U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	50-813
Drug Name:	APC-111 MP Tablet, 775 mg (Amoxicillin Pulsatile Formulation)
Indication(s):	Treatment of Tonsillitis and/or Pharyngitis Secondary to *Streptococcus Pyogenes (S. pyogenes)* in Adolescents and Adults
Applicant:	Middlebrook Pharmaceutical
Date(s):	Stamp Date: March 23, 2007 PDUFA due date: January 22, 2008
Review Priority:	Standard
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Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this NDA submission the sponsor, under the provisions specified in the Federal Food, Drug and Cosmetic Act, Section 505(b) (2), seeks approval of a once-a-day, pulsatile-release, multiparticulate tablet formulation of amoxicillin, APC-111 MP Tablet, 775 mg for a 10-day regimen for the treatment of tonsillitis and/or pharyngitis (b) (4) to *Streptococcus pyogenes* (*S. pyogenes*) in adolescents and adults.

This submission included data from two pivotal studies (studies 301 and 302) in patients with acute streptococcal tonsillitis and/or pharyngitis. Both studies were randomized, double blind, double-dummy, multi-center, and non-inferiority trials with penicillin VK 250 mg PO QID for 10 days as the active comparator. The primary efficacy endpoint was the bacteriological outcome at the Test-of-Cure (TOC) visit (day 14-18). A 10% of non-inferiority margin was used.

Study 301 failed to demonstrate the non-inferiority of APC-111 775 mg QD for 7 days compared with penicillin VK 250 mg QID for 10 days in terms of the rate of the satisfactory bacteriological outcome at TOC.

Study 302 demonstrated the non-inferiority of APC-111 775 mg QD for 10 days compared with penicillin VK 250 mg QID for 10 days in terms of the rate of the satisfactory bacteriological outcome at TOC. This study demonstrated that the 10-day APC-111 775 mg QD regimen was effective for the treatment of tonsillitis and/or pharyngitis due to *S. pyogenes* in adolescents and adults.

Based on existing supportive evidence of efficacy of amoxicillin and the efficacy results observed in the current NDA submission, it is recommended that this NDA receive an approval action.

1.2 Brief Overview of Clinical Studies

The two pivotal studies (studies 301 and 302) had similar study designs. Both studies were randomized, double blind, double-dummy, multi-center, and non-inferiority trials with penicillin VK 250 mg PO QID for 10 days as the active comparator. The primary efficacy endpoint was the bacteriological outcome at TOC visit. A non-inferiority margin of 10% was used in the evaluation of non-inferiority of APC-111 775 mg QD (7 days in study 301 and 10 days in study 302) over penicillin VK 250 mg PO QID for 10 days. A claim of non-inferiority of APC-111 over penicillin was made if the lower limit of the 95% confidence interval (CI) for the difference in the satisfactory bacteriological outcome rates at the TOC visit between the APC-111 and penicillin treatments was above -10% in both the mITT[b] and PPb populations.

The major difference in the designs of these two pivotal studies was the duration of the APC-111 treatment: 7 days in study 301 and 10 days in study 302. Study 302 was designed and conducted

after study 301 failed to demonstrate the non-inferiority of APC-111 775 mg QD for 7 days compared with penicillin VK 250 mg QID for 10 days in terms of the rate of satisfactory bacteriological outcome at TOC. The sponsor contributed the failure of study 301 to the shorter treatment duration of APC-111 treatment (7 days) compared with penicillin treatment (10 days).

Study 301: There were 253 and 260 randomized subjects in the APC-111 and penicillin groups, respectively. In the mITT[b] population, the percentages of subjects with a satisfactory bacteriological outcome at the TOC visit were 71.9% and 83.7% for the APC-111 and penicillin groups, respectively. The difference between the APC-111 and penicillin groups was -11.9% with a 95% CI of (-20%, -3.7%). In the PPb population, the percentages of subjects with a satisfactory bacteriological outcome at the TOC visit were 76.6% and 88.5% for the APC-111 and penicillin groups, respectively. The difference between the APC-111 and penicillin groups was -11.9% with a 95% CI of (-19.7%, -4.0%).

