-positive bacteria by blocking the crucial transpeptidations that leads to mechanically strong peptidoglycan through the covalent cross-links of peptide strands in the cell wall. Loss of this peptidoglycan linkage leads to leakage of cytoplasmic content resulting in death of the bacteria.

MECHANISM(S) OR RESISTANCE

Currently there are no known clinically significant penicillin-resistance mechanisms recognized in *S. pyogenes*.

PHARMACOKINETICS/ PHARMACODYNAMICS

The Sponsor in a previous submission provided the results of four pharmacokinetic (PK) studies (Protocols 111.09, 111.110, 111.111, and 111.112) conducted in healthy volunteers to characterize the single and multiple dose pharmacokinetics of APC-111 MP tablet, to assess the effect of proton-pump inhibitor and food on the pharmacokinetics of the tablet. As a measure of pharmacodynamics performance, the time that free (non-plasma protein bound) plasma concentrations exceeded the minimum inhibitory concentration (MIC) of target pathogens (T>MIC) was assessed at MIC values of 0.015 and 0.06 µg/mL. The results of these studies are summarized in Table 2.

Table 2. Summary of pharmacokinetic parameters from phase I studies Table (8-2)

Study	Dose	C _{max} µg/mL	T _{max} hours	AUC _{0-t} h.µg/mL	AUC _{0-x} h.µg/mL	t _{1/2} Hour	MIC 0.06 µg/mL		MIC 0.015 µg/m	
							T>MIC (h)	%T>MIC	T>MIC (h)	%T>MIC
111.109										
Fed	775 mg 1 day	6.62±1.05	3.14±1.38	29.4±5.28	29.8±5.35	1.44±0.25	13.3±2.71	55.4±11.3	16.2±2.72	67.5± 1.
Fed	775mg 7 days	6.57±1.00	3.03±1.26	29.3±5.40	NA	NA	13.6±2.66	56.6±11.1	17.0±2.54	70.7±10
Fed	Amox Oral solution 1 day	10.6±1.48	1.75±0.38	33.1±5.78	33.3±5.77	1.63±0.27	11.7±1.32	48.6±5.50	14.8±1.64	61.8±6.8
111.11										

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Fed	775 mg 1 day	6.38±1.63	2.59±1.40	28.8±4.58	28.1±4.10	1.88±1.11	15.9±4.09	66.2±17.0	18.4±3.15	76.5±13
Fed with prevacid (proton pump)	775 mg 1 day	8.60±2.64	2.84±1.74	33.0±4.67	32.6±4.29	2.15±1.19	14.9±4.40	61.9±16.8	17.9±3.17	74.6±13
111.111 Fasting	775 mg 1 day	9.93±1.86	1.57±0.64	31.3±6.53	31.4±6.56	1.49±0.28	11.1±1.57	46.3±6.50	14.0±1.93	58.4±8.1
Low calorie meal	775 mg 1 day	8.38±2.20	2.70±1.34	31.7±7.39	31.7±6.69	1.53±0.46	12.4±2.79	51.9±11.6	15.4±2.80	64.2±11
High fat meal	775 mg 1 day	7.41±1.94	2.35±0.86	31.6±6.69	31.7±6.69	1.69±0.46	14.9±3.66	62.3±15.3	18.1±3.65	75.4±15
111.112 Fasting	775 mg 1 day fast release	8.25±2.68	1.80±1.00	27.3±6.42	27.4±6.42	1.39±0.21	11.0±1.42	45.8±5.90	13.8±1.74	57.77.2
Fasting	775 mg 1 day pulsatile	6.85±2.14	1.94±1.04	24.9±6.53	25.1±6.53	1.39±0.17	11.0±1.42	45.7±5.30	13.8±1.74	57.1±5.3
Fasting	775 mg 1 day sprinkle	7.21±1.72	1.88±0.8	26.6±5.88	26.9±6.00	1.45±0.40	11.6±2.13	48.2±8.90	14.6±2.93	60.9±12
Fasting	775 mg 1 day slow release sprinkle	6.47±1.76	2.58±1.06	25.4±5.86	25.7±5.94	1.40±0.25	11.8±2.91	49.4±12.1	14.6±2.91	60.9±12

The Applicant has based their choice of amoxicillin concentration (775 mg) in the tablet on the pharmacodynamic principle that the efficacy of β -lactam antibiotics, such as amoxicillin, correlates directly with the time plasma concentrations exceed the MIC of a target organism ($T > MIC$). Experiments in animals and humans have demonstrated that amoxicillin $T > MIC$ values greater than or equal to 40% predict success in the treatment of most bacterial pathogens including *S. pyogenes*.

The Applicant in a previous submission stated that it was the length of treatment (7 days) in the initial Phase 3 clinical trial that was responsible for the 775 mg amoxicillin pulsatile dose achieving a bacteriological eradication rate of 76.6% whereas the comparator drug (penicillin VK) given for 10 days achieved a bacteriological eradication

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rate of 88.5%. The Sponsor notes that there were no differences in the baseline population (demographics, disease characteristics) or MICs between treatment groups in their clinical study that they feel could explain the observed difference in the bacteriological eradication results. Therefore in their clinical trial to provide efficacy and safety information for this NDA a 775 mg amoxicillin with food for 10 days regimen was used.

The data in Table 2 suggest that a concentration of 775 mg of amoxicillin in the tablet formulation proposed by the Sponsor would achieve a concentration of amoxicillin in the blood for >40% of the dosing interval that would exceed the minimal inhibitory concentration required to inhibit the growth of the target pathogen *S. pyogenes* (MIC 0.015 to 0.06 µg/mL). However, it needs to be pointed out that the ≥40% of the dosing interval above the MIC was based on work done with *S. pneumoniae* (penicillin-susceptible, penicillin-intermediate, penicillin-resistant) in murine-thigh and lung-infection models not with a *S. pyogenes* pharyngitis infection in animal models. The correlation of the animal model *S. pneumoniae* findings showed clinical outcome success rates of 85 – 100% in cases of *S. pneumoniae* lower respiratory tract infections and otitis media. These studies did not look at clinical success rates for pharyngitis caused by *S. pyogenes*.

SUSCEPTIBILITY TEST METHODS FOR *STREPTOCOCCUS PYOGENES*

To determine the susceptibility of *S. pyogenes* to amoxicillin in vitro susceptibility test results for ampicillin can be used with susceptibility to ampicillin equating to susceptibility to amoxicillin. Ampicillin susceptibility criteria for *S. pyogenes* and the quality control parameters for this testing have been previously established. The studies done by the Applicant to determine the efficacy of their product to treat pharyngitis caused by *S. pyogenes* was not meant to establish amoxicillin susceptibility test interpretive criteria or quality control parameters. The Applicant used the interpretive criteria and quality control parameters noted in Tables 3 and 4 for their studies.

Routine susceptibility testing of *S. pyogenes* to determine their susceptibility to beta-lactams is not recommended because of the exquisite susceptibility of these organisms to date to bet-lactams. When susceptibility testing is done the methods for susceptibility testing of *S. pyogenes* as described in Clinical and Laboratory Standards Institute documents M7-A7, M2-A9 are recommended. When susceptibility testing is done the following interpretive criteria are used to determine the isolates susceptibility to ampicillin. No resistance criteria have been established because no *S. pyogenes* with elevated MICs have been identified.

Table 3. Ampicillin Interpretive Criteria for *Streptococcus pyogenes*

	<u>Minimal Inhibitory Concentration (µg/mL)</u>	<u>Disk Diffusion (zone diameters in mm)-10µg disk</u>
Susceptible	≤0.25	≥24

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Quality control parameters for susceptibility testing of *S. pyogenes* have been previously established and are indicated in the Table 2.

Table 4. Ampicillin Susceptibility Test Quality Control Parameters

<u>QC Strain</u>	<u>Minimum Inhibitory Range</u> <u>($\mu\text{g/mL}$)</u>	<u>Disk Diffusion Range</u> <u>(Zone diameter in mm)</u>
<i>Streptococcus pneumoniae</i> ATCC 49619	0.06 - 0.25	30 - 36

CLINICAL STUDY RESULTS

The data provided by the Applicant for the 10 day course once daily of APC-111 therapy shows that adequate clinical cures and bacteriological eradications were achieved in the mITT and PPb populations (see table 1.5.1.5.8 and 1.5.1.5.10 below).