S**tudy 302:** There were 306 and 312 randomized subjects in the APC-111 and penicillin groups, respectively. In the mITT[b] population, the percentages of subjects with a satisfactory bacteriological outcome at the TOC visit were 82.4% and 78.4% for the APC-111 and penicillin groups, respectively. The difference between the APC-111 and penicillin groups was 4.0% with a 95% CI of (-2.8%, 10.8%). In the PPb population, the percentages of subjects with a satisfactory bacteriological outcome at the TOC visit were 85% and 83.4% for APC-111 and penicillin groups, respectively. The difference between the APC-111 and penicillin groups was 1.6% with a 95% CI of (-5.1%, 8.2%).

1.3 Statistical Issues and Findings

There were no major statistical issues identified in this review.

The primary efficacy analysis was to test the hypothesis of non-inferiority of the APC-111 treatment to the penicillin treatment based on the percentage of subjects with a satisfactory bacteriological outcome at the TOC visit. A non-inferiority margin of 10% was used in the non-inferiority testing. The point estimate and its asymptotic two-sided 95% CI for the difference in the satisfactory bacteriological outcome rates were calculated. If the lower bound of the 95% CI was greater than -10%, the APC-111 treatment was considered non-inferior to the penicillin treatment. The primary analysis was performed using both the mITT[b] and PPb populations.

Justification of non-inferiority margin of 10%

As presented at the FDA anti-infective drugs advisory committee meeting in February 2002, an adequate non-inferiority margin should be the minimum of M1 and M2. Here M1 represents conservative estimate for the treatment effect of the active control over placebo and M2 represents the largest clinically acceptable difference between the test drug and the active control.

Estimate of M1 (penicillin treatment effect over placebo)

In order to evaluate the bacteriological effect of the penicillin treatment over placebo (M1) in the setting of APC-111 studies 301 and 302, the FDA medical team leader Dr. John Alexander has done a thorough literature search. Two lists from this search were provided: one for studies published before 1957 in Index Medicus (see Appendix 1) and one for studies obtained from PubMed (see Appendix 2).

The majority of these studies from the first list (based on Index Medicus) demonstrated that penicillin treatment was effective in preventing and treating Group A streptococcal pharyngitis. It was difficult from these studies, however, to extrapolate the treatment effect of penicillin over placebo in the setting of APC-111 studies 301 and 302 due to the dissimilarity in the study design parameters such as study population, endpoint definition, and treatment regimen.

The studies from the second list (based on PubMed) compared the treatment effect of penicillin with other antibiotics, or compared different doses/frequencies/duration of penicillin. These studies reported that longer treatment duration of penicillin was associated with better bacteriological outcome. The oral penicillin treatment of 7 days or longer yielded a bacteriological eradication rate of 70% to 100%. The majority of these studies, however, were not placebo-controlled studies. From this list three placebo-controlled trials were identified that had at least one post-baseline bacteriological outcome measured. These studies are:

1. Krober MS et al., Streptococcal pharyngitis. Placebo-controlled double-blind evaluation of clinical response to penicillin therapy. JAMA. 1985 Mar 1; 253(9):1271-4.

2. Dagnelie CF et al., Do patients with sore throat benefit from penicillin? A randomized double-blind placebo-controlled clinical trial with penicillin V in general practice. Br J Gen Pract. 1996 Oct; 46(411):589-93.

3. Zwart S et al., Penicillin for acute sore throat: randomised double blind trial of seven days versus three days treatment or placebo in adults. BMJ. 2000 Jan 15; 320(7228):150-4.

Krober's paper studied the clinical response to 3-day penicillin V therapy (250 mg three times daily) compared with placebo in children with symptomatic pharyngitis and throat cultures positive for group A beta-hemolytic streptococci (GABHA). The bacteriological outcome at 24, 48, and 72 hours after randomization was measured in this study. The results related to the bacteriological outcome were reported as follows:

> "Of the 26 culture-positive patients, all 11 in the penicillin-treated group had negative throat cultures at 24, 48, and 72 hours. Nearly all of the throat cultures taken at these time intervals from the 15 patients who had taken the placebo remained culture positive for GABHS."

The results from Krober's paper demonstrated that the 3-day penicillin V therapy was very effective in eradicating GABHS compared with placebo. However, given the difference in the duration of the penicillin treatment (3 days in Krober's study vs. 10 days in APC-111 studies 301 and 302) and the timing at which the bacteriological outcome was measured (≤3 days in

Krober's study vs. 14-18 days in APC-111 studies 301 and 302), the results from this study were not directly used to extrapolate the penicillin treatment effect in APC-11 studies 301 and 302.

Dagnelie's paper assessed the efficacy of 10-day penicillin V on the clinical course and bacteriological response. The bacteriological outcome at day 2 after randomization was measured in this study. Again, this study demonstrated that the penicillin treatment was very effective in eradicating GABHS compared with placebo. The bacteriological eradication rate was 75% (41/55) for penicillin and 4% (2/56) for placebo. The point estimate for the difference in the bacteriological eradication rates at day 2 between the 10-day penicillin and placebo treatments was 70% with a 95% CI of (58%, 84%). These results indicated that the bacteriological eradication rate at day 2 with 10-day penicillin treatment was 58% higher compared with placebo.

This study didn't collect bacteriological outcome data after day 2 post-randomization. Could the difference in the bacteriological eradication rate at the end of the 10-day treatment between the penicillin and placebo groups be as good as the one observed on day 2 during therapy? The statistical reviewer could not conclude this. If this can be concluded, then one could use 58% as an estimate for the penicillin treatment effect over placebo in APC-11 studies 301 and 302.

Zwart's paper evaluated the effectiveness of two penicillin treatment regimens compared with placebo in patients (aged 15-60 years) with sore throat and other pharyngitis symptoms. The study treatment groups were: (1) placebo for 7 days; (2) two 250 mg capsules of penicillin V three times daily for 3 days followed by placebo for 4 days; (3) two 250 mg capsules of penicillin V three times daily for 7 days. The bacteriological eradication rate at day 14 after randomization was 7% (5/70) for the placebo treatment, 41% (36/87) for the 3-day penicillin treatment, and 72% (57/79) for the 7-day penicillin treatment. Thus, the point estimate for the difference in the bacteriological eradication rates between the 7-day penicillin treatment and the placebo treatment was 65% with an asymptotic 95% CI of (53%, 77%). Consequently, a reasonable estimate for the bacterial eradication rate of 7-day penicillin treatment could be 53% higher than placebo.

It is noted that the duration of the penicillin treatment was 7 days in Zwart's study. If a 10-day regimen had been used, one could likely obtain a similar or even better bacteriological outcome at day 14 as demonstrated in a paper by Schwartz 1981 (Appendix 2). In addition, as mentioned above, the results from the other two placebo-controlled studies were also supportive of the results from Zwart's study. Thus it is reasonable to use 53% as an estimate for M1 (the treatment effect of bacteriological eradication at day 14 for a 10-day penicillin treatment compared with placebo).

It is also noted that one could obtain a more conservative estimate for M1 when taking into account for potential uncertainties with respect to constancy of the control effect, heterogeneity in the patient population and trial to trial variability.

Selection of an appropriate non-inferiority margin

If an estimate of 53% for the bacteriological effect of penicillin over placebo (M1) is used, and if 10% is the largest clinical acceptable difference between the test drug and penicillin (M2), then a non-inferiority margin of 10% is acceptable for AP-111 studies 301 and 302.

The sponsor's rationale for the selection of the non-inferiority margin of 10% was based on the results presented in Zwart's paper.

Sensitivity Analyses of Primary Efficacy Endpoint

The primary efficacy analysis for the primary efficacy endpoint was performed in the mITT[b] and PPb populations. To examine the sensitivity of the primary efficacy results in study 302, the statistical reviewer has performed an analysis for the primary efficacy endpoint in the PPb1 population in the same manner as the sponsor did in the mITT[b] and PPb populations.

According to the sponsor's SAP, the PPb1 population was determined prior to study unblinding and included all mITT subjects who had no major study protocol violations, including compliance with blinded study medications. The PPb population was determined after study unblinding, based on compliance with the actual study medication received. The only difference between the PPb and PPb1 populations was related to the determination of study medication compliance after unblinding and before unblinding. A subject who was non-compliant with placebo medication but compliant with active study medication could be included in the PPb population, if otherwise valid.

The results of this sensitivity analysis were consistent with the findings observed in the mITT[b] and PPb populations.

2. INTRODUCTION

2.1 Indication

The sponsor submitted this NDA, under the provisions specified in the Federal Food, Drug and Cosmetic Act, Section 505(b)(2), for a once-a-day, pulsatile-release, multiparticulate tablet formulation of amoxicillin, APC-111 MP Tablet, 775 mg for a 10-day regimen for the treatment of tonsillitis and/or pharyngitis (b) (4) to *Streptococcus pyogenes* (*S. pyogenes*) in adolescents and adults.