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Advancis Pharmaceutical Corporation

APC-111 MF Tablet, 775 mg
 New Drug Application 50-813

Table 1.4.1.5.4. Study Protocol 111.502: Frequency Table for Sponsor's Bacteriological and Clinical Response by Baseline Amoxicillin MIC

Baseline Pathogen	Baseline Amoxicillin MIC (µg/ml)	PPfs Population ¹				TOC Visit ²						
		Eradication		Non-Eradication ³		Eradication (%)		Clinical Response at TOC Visit ⁴				
		Eradication (N)	Bacteriological Response at TOC Visit	Non-Eradication (N)		Cure (N)	Failure (N)	Cure (%)				
<i>S. pyogenes</i>	> 8											
	8											
	7											
	6											
	5											
	0.5											
	0.12	3	0	0	100	3	0	100				
	0.06	2	0	0	100	2	0	100				
	0.03	10	1	1	90	10	1	91				
	0.015	177	33	33	84	102	16	92				
0.008	3	1	1	75	3	1	75					
≤ 0.004	1	0	0	100	1	0	100					
TOTAL		198	35	35	85	213	18	92				

Reference: Appendix D; Table 14.2.172.1.1 and Appendix E; Additional Table 1

¹ PPfs: eligible per-protocol bacteriological population

² TOC: Test-of-cure visit

³ Excludes all indeterminate (N = 2) and missing values (N=0)

⁴ Non-Eradication includes: Persistence and Presumed Persistence

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Advancis Pharmaceutical Corporation

APC-111 MP Tablet, 775 mg
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Table 1.5.1.5.9. Study Protocol 111.302: Frequency Table for Sponsor's Bacteriological and Clinical Response by Baseline Amoxicillin MIC

Baseline Pathogen	Baseline Amoxicillin MIC (µg/mL)	Bacteriological Response at TOC Visit ¹		Clinical Response at TOC Visit ²		Cure (%)
		Eradication (N)	Non-Eradication ³ (N)	Cure (N)	Failure (N)	
<i>S. pyogenes</i>	> 8					
	8					
	4					
	2					
	1					
	0.50	1	1	1	1	50
	0.25	2	0	2	0	100
	0.12	2	0	2	0	100
	0.06	2	0	2	0	100
	0.03	9	2	9	2	82
0.015	154	43	165	35	82	
0.008	3	1	3	1	75	
≤ 0.004	1	0	1	0	100	
TOTAL		172	47	181	39	82

Reference: Appendix D, Table 14.2.3.1.1 and Appendix I, Additional Table 3

¹PPb: eligible per protocol bacteriological population

²LPT: Late post-therapy visit

³Excludes all indeterminate (N = 8) and missing values (N = 5)

⁴Non-Eradication includes: Persistence, Presumed Persistence, Carrier or Re-colonization, Recurrence, Presumed Recurrence, and Reinfection

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The Applicant in section m5/clinstat/other/tr06-037/tech-report-tr06-037 provided information on the amoxicillin and penicillin G MICs for the treatment failures seen in study 111.302. This data showed that even though there were clinical and bacteriological failures the MICs for the *S. pyogenes* isolated were well within the category of susceptible to both of these antimicrobials. Thus it does not appear that the MIC value for the *S. pyogenes* is a good predictor of clinical or bacteriological success.

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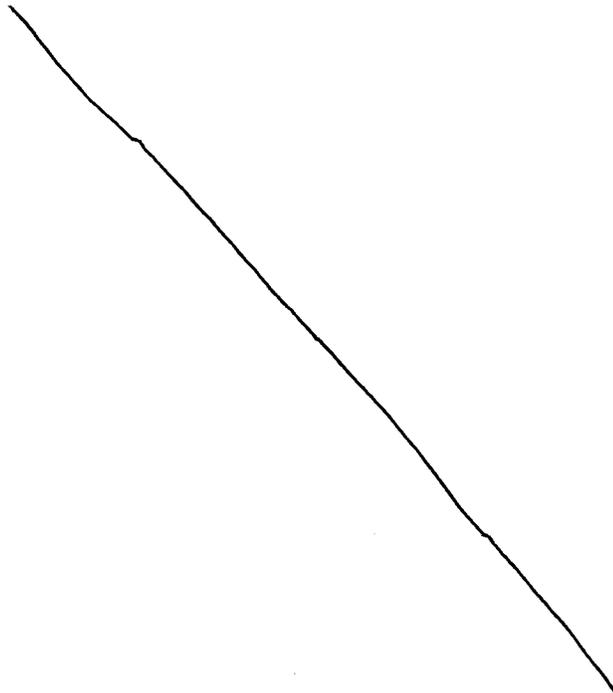
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CONCLUSION

From a "Clinical Microbiology" perspective the clinical microbiology information provided by the Applicant shows that the drug product, amoxicillin pulsatile was efficacious in eradicating *S. pyogenes* associated with pharyngitis/tonsillitis and that there was also a high degree of clinical success with a 10 day course of treatment with the drug. The reader is referred to the statistical analysis reviews and medical officer reviews for additional information on the efficacious of amoxicillin pulsatile for the treatment of pharyngitis/tonsillitis caused by *S. pyogenes*.

The Applicant has provided in vitro susceptibility information from the literature on the susceptibility of better than 100 isolates of Group B and G streptococci to penicillin. Based on this information the inclusion of these two organisms in the PI is appropriate. While the Applicant provided in vitro susceptibility information on less than 100 isolates of Group C streptococcus from the literature it is appropriate to include this organism in the PI because its susceptibility to penicillin is similar to Group A and G streptococci and there have no major reports of penicillin failing to treat pharyngitis due to Group C streptococcus.

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3 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

INTRODUCTION

The Sponsor in previous submissions had provided information on a new formulation of the antimicrobial amoxicillin. This formulation allows for the release of amoxicillin from a tablet over a period of time. The tablet is designed to sequentially deliver an immediate release and two delayed release pulses of amoxicillin in the first six hours of the dosing interval. The Sponsor feels that this formulation provides a lower dose, once a day alternative to current approved penicillin and amoxicillin regimens for the treatment of pharyngitis — to *Streptococcus pyogenes*. The Sponsor also feels that a once-a-day product with a lower daily dose and shorter duration of therapy than conventional amoxicillin and penicillin therapies will increase convenience and likely improve compliance.

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Streptococcus pyogenes is the primary bacterial cause of pharyngitis. The peak incidence of pharyngitis caused by *S. pyogenes* occurs between 5 to 15 years of age (1). While streptococcal pharyngitis is a self limiting disease it is critical to treat the disease early to prevent the occurrence of acute rheumatic fever, glomerulonephritis, suppurative complications, and reduce the transmission of the organisms to close contacts. Penicillin has long been and remains the drug of choice for the treatment of streptococcal pharyngitis due to its efficacy, safety, narrow spectrum of activity, and low cost (2). Amoxicillin is an accepted alternative to penicillin for eradication of *S. pyogenes* also because of its safety, efficacy, and narrow spectrum of activity (2,3). Despite the development of antimicrobial resistance among bacterial pathogens, *S. pyogenes* (e.g. erythromycin resistance) remains uniformly susceptible to the penicillin class of antimicrobials even when it is resistant to erythromycin (4). In fact, routine in vitro susceptibility testing of isolates of *S. pyogenes* is not recommended (5).

IN VITRO

SPECTRUM OF ACTIVITY

As shown in Table 1 the amoxicillin MIC₉₀ is similar to the penicillin MIC₉₀ for *S. pyogenes* even when the *S. pyogenes* is resistant to erythromycin. To date there have been no reported instances of *S. pyogenes* being resistant to the penicillin class of antimicrobials. All susceptibility testing of the isolates in Table 1 were done by National Committee for Clinical Laboratory Standards [now Clinical and Laboratory Standards Institute (CLSI)] methods (5).

Table 1. In vitro susceptibility of *Streptococcus pyogenes* to penicillin and amoxicillin

Antimicrobial	Number of isolates	Mode	MIC ug/mL		Range	% susceptib
			MIC ₅₀	MIC ₉₀		
Penicillin (reference 6)	3918	≤ 0.06	≤0.06	≤0.06	≤0.06 - 0.12	100
Amoxicillin/clavulanate	3918	≤0.012	<0.012	<0.012	≤0.012 - 0.5	

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Amoxicillin (reference 7)	40	≤ 0.015	≤ 0.015	100*	
Amoxicillin/clavulanate	40	≤ 0.015	≤ 0.015	100*	
Penicillin (reference 8)	210	0.06	0.06	0.015 - 0.125	100
Amoxicillin	210	0.03	0.06	0.015 - 0.125	100*
Amoxicillin/clavulanate	210	0.03	0.06	0.015 - 0.125	100*
Penicillin (reference 9)	34 erythromycin-resistant	0.008	0.008		
Penicillin (reference 4)	Erythromycin-susceptible = 3700 Erythromycin-resistant = 214		≤ 0.06 ≤ 0.06		

*Predicted on the basis of penicillin susceptibility

MECHANISM OF ACTION

Amoxicillin kills Gram-positive bacteria by blocking the crucial transpeptidations that leads to mechanically strong peptidoglycan through the covalent cross-links of peptide strands in the cell wall. Loss of this peptidoglycan linkage leads to leakage of cytoplasmic content resulting in death of the bacteria.

MECHANISM(S) OR RESISTANCE

Currently there are no known clinically significant penicillin-resistance mechanisms recognized in *S. pyogenes*.

POST ANTIBIOTIC EFFECT

Beta-lactams such as amoxicillin do not have prolonged post-antibiotic effects because the pharmacodynamic of this class of antimicrobials that relates to efficacy of the drug class against organisms is $T > MIC$.

PHARMACODYNAMICS/PHARMACOKINETICS

The Sponsor in a previous submission provided the results of four pharmacokinetic (PK) studies (Protocols 111.09, 111.110, 111.111, and 111.112) conducted in healthy volunteers to characterize the single and multiple dose pharmacokinetics of APC-111 MP tablet, to assess the effect of proton-pump inhibitor and food on the pharmacokinetics of the tablet. As a measure of pharmacodynamics performance, the time that free (non-plasma protein bound) plasma concentrations exceeded the minimum inhibitory concentration (MIC) of target pathogens ($T > MIC$) was assessed at MIC values of 0.015 and 0.06 $\mu\text{g/mL}$. The results of these studies are summarized in Table 2.