Amoxicillin is a semi-synthetic antibiotic effective for the treatment of middle ear infections, urinary tract infections, gonorrhoea, and exacerbations of chronic bronchitis. It is also indicated for endocarditis caused by enterococci, listerial meningitis, and helicobacter pylori eradication.

Amoxicillin is available as 250 mg and 500 mg capsules. The typical adult dose is 250 mg taken orally every 8 hours. This dose may be doubled in severe infections. It is also available in tablet form (500 mg and 875 mg) and as an oral suspension (250 mg or 500 mg per 5 mL suspension).

The APC-111 MP Tablet represents a change in formulation, dosing regimen and indication from the following available marketed products of amoxicillin for oral administration, which are listed in the *Orange Book*:

- Amoxicillin capsules 250 mg (NDA 62-216)
- Amoxicillin tablets 500 mg (NDA-50-574), and
- Amoxicillin tablets 875 mg (NDA-50574)

A comparison of the proposed indication and dosing regimen of APC-111 MP Tablet, 775 mg to the approved indication and dosing regimen for Amoxil® is shown in the following table:

	APC-111	**Amoxicillin 250 mg (ANDA 62-216)**	**Amoxil® 500 mg (NDA 50-754)**	**Amoxil® 875 mg (NDA 50-754)**
Strength	**775 mg**	**250 mg**	**500 mg**	**875 mg**
Formulation	Multiparticulate pulsatile release tablet	Immediate release capsule	Immediate release tablet	Immediate release tablet
Dosing regimen Frequency Duration	Once daily 10 days	Every 8 h ≥ 10 days	Every 8 h to 12 h ≥ 10 days	Every 12 h ≥ 10 days
Total daily dose	775 mg	750 mg	1000 mg – 1500 mg	1750 mg
Total treatment dose	7.75 g	7.5 g	10 g – 15 g	17.5 g
Indication	Tonsillitis and/or pharyngitis (b) (4) to *S. pyogenes*	Infections of the ear, nose, and throat – due to *Steptococcus spp.* (α- and β-hemolytic) strains only, *S. pneumoniae, Staphylococcus spp., or H. influenzae*.[1]		
			Mild/Moderate	500 mg every 12h 250 mg every 8h
			Severe	875 mg every 12h 500 mg every 8h

[1]Various other indications are included in the package insert.
Data Source: Table 2.5.5-5 in Section 2.5.5.4.1 of m2\summary\summary.pdf of the NDA submission.

The sponsor has developed the APC-111 MP Tablet, 775 mg as a multipariculate, modified-release tablet, delivering an immediate-release (Pulse 1) and two delayed-release pulses (Pulse 2 and Pulse 3) of amoxicillin, for once-a-day oral administration. The sponsor believes that a once-a-day amoxicillin product will provide the benefits of reduced pill burden and dosing convenience and likely improve compliance.

2.2 History of Drug Development

The initial IND for APC-11 MP Tablet, IND 62576, was submitted to the FDA prior to 2002. The sponsor had two pre-phase 3 meeting with the FDA on September 22 of 2004 and on November 2 of 2005.

2.3 Specific Studies Reviewed and Major Statistical Issues

The two pivotal studies were reviewed to evaluate the efficacy of APC-111 in the treatment of tonsillitis and/or pharyngitis (b) (4) to Streptococcus pyogenes in adolescents and adults. There were no major statistical issues identified in this review.

2.4 Data Sources

The sponsor's study reports and data sets for studies 301 and 302 are available on the EDR at "Cdsesub1\n50813\N_000".

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy (Studies 301 and 302)

3.1.1 Study Design and Endpoints

3.1.1.1 Study 302

Study 302 was a randomized, double-blind, parallel-group, multi-center, and non-inferiority Phase III study. In this study subjects presenting with protocol-defined acute streptococcal tonsillitis and/or pharyngitis suitable for treatment with oral antibiotics were randomized to receive one of two treatment arms, APC-111 700 mg PO QD for 10 days, or Penicillin VK 250 mg PO QID for 10 days in a blinded fashion and with a 1:1 ratio. The study subjects were to have signs and symptoms compatible with pharyngeal disease due to S. pyogenes and a positive enzyme immunoassay (b) (4) Strep A Test) for *S. pyogenes* from a pharyngeal swab at the Screening/Baseline visit. There were four study visits: Screening/Baseline (Visit 1, Day 1), During Therapy (Visit 2, Day 3-5), Test-of-Cure (TOC) (Visit 3, Day 14-18), and Late Post-Therapy (LPT) (Visit 4, Day 38-45).