Table 2. Summary of pharmacokinetic parameters from phase I studies Table (8-2)

C_{max}	T_{max}	AUC_{0-1}	AUC_{0-x}	$t_{1/2}$	MIC 0.06 $\mu\text{g/mL}$	MIC 0.015 $\mu\text{g/mL}$
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<u>Study</u>	<u>Dose</u>	<u>µg/mL</u>	<u>hours</u>	<u>h.µg/mL</u>	<u>h.µg/mL</u>	<u>Hour</u>	<u>T>MIC (h)</u>	<u>%T>MIC</u>	<u>T>MIC (h)</u>	<u>%T>MIC</u>
111.109										
Fed	775 mg 1 day	6.62±1.05	3.14±1.38	29.4±5.28	29.8±5.35	1.44±0.25	13.3±2.71	55.4±11.3	16.2±2.72	67.5± 1.
Fed	775mg 7 days	6.57±1.00	3.03±1.26	29.3±5.40	NA	NA	13.6±2.66	56.6±11.1	17.0±2.54	70.7±10
Fed	Amox Oral solution 1 day	10.6±1.48	1.75±0.38	33.1±5.78	33.3±5.77	1.63±0.27	11.7±1.32	48.6±5.50	14.8±1.64	61.8±6.8
111.11										
Fed	775 mg 1 day	6.38±1.63	2.59±1.40	28.8±4.58	28.1±4.10	1.88±1.11	15.9±4.09	66.2±17.0	18.4±3.15	76.5±13
Fed with prevacid (proton pump)	775 mg 1 day	8.60±2.64	2.84±1.74	33.0±4.67	32.6±4.29	2.15±1.19	14.9±4.40	61.9±16.8	17.9±3.17	74.6±13
111.111										
Fasting	775 mg 1 day	9.93±1.86	1.57±0.64	31.3±6.53	31.4±6.56	1.49±0.28	11.1±1.57	46.3±6.50	14.0±1.93	58.4±8.1
Low calorie meal	775 mg 1 day	8.38±2.20	2.70±1.34	31.7±7.39	31.7±6.69	1.53±0.46	12.4±2.79	51.9±11.6	15.4±2.80	
High fat meal	775 mg 1 day	7.41±1.94	2.35±0.86	31.6±6.69	31.7±6.69	1.69±0.46	14.9±3.66	62.3±15.3	18.1±3.65	75.4±15
111.112										
Fasting	775 mg 1 day fast release	8.25±2.68	1.80±1.00	27.3±6.42	27.4±6.42	1.39±0.21	11.0±1.42	45.8±5.90	13.8±1.74	57.77.2
Fasting	775 mg 1 day pulsatile	6.85±2.14	1.94±1.04	24.9±6.53	25.1±6.53	1.39±0.17	11.0±1.42	45.7±5.30	13.8±1.74	57.1±5.3
Fasting	775 mg 1 day sprinkle	7.21±1.72	1.88±0.8.	26.6±5.88	26.9±6.00	1.45±0.40	11.6±2.13	48.2±8.90	14.6±2.93	60.9±12
Fasting	775 mg 1 day slow release sprinkle	6.47±1.76	2.58±1.06	25.4±5.86	25.7±5.94	1.40±0.25	11.8±2.91	49.4±12.1	14.6±2.91	60.9±12

The Applicant has based their choice of amoxicillin concentration in the tablet on the pharmacodynamic principle that the efficacy of β-lactam antibiotics, such as amoxicillin,

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correlates directly with the time plasma concentrations exceed the MIC of a target organism ($T > MIC$). Experiments in animals and humans have demonstrated that amoxicillin $T > MIC$ values greater than or equal to 40% predict success in the treatment of most bacterial pathogens including *S. pyogenes* (10).

The Applicant in a previous submission stated that it was the length of treatment (7 days) in the initial Phase 3 clinical trial that was responsible for the 775 mg amoxicillin pulsatile dose achieving a bacteriological eradication rate of 76.6% whereas the comparator drug (penicillin VK) given for 10 days achieved a bacteriological eradication rate of 88.5%. The Sponsor notes that there were no differences in the baseline population (demographics, disease characteristics) or MICs between treatment groups in their clinical study that they feel could explain the observed difference in the bacteriological eradication results. Therefore in their clinical trial to provide efficacy and safety information for this NDA a 775 mg amoxicillin with food for 10 days regimen was used.

The data in Table 2 suggest that a concentration of 775 mg of amoxicillin in the tablet formulation proposed by the Sponsor would achieve a concentration of amoxicillin in the blood for $>40\%$ of the dosing interval that would exceed the minimal inhibitory concentration required to inhibit the growth of the target pathogen *S. pyogenes* (MIC 0.015 to 0.06 $\mu\text{g/mL}$). However, it needs to be pointed out that the $\geq 40\%$ of the dosing interval above the MIC was based on work done with *S. pneumoniae* (penicillin-susceptible, penicillin-intermediate, penicillin-resistant) in murine-thigh and lung-infection models not with a *S. pyogenes* pharyngitis infection in animal models. The correlation of the animal model *S. pneumoniae* findings showed clinical outcome success rates of 85 – 100% in cases of *S. pneumoniae* lower respiratory tract infections and otitis media. These studies did not look at clinical success rates for pharyngitis caused by *S. pyogenes*.

SUSCEPTIBILITY TEST METHODS FOR *STREPTOCOCCUS PYOGENES*

NOTE: This Application does not require the establishment of new in vitro MIC or disk diffusion interpretive criteria for either penicillin or amoxicillin. Currently recognized interpretive criteria are acceptable. The same is true for in vitro susceptibility test quality control parameters.

To determine the susceptibility of *S. pyogenes* to amoxicillin in vitro susceptibility test results for ampicillin can be used with susceptibility to ampicillin equating to susceptibility to amoxicillin. Ampicillin susceptibility criteria for *S. pyogenes* and the quality control parameters for this testing have been previously established. The studies done by the Applicant to determine the efficacy of their product to treat pharyngitis caused by *S. pyogenes* was not meant to establish amoxicillin susceptibility test interpretive criteria or quality control parameters. The Applicant used the interpretive criteria and quality control parameters noted in Tables 3 and 4 for their studies.

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Routine susceptibility testing of *S. pyogenes* to determine their susceptibility to beta-lactams is not recommended because of the exquisite susceptibility of these organisms to date to bet-lactams. When susceptibility testing is done the methods for susceptibility testing of *S. pyogenes* as described in Clinical and Laboratory Standards Institute documents M7-A7 (11), M2-A9 (12) are recommended. When susceptibility testing is done the following interpretive criteria are used to determine the isolates susceptibility to ampicillin. No resistance criteria have been established because no *S. pyogenes* with elevated MICs have been identified.

Table 3. Ampicillin Interpretive Criteria for *Streptococcus pyogenes*

	<u>Minimal Inhibitory Concentration (µg/mL)</u>	<u>Disk Diffusion (zone diameters in mm)-10µg disk</u>
Susceptible	≤0.25	≥24

Quality control parameters for susceptibility testing of *S. pyogenes* have been previously established and are indicated in the Table 4.

Table 4. Ampicillin Susceptibility Test Quality Control Parameters

<u>QC Strain</u>	<u>Minimum Inhibitory Range (µg/mL)</u>	<u>Disk Diffusion Range (Zone diameter in mm)</u>
<i>Streptococcus pneumoniae</i> ATCC 49619	0.06 - 0.25	30 - 36

CLINICAL STUDY

Following is the Applicant's "Integrated Clinical and Statistical Report".

X Page(s) Withheld

 X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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CLINICAL STUDY MICROBIOLOGY DATA

Primary Efficacy

The primary efficacy variable in Protocol 111.302 was the satisfactory bacteriological outcome rate at the TOC (test of cure) visit. This was performed via throat cultures taken 14-18 days after treatment began in accordance with the FDA draft guidance document for the development of antimicrobial drug products for the treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes*. The primary efficacy analysis of the clinical study report was originally to be conducted in the PPb population only. The statistical analysis plan of the clinical study report was amended based on FDA feedback to include both the PPb and mITT populations as co-primary efficacy populations. The Statistical Analysis plan was further amended in line with FDA recommendations such that the analyses were to be presented unadjusted for region. The PPb population consisted of all subjects with a positive baseline visit throat swab for *S. pyogenes*, an evaluable throat swab at the TOC visit and no major protocol violations, as well as clinical failures who withdrew early from the study and started a new antimicrobial for the treatment of tonsillitis and/or pharyngitis. The mITT (b) population consisted of all subjects with a positive baseline visit throat swab for *S. pyogenes*, who received at least one dose of study medication and who had one post-baseline clinical safety assessment. The mITT (b) population included subjects with an indeterminate bacteriological response as an unsatisfactory outcome.

The primary analysis consisted of the testing of non-inferiority of the APC-111 treatment compared with penicillin VK treatment based on the percentage of subjects in each treatment group with a satisfactory bacteriological outcome at the TOC visit. The treatment group differences were compared by calculating the asymptomatic point estimate and two-sided 95% confidence interval (95% CI) for the difference in satisfactory bacteriological outcome rates. If and only if, the lower confidence bound was greater than -10% was the APC-111 treatment considered non-inferior to the penicillin VK treatment.

Secondary Efficacy

Key secondary efficacy variables included the satisfactory bacteriological outcome rate at the Late-Post Therapy (LPT) visit (days 38-45 after randomization) and successful clinical outcome rates at the TOC and LPT visits. Secondary efficacy variables were tested for non-inferiority between the two treatment groups with the same unadjusted analysis model as used for the primary efficacy analysis.

A satisfactory bacteriological outcome at TOC was defined as eradication (a positive throat culture for *S. pyogenes* at baseline and confirmed by a negative throat culture at the TOC visit [primary efficacy variable]) or presumed eradication (a positive throat culture for *S. pyogenes* at baseline, no available throat culture at the TOC visit, but assessed as a clinical cure at TOC visit). At LPT, an assignment of satisfactory bacteriological outcome required bacteriological responses of eradication or presumed eradication at both the TOC and LPT visits (secondary efficacy variables at the LPY visit). Subjects with a presumed eradication were excluded from the PPb population.

A successful outcome at the Toc and LPT visits was defined as the absence of the signs and symptoms of tonsillitis and/or pharyngitis at the visit. Subjects missing clinical evaluations of the signs and symptoms of tonsillitis and/or pharyngitis were included as an outcome of non-success.

Primary efficacy analysis: Satisfactory Bacteriological Outcome at the TOC Visit

The results of the primary efficacy analysis are shown in Table 2.5.4.1. The results in this table show APC-111 775 mg QD for 10 days was non-inferior to penicillin VK 250 mg QID for 10 days with respect to the bacteriological outcome at TOC in subjects considered eligible for the PPb and mITT(b) co-primary populations.

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Table 2.5.4-1 Bacteriological Outcome at the TOC Visit – PPb and mITT [b] Co-Primary Populations

Bacteriological outcome/ Bacteriological response	Number of subjects (%)			
	PPb ^a		mITT [b] ^b	
	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 consisted of all subjects with a positive baseline visit throat swab for *S. pyogenes*, an evaluable throat swab at the TOC visit, and no major protocol violations, as well as clinical failures who withdrew early from the study and started a new antimicrobial for the treatment of tonsillitis and/or pharyngitis.

^b The mITT population consisted of all subjects with a positive baseline visit throat swab for *S. pyogenes*, who received at least one dose of study medication and who had at least one post-baseline clinical safety assessment. The mITT [b] principal analysis included subjects with an indeterminate bacteriological response.

^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.

Source: Protocol 111.302, Table 14.2.1-1.1.

Secondary Efficacy Analyses: Bacteriological and Clinical Outcomes at the TOC and LPT Visits

The results of the analyses of secondary efficacy variables (bacteriological and clinical outcome at the TOC and LPT visits in relevant analysis populations) supported the primary efficacy findings, namely the non-inferiority of APC-111 mg QD for 10 days compared with penicillin VK 250 mg QID for 10 days. The secondary efficacy analyses were designed to test the sensitivity of the primary analysis and were also measures of the persistence of the effect of treatment at the LPT visit. Treatment with APC-111 was non-inferior (95% CI lower confidence bound greater than -10%) to penicillin VK in all secondary efficacy variables corroborating the findings of the primary efficacy analysis.

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Table 2.5.4-2 Secondary Efficacy Analyses Results

Outcome variable (visit)	Treatment Comparison (Point Estimate and 95% CI) ^a				
	ITT/Safet y ^b	mITT [a] ^c	mITT [b] ^c	PPc ^d	PPb ^e
Bacteriological (TOC)	-	2.9 -3.5, 9.4	-	-	-
Bacteriological (LPT)	-	1.9 -5.9, 9.7	2.1 -5.8, 10.1	-	1.6 -6.4, 9.6
Clinical (TOC)	1.5 -3.9, 6.8	-	1.9 -3.8, 7.6	-1.8 -6.1, 2.6	-1.2 -6.1, 3.8
Clinical (LPT)	0.3 -6.5, 7.2	-	-	-2.8 -9.5, 3.8	-

- = Not applicable; Endpoints not part of secondary efficacy analyses.

^a Comparison between treatment groups: asymptotic point estimate and two-sided 95% confidence interval for the treatment group difference in satisfactory bacteriological outcome rates or successful clinical outcome rates.

^b The ITT/Safety population consisted of all subjects who received at least one dose of study medication and had post-baseline clinical safety assessment data.

^c The mITT population consisted of all subjects with a positive baseline visit throat swab for *S. pyogenes*, who received at least one dose of study medication and who had at least one post-baseline clinical safety assessment. The mITT [a] population excluded subjects with an indeterminate bacteriological response. The mITT [a] analysis at LPT excluded subjects with an indeterminate bacteriological response at TOC, regardless of outcome at LPT, and also excluded subjects with an indeterminate response at LPT. The mITT [b] analysis included subjects with an indeterminate bacteriological response as an unsatisfactory outcome.

^d The PPc population consisted of all subjects with either a positive rapid Strep A Test at baseline or a positive baseline visit throat swab for *S. pyogenes*, and no major protocol violations, as well as clinical failures who withdrew early from the study and started a new antimicrobial for the treatment of tonsillitis and/or pharyngitis or died due to tonsillitis and/or pharyngitis.

^e The PPb population consisted of all subjects with a positive baseline visit throat swab for *S. pyogenes*, an evaluable throat swab at the TOC visit, and no major protocol violations, as well as clinical failures who withdrew early from the study and started a new antimicrobial for the treatment of tonsillitis and/or pharyngitis.

Source: Protocol 111.302, Table 14.2.1.1.1, Table 14.2.1.2, Table 14.2.1.5, and Table 14.2.1.6.

PHASE III CLINICAL STUDIES

Following is a description of how patients were categorized in the Phase III studies.

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1.5 Phase III Clinical Studies

Phase I data demonstrated that once-daily dosing achieved plasma concentrations that exceeded the target $T > MIC$ of 40 % for *S. pyogenes*. Based on the Phase I data, a 775 mg dosage regimen was selected for Phase III testing. The Phase III clinical evaluation of APC-111 MP Tablet 775 mg has been well-described by the Sponsor in the Clinical Study Reports. An overview of the Phase III clinical studies is presented in Table 1.5.1.

Efficacy Assessments

Efficacy assessments in Protocol 111.302 and 111.301 included bacteriological and clinical response determinations at the TOC and LPT visits.

In addition, subject activity levels were assessed at the during-therapy and TOC visits, baseline MIC levels were determined, and for those subjects with a positive culture at baseline, a negative culture 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*, concordance/discordance of the baseline and the LPT isolates were determined by pulse field gel electrophoresis (PFGE).

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.

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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 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*.

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.

Bacteriological Response at the TOC Visit

Based on the bacteriologic responses at the TOC visit, subjects were assigned to one of three bacteriological responses of satisfactory, unsatisfactory, or indeterminate as follows:

The bacteriological response at TOC was categorized as defined below based on the results of the culture at TOC. The acceptable time window for the repeat culture to be conducted at TOC Visit was Day 14 to Day 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.

*Subjects with a bacteriological response of Indeterminate were excluded from the PPb and the mITT [a] analyses, except in the case where subjects were evaluated as treatment failures and started a new anti-microbial therapy for the indication under investigation prior to the TOC Visit and did not have follow-up cultures at TOC. The bacteriological response at TOC for such subjects was categorized as unsatisfactory.

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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 (Day 14-18) 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'.

Bacteriological Response at the LPT Visit

The bacteriological response at LPT was categorized as defined below based on the bacteriological response at TOC and results of the repeat culture at LPT Visit. The

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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 (Day 14-18) 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'.

Bacteriological Response at the LPT Visit

The bacteriological response at LPT was categorized as defined below based on the bacteriological response at TOC and results of the repeat culture at LPT Visit. The

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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 response at the TOC visit of:

- Unsatisfactory:

- 1 Bacteriological response was persistence or presumed persistence (excluded from PPb*) at the TOC visit, or
- 2 The bacteriological response was indeterminate at the TOC visit with persistence at the LPT visit.

- Satisfactory with secondary failure:

- 3 The bacteriological response was eradication or presumed eradication at the TOC visit, but carrier / re-colonization at the LPT visit.
- 4 The bacteriological response was eradication or presumed eradication at the TOC visit, but recurrence at the LPT visit.
- 5 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 response because of:
- Withdrawal of the subject from the study before follow-up cultures can be obtained for reasons other than treatment failure OR
- Incomplete microbiological data OR
- 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 response 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 response at LPT for such subjects was categorized as unsatisfactory.

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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 response at the TOC visit of:

- Unsatisfactory:

- 1 Bacteriological response was persistence or presumed persistence (excluded from PPb*) at the TOC visit, or
- 2 The bacteriological response was indeterminate at the TOC visit with persistence at the LPT visit.

- Satisfactory with secondary failure:

- 3 The bacteriological response was eradication or presumed eradication at the TOC visit, but carrier / re-colonization at the LPT visit.
- 4 The bacteriological response was eradication or presumed eradication at the TOC visit, but recurrence at the LPT visit.
- 5 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 response because of:
- Withdrawal of the subject from the study before follow-up cultures can be obtained for reasons other than treatment failure OR
- Incomplete microbiological data OR
- 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 response 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 response at LPT for such subjects was categorized as unsatisfactory.

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Evaluation of Signs and Symptoms of Tonsillitis and/or Pharyngitis

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

- 1 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.
- 2 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.

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.)

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Clinical Response 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 responses 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 response 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 response of non-success.