There were 306 and 312 randomized subjects in the APC-111 and Penicillin groups, respectively. The key inclusion and exclusion criteria are shown in Table 1.

The primary efficacy endpoint was the bacteriological outcome at TOC (definition was provided in Table 2). The primary analysis was to compare the proportions of subjects who had a satisfactory bacteriological outcome between the APC-111 and Penicillin groups. The primary analysis was performed for both the PPb and mITT[b] populations (defined below). A 95% confidence interval was to construct for the difference in the proportions of subjects who had a satisfactory bacteriological outcome between the APC-111 and Penicillin groups. The assessment of non-inferiority of APC-111 to Penicillin was based on comparing the lower limit of the 95% confidence interval with the non-inferiority margin of -10%.

The secondary efficacy endpoints included the bacteriological outcome at LPT and clinical outcome at TOC and LPT visits.

The following analysis populations were used in the statistical analyses:

Intent-to-Treat (ITT)/Safety population: included all subjects who received at least one dose of randomized study medication and have post-baseline clinical safety assessment data available.

Modified Intent-to-Treat (mITT) population: included all ITT subjects who had a baseline throat swab culture positive for *S. pyogenes*.

Two mITT groups for analysis, [a] and [b], were defined as follows:

mITT[a] population: included all mITT subjects with the exception of subjects with a bacteriological outcome of "Indeterminate" at TOC and a clinical outcome of "Unable to Evaluate" at the same visit (see Table 3).

mITT[b] population (Co-primary efficacy analysis population): included all mITT subjects and considered subjects who had a bacteriological outcome of "Indeterminate" at TOC and a clinical outcome of "Unable to Evaluate" at the same visit as "Unsatisfactory" at TOC (see Table 3).

Note: the mITT population is the same as the mITT[b] population. The mITT[b] population was an analysis population and specified that the bacteriological outcome for subjects with a bacteriological outcome of "Indeterminate" at TOC and a clinical outcome of "Unable to Evaluate" at the same visit was considered as "Unsatisfactory".

Per-Protocol clinical (PPc) population – determined prior to unblinding (PPc1 population) and revised after treatment unblinding (PPc2 population): included all ITT subjects who had no major protocol violations.

The PPc1 population was determined prior to unblinding using the pre-specified criteria outlined in the sponsor's statistical analysis plan, with the assessment of 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 (that is, PPc) analysis population to be used in the relevant efficacy analyses (for details, see the sponsor's SAP).

Per-Protocol bacteriological (PPb) population – determined prior to unblinding (PPb1) and revised after treatment unblinding (PPb2): included all mITT subjects who had no major protocol violations.

The PPb1 population was determined prior to unblinding using the pre-specified criteria outlined in the sponsor's statistical analysis plan, with the assessment of 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 (that is, PPb) analysis population to be used in the primary and secondary efficacy analyses (for details, see the sponsor's SAP).

Table 1: Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	
1	Age ≥ 12 years.
2	Had a clinical diagnosis of acute tonsillitis and/or pharyngitis defined as having the clinical signs and symptoms compatible with tonsillitis and/or pharyngitis, including sore throat with at least one of the following: • Tonsillar or pharyngeal exudates • Tender cervical lymph nodes • Fever or history of fever treated with antipyretics (within 24-48 hours from onset of symptoms)