Efficacy Analysis Variables

The primary efficacy variable in both Protocol 111.302 and 111.301 was bacteriological response at the TOC visit. Secondary efficacy variables included bacteriological response at the LPT visit and clinical response at the TOC and LPT visits.

Analysis Populations

The following analysis populations were defined for the statistical analyses and data tabulation in both Protocol 111.302 and 111.301 unless otherwise noted. For the purposes of this report, only the mITT [b] and PPb populations were evaluated in the analysis of MIC versus response.

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

Modified intent-to-treat (mITT): All ITT/Safety patients with a positive baseline throat swab culture for *S. pyogenes*. In Protocol 111.302, two mITT groups were further defined, mITT [a] and [b]. The mITT [b] was considered the co-primary population with the PPb population. In Protocol 111.301, three mITT groups for sensitivity analysis, [a], [b], and [c]. The three mITT populations were defined as follows:

mITT [a]: All mITT patients with the exception of patients with a bacteriological response at TOC of indeterminate and a clinical response of unable to evaluate (or indeterminate as per Protocol 111.301).

mITT [b]: All mITT patients, including patients with a bacteriological response at TOC of indeterminate and a clinical response of unable to evaluate (or indeterminate as per Protocol 111.301). A bacteriological response of indeterminate with a clinical response of unable to evaluate (or indeterminate as per Protocol 111.301) was included in the analysis as an unsatisfactory response.

mITT [c] (*Protocol 111.301 only*): All mITT patients, including all APC-111 patients with a bacteriological response at TOC of indeterminate, were included in the analysis as unsatisfactory and 11.5% penicillin VK patients with a bacteriological response at TOC of indeterminate were included in the analysis as unsatisfactory (the percentage was based on the proportion of unsatisfactory responses relative to satisfactory and unsatisfactory responses observed in the penicillin VK treatment group).

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Per-protocol clinical (PPc): All ITT/Safety subjects who completed the study according to protocol and had no major protocol violations were considered eligible for inclusion in the PPc population. Protocol violations were defined as major if they had an effect on the efficacy response (clinical and bacteriological response), or the treatment of the subject. Subjects who were prematurely withdrawn from the study due to 'Insufficient Therapeutic Effect' or due to an adverse event evaluated as 'Related' or 'Possibly Related' to the study medication were considered eligible for inclusion in the PPc population if they are otherwise valid. Premature withdrawal was also considered treatment-related in those subjects for whom the reason at 'End of Study' is not necessarily indicated as 'Adverse Event', but who have an adverse event for which the action taken is 'Permanent Discontinuation'.

Protocol 111.302: Two PPc populations were defined, PPc1 and PPc2. The PPc1 population was determined prior to unblinding with treatment compliance based on both tablet and capsule utilization, irrespective of randomized treatment allocated. After unblinding, compliance was re-assessed based on active study medication allocated and, as appropriate, subject eligibility was revised resulting in the possible inclusion in the PPc2 analysis population (referred to as PPc population in this and other documents, including tables and listings) to be used in the relevant secondary efficacy analyses.

Per-protocol bacteriological (PPb): The primary efficacy population, which consisted of all PPc subjects with a baseline throat swab culture positive for *S. pyogenes* and who had throat swab culture results available at the TOC visit. Efficacy results for clinical failures that withdrew early from the study and started a new antimicrobial for tonsillitis and/or pharyngitis or died due to tonsillitis and/or pharyngitis were included in the PPb analyses.

Protocol 111.302: As described for the PPc population, two PPb populations were defined, PPb1 and PPb2. The PPb1 population was determined prior to unblinding with treatment compliance based on both tablet and capsule utilization, irrespective of randomized treatment allocated. After unblinding, compliance was re-assessed based on active study medication allocated and, as appropriate, subject eligibility was revised resulting in the possible inclusion in the PPb2 analysis population (referred to as PPb population in this and other documents, including tables and listings) to be used in the relevant efficacy analyses. The PPb population corresponds to the PPb2 population and is the population used in primary and secondary efficacy analyses.

The PPb population and the mITT [b] population were considered the co-primary populations in Protocol 111.302. In Protocol 111.301, only the PPb population was considered to the primary population.

Overall Results

The first Phase III trial (Protocol 111.301) failed to demonstrate the non-inferiority of APC-111 775 mg administered QD for 7 days to penicillin VK 250 mg QID for 10 days. The percentage of subjects with a satisfactory bacteriological response at test-of-cure was 76.6% for APC-111 and 88.5% for penicillin VK (95% lower confidence

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bound = -19.7%; upper confidence bound = -4.0). APC-111 provided T > MIC coverage for at least 40% of the 24-hour dosing interval, thereby satisfying this widely accepted pharmacodynamic endpoint. In fact, the observed MIC₉₀ was 0.015 µg/mL, resulting in greater daily T > MIC coverage than predicted.

Therefore, in addition to daily T > MIC, the duration of dosing was considered as a possible critical parameter for the success of β-lactam treatment in tonsillitis and/or pharyngitis secondary to *S. pyogenes*. Analysis of various penicillin VK treatment regimens of different lengths indicated that the duration of treatment is of critical importance to the success of β-lactam treatment in tonsillitis and/or pharyngitis. The bacterial eradication rate (76.6%) for APC-111 dosed once-daily for 7 days observed in the Protocol 111.301 study is consistent with the eradication rate of 72% observed for the 7-day Penicillin VK 500 mg TID treatment course, whereas a 10-day course of treatment with penicillin VK 500 mg TID resulted in reported bacterial eradication rates of 89% and 90%. Therefore, it was hypothesized that APC-111 given once daily for 10 days would have a high likelihood of success in treating tonsillitis and/or pharyngitis secondary to *S. pyogenes* in adolescents and adults.

Study Protocol 111.302 was designed to assess the safety and efficacy of APC-111 QD for 10 days compared to penicillin VK for 10 days. To further maximize the probability that APC-111 will attain a satisfactory therapeutic response, APC-111 was to be administered with food. APC-111 QD for 10 days achieved a bacteriological eradication rate of 85.0% and was non-inferior when compared with the penicillin VK QID for 10 days (83.4%; 95% CI of -5.1, 8.2) at the test-of-cure visit. Results for the co-primary and other statistical populations (described in the Clinical Study Report) were consistent with the findings in the PPb population, confirming the non-inferiority of APC-111 QD for 10 days compared with penicillin VK QID for 10 days.

The successful response of Study Protocol 111.302 (APC-111 QD for 10 days) confirmed the hypothesis conceived after the evaluation of Study Protocol 111.301 (APC-111 QD for 7 days) results, that duration of therapy is important for the treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes*.

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Table 1.5.1. Phase III Studies for APC-111

Clinical Phase	Protocol Number	Study Population	Number of Subjects/Patients	Study Design and Objective	Number of Doses
III	111.301	Adolescent/Adults Male/Female	513	A multi-center, double-blind, double-dummy, randomized, parallel group study to evaluate the safety and efficacy of APC-111 MP tablet 775 mg PO QD for 7 days compared to penicillin VK 250 mg PO QID for 10 days in the treatment of tonsillitis and/or pharyngitis secondary to <i>Streptococcus pyogenes</i> .	775 mg APC-111 – QD for 7 days 250 mg Pen VK – QID for 10 days
III	111.302	Adolescent/Adults Male/Female	618	A multi-center, double-blind, double-dummy, randomized, parallel group 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 <i>Streptococcus pyogenes</i> .	775 mg APC-111 – QD for 10-days 250 mg Pen VK – QID for 10 days

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Antimicrobial Susceptibility Testing

The assessment of MIC versus clinical and bacteriological response was undertaken during the conduct of the Phase III trials.

Specimens from patients enrolled in the study were transported to and processed by b(4)
All specimen
 collection and transport followed → standard operating procedures. Throat swabs were collected and transported to → under ambient conditions. The swabs were cultured onto selective and non-selective media in a semi-quantitative manner, and incubated for 24-48 hours. Gram-positive cocci in pairs or chains were tested with catalase, and catalase-negative isolates were assessed for type of hemolysis. The Streptex kit was then employed to group the beta-hemolytic cultures as A, B, C, D, F, and G. For Group A colonies, a PYR test is conducted and a report of *S. pyogenes* was issued if the test was positive. Cultures with any other group identification are examined by biochemical test methods including ID 32 Strep, Vitek GPI card, and/or Microscan PID Panel (with supplemental biochemicals as needed).

Antimicrobial susceptibility testing of isolates was conducted by → according to their standard operating procedures. Minimal inhibitory Concentration (MIC) values were determined using the broth microdilution method recommended by the National Committee for Clinical and Laboratory Standards (National Committee for Clinical Laboratory Standards, 2003). The National Committee for Clinical and Laboratory Standards (NCCLS) is now known as the Clinical and Laboratory Standards Institute (CLSI). The microdilution trays were prepared in-house, and quality control was performed daily. b(4)

the central laboratory for antimicrobial susceptibility testing, conducted quality control measures for all antimicrobial susceptibility tests on a daily basis. That is, on each day that patient samples were tested, appropriate quality control strains were tested. During the conduct of the study, quality controls of MIC values were never out of range. b(4)

MIC Population Distributions for Phase III Clinical Trial Isolates from Study 111.302

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MIC population distributions for the baseline *S. pyogenes* isolates in the mITT and PPb populations in Study Protocol 111.302 are shown in Tables 1.5.1.4.3 and 1.5.1.4.4. Isolates from both the APC-111 and penicillin treatment groups, and both the mITT and PPb populations were highly susceptible to amoxicillin and penicillin G. The MIC₅₀ and MIC₉₀, and the modal MIC values for both agents were 0.025 µg/mL in both populations. Several isolates in the APC-111 and penicillin treatment groups demonstrated unusually high MIC values (0.12 µg/mL or greater) for amoxicillin and penicillin G, however, confirmatory data were not available. Resistance to macrolides and clindamycin were demonstrated in a small number of isolates. Two isolates from the penicillin treatment group demonstrated MIC values interpreted as penicillin non-susceptible. MIC retest data was not available to confirm these results.

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Table 1.5.1.4.3. Study Protocol 111.302: Population Distribution of *Streptococcus pyogenes* Minimal Inhibitory Concentration (MIC) Values for Baseline Clinical Trial Isolates (mITT Population)

Treatment Group	Agent	No.	No. Isolates Inhibited at MIC (µg/mL)								MIC (µg/mL)					
			≤ 0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	Range	MIC ₅₀	MIC ₉₀			
APC-111	Ampicillin	1	5	229	14	2	2	3						≤ 0.004 - 0.25	0.015	0.015
	Pen G	2	90	154	2	7	1	8	224	17	1	3	2	≤ 0.004 - 0.12	0.015	0.015
	Cephaloslin													0.12 - 8	0.5	0.5
	Erythromycin					138	94	6				10		0.06 - > 8	0.06	0.12
	Asahromycin					41	181	15	1	2	15	2		0.12 - > 8	0.25	0.5
	Clindamycin					194	53	6			2		0.03 - > 8	0.06	0.12	
Penicillin	Ampicillin	1	12	317	10	1	1	1						≤ 0.004 - 1	0.015	0.015
	Pen G	8	80	169	3	2	2	6	16	225	12	3	1	0.12 - > 8	0.5	0.5
	Cephaloslin													0.008 - > 8	0.06	0.25
	Erythromycin					150	84	6	1	1	3	5	4	0.12 - > 8	0.25	0.5
	Asahromycin					193	31	196	12	2	3	14	1	≤ 0.004 - > 8	0.06	0.12

¹ Minimal Inhibitory Concentration for 50 % of the test isolates
² Minimal Inhibitory Concentration for 90 % of the test isolates

Reference: Appendix F, Table 14.2.3/1.2

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Correlation of MIC with Clinical and Bacteriological Response

In this section the clinical and bacteriological response for *S. pyogenes* isolates in Study Protocol 111.302 are correlated with the amoxicillin MIC value. In addition, since MIC testing is commonly conducted with penicillin G rather than amoxicillin, responses relative to the penicillin G MIC value is also shown. All evaluations focus on the mITT and PPb populations and the key pathogen *S. pyogenes*. The source data for the summary tables presented below are in the Appendices of the submission.

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The clinical and bacteriological response versus amoxicillin MIC value for patients treated with APC-111 in the PPb population at TOC is summarized in Table 1.5.1.5.8. A range of MIC values of $\leq 0.004 - 0.25 \mu\text{g/mL}$ was evident, with the majority of isolates having an MIC value of $0.015 \mu\text{g/mL}$. MIC versus bacteriological response data was obtained for 223 subjects and bacterial eradication was achieved in 85 % of subjects. There were bacteriological failures spread across the lower end of the MIC range, but all isolates with MIC values $\geq 0.06 \mu\text{g/mL}$ were eradicated. Therefore, there was no correlation of response with MIC value, and excellent efficacy rates were achieved across the MIC range. A positive clinical response was achieved in 213 of 231 subjects (2 Indeterminate) for a cure rate of 92%.

The clinical and bacteriological response versus amoxicillin MIC value for patients treated with APC-111 in the PPb population at LPT is summarized in Table 1.5.1.5.9. A range of MIC values of $\leq 0.004 - 0.25 \mu\text{g/mL}$ was evident, with the majority of isolates having an MIC value of $0.015 \mu\text{g/mL}$. MIC versus bacteriological response data was obtained for 219 subjects and bacteriological eradication was achieved in 79 % of subjects. There were bacteriological failures spread across the MIC range. Notably, 1 of 2 subjects with an isolate MIC of $0.25 \mu\text{g/mL}$ was not eradicated. With the exception of $0.25 \mu\text{g/mL}$ (though only 2 subjects), excellent efficacy rates were achieved across the MIC range. A positive clinical response was achieved in 181 of 220 subjects (8 Indeterminate and 5 Missing) for a cure rate of 82%.

The clinical and bacteriological response versus amoxicillin MIC value for patients treated with APC-111 in the mITT population at TOC is summarized in Table 1.5.1.5.10. A range of MIC values of $\leq 0.004 - 0.25 \mu\text{g/mL}$ was evident, with the majority of isolates having an MIC value of $0.015 \mu\text{g/mL}$. MIC versus bacteriological response data was obtained for 248 subjects (8 Indeterminate) and bacterial eradication was achieved in 85 % of subjects. There were bacteriological failures spread across the lower end of the MIC range, but all isolates with MIC values $\geq 0.06 \mu\text{g/mL}$ were eradicated. Therefore, there was no correlation of response with MIC value, and excellent efficacy rates were achieved across the MIC range. A positive clinical response was achieved in 226 of 246 subjects (8 Indeterminate and 2 Missing) for a cure rate of 92%.

The clinical and bacteriological response versus amoxicillin MIC value for patients treated with APC-111 in the mITT population at LPT is summarized in Table 1.5.1.5.11. A range of MIC values of $\leq 0.004 - 0.25 \mu\text{g/mL}$ was evident, with the majority of isolates having an MIC value of $0.015 \mu\text{g/mL}$. MIC versus bacteriological response data was obtained for 236 subjects (20 Indeterminate) and bacterial eradication was achieved in 77% of subjects. There were bacteriological failures spread across the MIC range. Notably, 1 of 2 subjects with an isolate MIC of $0.25 \mu\text{g/mL}$ was not eradicated. With the exception of $0.25 \mu\text{g/mL}$ (though only 2 subjects), excellent efficacy rates were achieved across the MIC range. A positive clinical response was achieved in 191 of 234 subjects (14 Indeterminate and 8 Missing) for a cure rate of 82%.

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Since MIC testing is commonly conducted with penicillin G rather than amoxicillin, clinical and bacteriological response relative to the penicillin G MIC value was also tabulated. The bacteriological response versus penicillin MIC value for patients treated with APC-111 in the PPb population at TOC is summarized in Table 1.5.1.5.14. A narrow range of MIC values ($\leq 0.004 - 0.12 \mu\text{g/mL}$) was evident, with most isolates having an MIC value of $0.015 \mu\text{g/mL}$. MIC versus bacteriological response data was obtained for 233 subjects and bacterial eradication was achieved in 85 % of subjects. There were bacteriological failures spread across the lower end of the MIC range, therefore, reduced efficacy was not correlated with penicillin MIC value. On the basis of penicillin MIC value, all of the strains would be considered penicillin-susceptible. A positive clinical response was achieved in 213 of 231 subjects (2 Indeterminate) for a cure rate of 92%.

The clinical and bacteriological response versus penicillin MIC value for patients treated with APC-111 in the mITT population at TOC is summarized in Table 1.5.1.5.15. A narrow range of MIC values ($\leq 0.004 - 0.12 \mu\text{g/mL}$) was evident, with most isolates having an MIC value of $0.015 \mu\text{g/mL}$. MIC versus bacteriological response data was obtained for 248 subjects (8 Indeterminate) and bacterial eradication was achieved in 85% of subjects. There were bacteriological failures spread across the lower end of the MIC range, therefore, reduced efficacy was not correlated with penicillin MIC value. On the basis of penicillin MIC value, all of the strains would be considered penicillin-susceptible. A positive clinical response was achieved in 226 of 246 subjects (8 Indeterminate and 2 Missing) for a cure rate of 92%.

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Table 1.S.1.S.8. Study Protocol 111.302: Frequency Table for Sponsor's Bacteriological and Clinical Response by Baseline Amoxicillin MIC

Baseline Pathogen <i>S. pneumoniae</i>	Baseline Amoxicillin MIC (µg/ml)	PP1b Population ¹				TOC Visit ¹		Treatment: APC-111	
		Eradication (N)	Non-Eradication (N)	Eradication (%)	Cure (N)	Failure (N)	Cure (%)	Cure (%)	
	> 8	3	0	100	3	0	100	100	
	8	2	0	100	2	0	100	100	
	4	2	0	100	2	0	100	100	
	2	2	0	100	2	0	100	100	
	1	10	1	91	10	1	91	92	
	0.25	177	33	84	192	15	75	75	
	0.12	3	1	75	3	1	75	100	
	0.06	1	0	100	1	0	100	100	
	0.03	1	0	100	1	0	100	100	
	0.015	1	0	100	1	0	100	100	
	0.008	1	0	100	1	0	100	100	
	≤ 0.004	1	0	100	1	0	100	100	
TOTAL		198	35	85	213	18	92	92	

Reference: Appendix D, Table 14.2.3C.1.1 and Appendix I, Additional Table 1
¹ PP1b: eligible per-protocol bacteriological population
² TOC: Test-of-cure visit
³ Excludes all indeterminate (N = 2) and missing values (N=0)
⁴ Non-Eradication includes: Persistence and Presumed Persistence

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Table 1.5.1.5.9. Study Protocol 111.302: Frequency Table for Sponsor's Bacteriological and Clinical Response by Baseline Amoxicillin MIC

FPb Population¹
 LPT Visit²

Baseline Pathogen	Baseline Amoxicillin MIC (µg/mL)	Bacteriological Response at TOC Visit ³		Clinical Response at TOC Visit ³		Cure (%)
		Eradication (N)	Non-Eradication ⁴ (N)	Cure (N)	Failure (N)	
<i>S. pyogenes</i>	> 8					
	8					
	4					
	2					
	1					
	0.50	1	1	1	1	50
	0.25	2	0	2	0	100
	0.12	2	0	2	0	100
	0.06	2	0	2	0	100
	0.03	9	2	9	2	82
0.015	154	43	163	55	75	
0.008	3	1	3	1	100	
≤ 0.004	1	0	1	0	100	
TOTAL		172	47	181	39	82

Reference: Appendix D; Table 14.2.303.1.1 and Appendix I; Additional Table 3

¹FPb: eligible per-protocol bacteriological population

²LPT: Late post-therapy visit

³Excludes all indeterminate (N = 8) and missing values (N=5)

⁴Non-Eradication includes: Persistence, Presumed Persistence, Carrier or Re-colonization, Recurrence, Presumed Recurrence, and Reinfection

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Table 1.5.1.5.10. Study Protocol 111.302: Frequency Table for Sponsor's Bacteriological and Clinical Response by Baseline Amoxicillin MIC

Baseline Pathogen	Baseline Amoxicillin MIC (µg/mL)	Bacteriological Response at TOC Visit ¹		Clinical Response at TOC Visit ²		Cure (%)	Failure (N)	Cure (%)
		Eradication ³ (N)	Non-Eradication ⁴ (N)	Eradication ³ (%)	Failure (N)			
<i>S. pyogenes</i>	> 8							
	8							
	4							
	2							
	1							
	0.50	3	0	100	0	3	0	100
	0.25	2	0	100	0	2	0	100
	0.12	2	0	100	0	2	0	100
	0.06	12	1	85	18	12	1	92
	0.03	187	35	82	105	202	18	92
0.015	4	1	80	3	4	1	80	
0.008	1	0	100	0	1	0	100	
≤ 0.004								
TOTAL		211	37	85	226	20	92	

Reference: Appendix D; Table 14.2.3/2.1 and Appendix I; Additional Table 2

¹ mITT: Modified intent-to-treat population

² TOC: Test-of-cure visit

³ Excludes indeterminate (N = 8) and missing (N = 0) values

⁴ Excludes indeterminate (N = 8) and missing (N = 2) values

⁵ Eradication includes Eradication plus Presumed Eradication

⁶ Non-Eradication includes: Persistence and Presumed Persistence

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Table 4.5.1.5.11. Study Protocol 111.502: Frequency Table for Sponsor's Bacteriological and Clinical Response by Baseline Amoxicillin MIC

Baseline Pathogen	Baseline Amoxicillin MIC (µg/mL)	Bacteriological Response at TOC Visit ¹		Clinical Response at TOC Visit ²	
		Eradication ³ (N)	Non-Eradication ⁴ (N)	Cure (N)	Failure (N)
<i>S. Pyogenes</i>	> 8				
	8				
	4				
	2				
	1				
	0.50	1	1	1	1
	0.25	2	0	2	0
	0.12	2	0	2	0
	0.06	9	3	10	2
	0.03	164	48	171	39
0.015	3	2	4	1	
0.008	1	0	1	0	
≤ 0.004	1	0	1	0	
TOTAL		182	54	191	43

Reference: Appendix D, Table 4.2.3A.2.1 and Appendix I, Additional Table 4

¹ mITT, Modified intent-to-treat population

² LPT, Last-visit-therapy visit

³ Excludes indeterminate (N= 20) and missing values (N= 0)

⁴ Excludes indeterminate (N= 14) and missing (N= 8) values

⁵ Eradication includes Eradication plus Presumed Eradication

* Non-eradication includes: Persistence, Presumed Persistence, Carrier or Re-colonization, Recurrence, Presumed Recurrence, and Reinfection

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Table 1.5.1.5.14. Study Protocol 111.302: Frequency Table for Sponsor's Bacteriological and Clinical Response by Baseline Penicillin G MIC
 PPb Population¹
 TOC Visit²

Baseline Pathogen	Baseline Penicillin G MIC (µg/mL)	Bacteriological Response at TOC Visit ³		Clinical Response at TOC Visit ³			
		Eradication (N)	Non-Eradication ⁴ (N)	Eradication (%)	Cure (N)	Failure (N)	Cure (%)
<i>S. pyogenes</i>	>8						
	4						
	2						
	1						
	0.50	1	0	100	1	0	100
	0.12	6	0	100	6	0	100
0.06	2	0	100	2	0	100	
0.03	114	82	25	124	13	91	
0.015	73	10	88	78	5	94	
0.008	2	0	0	100	0	100	
≤0.004							
TOTAL		198	35	85	213	18	92

Reference: Appendix D; Table 14.2.3/2.1.1 and Appendix I; Additional Table 1

¹ PPb: eligible per-protocol bacteriological population

² TOC: Test-of-cure visit

³ Excludes indeterminate (N=2) and missing (N=0) values

⁴ Non-Eradication includes: Persistence and Presumed Persistence

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Table 1.5.1.5.15. Study Protocol 111.302: Frequency Table for Sponsor's Bacteriological and Clinical Response by Baseline Fusidicillin G MIC

Baseline Pathogen	Baseline Fusidicillin G MIC (µg/mL)	mITT Population ¹				TOC Visit ²							
		Eradication		Non-Eradication		Eradication		Non-Eradication					
		(N)	(%)	(N)	(%)	(N)	(%)	(N)	(%)				
<i>S. pyogenes</i>	> 8												
	4												
	2												
	1												
	0.50	1	100	0	0	1	100	0	0	100	0	0	100
	0.12	7	100	0	0	7	100	0	0	100	0	0	100
	0.06	2	100	0	0	2	100	0	0	100	0	0	100
0.03	122	100	27	22	132	90	15	13	90	5	94	100	
0.015	77	100	0	0	82	100	0	0	100	0	0	100	
0.008	2	100	0	0	2	100	0	0	100	0	0	100	
≤ 0.004	2	100	0	0	2	100	0	0	100	0	0	100	
TOTAL		211	85	37	226	92	20						

Reference: Appendix D, Table 14.2.3/2.2.1 and Appendix I, Additional Table 2
 mITT: Modified Intact-to-treat population
 TOC: Test-of-cure visit
 † Excludes indeterminate (N= 8) and missing (N=2) values
 ‡ Excludes indeterminate (N = 8) and missing (N = 2) values
 * Eradication includes Eradication plus Presumed Eradication
 † Non-Eradication includes Persistence and Presumed Persistence

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CONCLUSION

The data provided by the Applicant for the 10 day course once daily of APC-111 therapy shows that adequate clinical cures and bacteriological eradications were achieved in the mITT and PPb populations. The Applicant in section m5/clinstat/other/tr06-037/tech-

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report-tr06-037 provided information on the amoxicillin and penicillin G MICs for the treatment failures seen in study 111.302. This data showed that even though there were clinical and bacteriological failures the MICs for the *S. pyogenes* isolated were well within the category of susceptible to both of these antimicrobials. Thus it does not appear that the MIC value for the *S. pyogenes* is a good predictor of clinical or bacteriological success.

Reinfection versus recurrence

The Applicant during the study attempted to determine in the case of failures whether the failures may be due to reinfection with a different stain of *S. pyogenes* or reoccurrence of infection. They did this by pulse-field gel electrophoresis typing of the *S. pyogenes* that were isolated. The following describes what was done and the results. The amount of data was too small to make any overall conclusions as to whether the failures were due primarily to reinfection or reoccurrence.

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1.5.1.6 Pulsed Field Gel Electrophoresis Analysis of Baseline and LPT Isolates for Study Protocol 111.302

For all subjects who had 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 of the baseline organism has occurred ('Recurrence'), or
- The organism isolated at baseline and the organism isolated at LPT were not identical (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 response at LPT. All such cases were considered to have an unsatisfactory bacteriological response.

The data in Table 1.5.6.1 demonstrates that PFGE results were obtained for 16 subjects enrolled in Study Protocol 111.302 comprised of 6 treated with APC-111 and 10 treated with penicillin. PFGE analysis of *S. pyogenes* isolated from 2 of the APC-111 treated subjects revealed discordance, indicating that these subjects were re-infected with a new strain of *S. pyogenes*. For the 10 penicillin-treated subjects from which a *S. pyogenes* culture was isolated at both baseline and LPT, 1 of the isolates was discordant and 1 was indeterminate. This small sampling indicated that in the majority of cases, the *S. pyogenes* isolated persisted or recurred.

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Table 1.5.1.6.1. Study Protocol 111.302: PRGE; Baseline Isolate Versus LFT Isolate By Subject

Center	Region	Subject number	Treatment group	6. Progress Isolated at T0C (Yes/No)	7. Progress Isolated at T0C (Yes/No)	8. Progress Isolated at LFT (Yes/No)	9. Progress Isolated at LFT (Yes/No)
0284	MI USA	0284/1003	APC-111	Yes	No	Yes	Yes
0285	IL USA	0285/1005	APC-111	Yes	No	Yes	Yes
		0285/1026	Penicillin	Yes	No	Yes	Yes
0288	MI USA	0288/1014	Penicillin	Yes	No	Yes	Yes
0291	MI USA	0291/1002	APC-111	Yes	No	Yes	Yes
0292	Utah	0292/1029	Penicillin	Yes	No	Yes	Yes
0293	Utah	0293/1001	Penicillin	Yes	No	Yes	Yes
0294	IL USA	0294/1009	Penicillin	Yes	No	Yes	Yes
0295	IL USA	0295/1012	Penicillin	Yes	No	Yes	Yes
0298	Utah	0298/1001	APC-111	Yes	No	Yes	Yes
0299	MI USA	0299/1015	Penicillin	Yes	No	Yes	Yes
0299	Canada	0299/1002	APC-111	Yes	No	Yes	Yes
		0299/1003	Penicillin	Yes	No	Yes	Yes
		0299/1010	APC-111	Yes	No	Yes	Yes
0468	MI USA	0468/1007	Penicillin	Yes	No	Yes	Yes
0470	IL USA	0470/1001	Penicillin	Yes	No	Yes	Yes

MI: Midwestern; NE: Northeastern; S: Southern; W: Western.
 PRGE: Pooled Field and Reference Group Evaluation.
 T0C: Test-of-cure (Visit 3 Day 14-18); LFT: Late Post-Therapy (Visit 4 Day 30-45).
 Progress Isolated at T0C: Yes/No. Test-of-cure (Visit 3 Day 14-18); LFT: Late Post-Therapy (Visit 4 Day 30-45).
 Progress Isolated at LFT: Yes/No. Test-of-cure (Visit 3 Day 14-18); LFT: Late Post-Therapy (Visit 4 Day 30-45).
 Subjects presented in table are subjects with a positive culture result at baseline, negative result at T0C, and a bacteriological response of 'eradication', or a bacteriological response of 'eradication' and a positive result again at LFT.

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Package Insert Request

The Applicant is requesting that in the Microbiology Section of the package insert in the "Second List" that Streptococcus Groups C and G beta hemolytic be listed. They are requesting this because both of these organism groups are associated with pharyngitis.

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Large colony forming (>0.5 mm in diameter) group C and G strains are “pyogenic” streptococci, replete with a variety of effective virulence mechanisms. Strains of large-colony-forming beta-hemolytic group C and G streptococci are currently classified in the same subspecies, *Streptococcus dysgalactiae* subsp. *equisimilis*. The small-colony-forming (<0.5 mm in diameter) beta-hemolytic strains with group A, C or G Lancefield antigens are genetically different from the “pyogenic” strains and belong to the *anginosus* or “*Streptococcus milleri*” species group, composed of *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*. Although the small-colony-forming strains may participate in infection (notably abscesses), they are also found as commensals whose pathogenic abilities appear to be much more subtle than those of the pyogenic streptococci.

Both Group C and G are associated with pharyngitis/tonsillitis in adults and children (13 - 21). In vitro susceptibility data for the beta-hemolytic group C and G streptococci show that $\geq 90\%$ of the isolates tested were susceptible to a concentration that is achievable in the blood suggesting that amoxicillin pulsatile would be efficacious in treating pharyngitis/tonsillitis due to these organisms. In vitro susceptibility data for amoxicillin against groups C and G is shown below.

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Table 1.3.3.2. Minimal Inhibitory Concentration (MIC) Data for *Streptococcus* spp.
 (Group C and G; β -hemolytic) From Studies Reported in the Literature

Organism (No. Isolates)	Agent	MIC (µg/mL)			Reference
		Range	MIC ₅₀ ¹	MIC ₉₀ ²	
β -hemolytic streptococci (769) includes: (372) group B (240) group A (108) group G (29) group C (7) group F (7) β -hemolytic (4) <i>S. dysgalactias</i> (1) <i>S. equi</i> (1) <i>S. equisimilis</i>	Penicillin	$\leq 0.016 - 0.12$	≤ 0.016	0.06	Sader et al., 2005
	Erythromycin	$\leq 0.06 - > 8$	≤ 0.06	2	
	Levofloxacin	$\leq 0.05 - \geq 4$	0.5	1	
β -hemolytic streptococci (556) includes: (300) group A (228) group B (6) group C (5) group F (15) group G (2) β -hemolytic	Penicillin	$\leq 0.016 - 0.12$	≤ 0.016	0.06	Jones et al., 2005
	Cefepime	$\leq 0.12 - 0.5$	≤ 0.12	≤ 0.12	
	Erythromycin	$\leq 0.06 - > 32$	≤ 0.06	2	
	Levofloxacin	$\leq 0.03 - > 4$	0.5	1	

¹ Minimal Inhibitory Concentration for 50 % of the test isolates
² Minimal Inhibitory Concentration for 90 % of the test isolates

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CONCLUSION

From a "Clinical Microbiology" perspective the clinical microbiology information provided by the Applicant shows that the drug product, amoxicillin pulsatile was efficacious in eradicating *S. pyogenes* associated with pharyngitis/tonsillitis and that there was also a high degree of clinical success with a 10 day course of treatment with the drug. The reader is referred to the statistical analysis reviews and medical officer reviews for additional information on the efficacy of amoxicillin pulsatile for the treatment of pharyngitis/tonsillitis caused by *S. pyogenes*.

The Applicant has provided in vitro susceptibility information from the literature on the susceptibility of better than 100 isolates of Group B and G streptococci to penicillin. Based on this information the inclusion of these two organisms in the PI is appropriate. While the Applicant provided in vitro susceptibility information on less than 100 isolates of Group C streptococcus from the literature it is appropriate to include this organism in the PI because its susceptibility to penicillin is similar to Group A and G streptococci and there have no major reports of penicillin failing to treat pharyngitis due to Group C streptococcus.

2 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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AGENCY'S PROPOSED SECTION OF THE "MICROBIOLOGY" PORTION OF THE
PACKAGE INSERT

SEE "EXECUTIVE SUMMARY" FOR PROPOSED "MICROBIOLOGY" PORTION
OF THE PACKAGE INSERT

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Fred Marsik, Ph.D.
Clinical Microbiology Reviewer

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/s/

Frederic Marsik
12/19/2007 08:16:19 AM
MICROBIOLOGIST

CLINICAL Microbiology: 45-Day Meeting Checklist
NDA Fileability
NDA 50-813 Amoxicillin Pulsatile
Advancis Pharmaceutical Corporation
Date Completed: 9 May 07

On **initial** overview of the NDA application for RTF:

No.	Item	Yes	No	Comments
1	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA indexed, paginated, and/or linked in a manner to allow substantive review to begin?	X		
3	Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin?	X		
4	On its face, has the applicant <u>submitted</u> <i>in vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains/ isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	X		
5	Has the applicant <u>submitted</u> draft provisional breakpoint and interpretive criteria, along with quality control (QC) parameters, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?			Not Applicable
6	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			Not Applicable
7	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	X		
8	Has the applicant <u>submitted</u> the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcomes exhibited by relevant pathogens isolated from test of cure or end of treatment?	X		
9	Has the applicant <u>submitted</u> a clinical microbiology dataset in a format which intends to determine resistance development by correlating changes in the	X		

CLINICAL Microbiology: 45-Day Meeting Checklist
NDA Fileability
NDA 50-813 Amoxicillin Pulsatile
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	phenotype (such as <i>in vitro</i> susceptibility) and/or genotype (such as mutations) of the baseline relevant pathogen with clinical and microbiologic outcome as exhibited by relevant pathogens isolated from test of cure or end of treatment?			
10	Has the applicant used standardized methods or if non-standardized methods were used has the applicant included full details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	X		
11	Is the clinical microbiology draft labeling consistent with 21 CFR Parts 201, 314, 601 and current Divisional policy.	X		
12	FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? IF NO, GIVE REASONS BELOW.	X		

y Additional Clinical Microbiology Comments:

Name: Fred Marsik, Ph.D.
Team Leader Clinical Microbiology – HFD-520

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:

YES

NO

BIOPHARMACEUTICAL:

- (1) On its face, is the biopharmaceutics section of the NDA organized in a manner to allow substantive review to begin?
- (2) Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?
- (3) On its face, is the biopharmaceutics section of the NDA legible so that substantive review can begin?
- (4) Are the Phase 1 studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?
- (5) If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmaceutics data to allow comparison between the product to be marketed and the product (s) used in the clinical development?
- (6) From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not?

✓

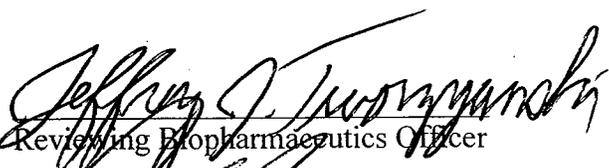
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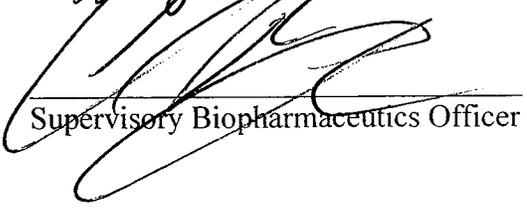
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Reviewing Biopharmaceutics Officer



Supervisory Biopharmaceutics Officer