	• Odynophagia • Chills • Uvular edema • Elevated white blood cell (WBC) >12,000/mm^3 or ≥ 10% bands • Red tongue and prominent papillae (Strawberry tongue)
3	Had a positive rapid screening test for *S. pyogenes* (enzyme immunoassay; (b) (4) Strep A Test).
4	Was an appropriate candidate for oral antibiotic therapy and could swallow the study dosage forms.
5	Females must be non-lactating and: • At no risk of pregnancy for one of the following reasons: post-menopausal for at least one year, hysterectomy, or tubal ligation, **OR** • If of child-bearing potential and sexually active, the patient must have a negative baseline urine pregnancy test and be utilizing oral contraceptives or barrier methods throughout the study.
Key Exclusion Criteria	
1	Chronic or recurrent odynophagia or enlarged tonsils of obscure etiology (two weeks duration a minimum of two times per year or longer duration occurring less frequently).
2	More than one episode of acute tonsillitis and/or pharyngitis in the 6 months prior to baseline visit.
3	Pharyngitis known or suspected to be due to a pathogen resistant to beta-lactam antimicrobials.
4	Patients who are known carriers of S. *pyogenes*
5	Previous allergy, serious adverse reaction to, or intolerance to, Penicillin or any other member of the beta-Iactam class of antimicrobials.
6	Any serious illness or concomitant condition that the investigator judges would preclude the study evaluations or make it unlikely that the course of study therapy and follow-up could be completed. This would also include: • Any rapidly progressive underlying disease with a shortened life expectancy. • The inability to swallow the study dosage form. • Unable to understand the requirements of the study. • Neutropenia (<1000 *PMNs/mm3)* or other immunocompromised state.
7	Concurrent condition of upper/lower respiratory tract infections (e.g. sinusitis, bronchitis, and acute otitis media)
8	Concurrent symptoms of viral etiology including: • Conjunctivitis, coryza, and cough • Diffuse adenopathy or rash suggestive of mononucleosis • Rash or arthropathy suggestive of scarlet fever
9	Seizure disorder, lowered seizure threshold, or psychiatric condition requiring use of major tranquilizers.
10	Pregnancy or nursing.
11	Expectation that additional effective systemic antibacterials would be required for any condition during the duration of the study.
12	Current drug or alcohol abuse.
13	Receipt of any experimental drug or medical device within the previous 30 days (or are scheduled to receive any other experimental procedures during the study period or current involvement in another clinical study).
14	Previous treatment under this protocol.
15	The need for hospitalization or LV. Antimicrobial therapy.
16	Previous systemic antimicrobial therapy within 30 days.
17	The presence of clinically significant hematologic conditions (specifically Neutropenia)
18	History of cardiovascular disease, renal disease, or neurological disease secondary to previous infection with S. pyogenes or previous rheumatic fever.
19	Probenecid treatment or systemic steroids during the duration of the study.

Table 2: Bacteriological Outcome at TOC

Baseline	Withdrawal	Results of culture for Streptococcus pyogenes at TOC	Clinical response at TOC	Bacteriological response at TOC	Bacteriological outcome at TOC
Streptococcus pyogenes isolated	Not applicable	Streptococcus pyogenes not isolated	Cure	Eradication	Satisfactory
			Failure		
			Unable to Evaluate		
Streptococcus pyogenes isolated	Not applicable	Streptococcus pyogenes isolated	Cure	Persistence	Unsatisfactory
			Failure		
			Unable to Evaluate		
Streptococcus pyogenes isolated	Not applicable	No culture results available	Cure	Presumed Eradication	Satisfactory (excluded from PPb)
			Failure	Presumed Persistence	Unsatisfactory (included/excluded from PPb)
			Unable to Evaluate	Indeterminate	Indeterminate (excluded from PPb and mITT[a])

Subjects with a bacteriological outcome of 'Indeterminate' will be excluded from the mITT [a] analysis, but will be included as 'Unsatisfactory' in the mITT [b] co-primary efficacy analysis.
Subjects with a bacteriological response of 'Presumed Persistence' at TOC will be included in the PPb analysis if the subject is considered a 'Clinical Failure', has prematurely withdrawn from the study and has started a new systemic antibacterial for tonsillitis and/or pharyngitis or has died due to the indication. The bacteriological outcome in such cases will be regarded as 'Unsatisfactory'.
Data source: table 7.4.1-1 in study 302 statistical analysis plan.

Table 2: Bacteriological Outcome at TOC (continued) (Subjects who prematurely withdraw from the study prior to or at TOC)

Baseline	Withdrawal	Results of culture for Streptococcus pyogenes at TOC	Clinical response at TOC	Bacteriological response at TOC	Bacteriological outcome at TOC
Streptococcus pyogenes isolated	New systemic antibacterial for tonsillitis/pharyngitis	Not applicable	Failure	Presumed Persistence	Unsatisfactory (included in PPb)
Streptococcus pyogenes isolated	New systemic antibacterial not for tonsillitis/pharyngitis	Not applicable	Unable to Evaluate	Indeterminate	Indeterminate (excluded from PPb and mITT [a])
Streptococcus pyogenes isolated	Death due to tonsillitis/pharyngitis	Not applicable	Failure	Presumed Persistence	Unsatisfactory (included in PPb)
Streptococcus pyogenes isolated	Death not due to tonsillitis/pharyngitis	Not applicable	Unable to Evaluate	Indeterminate	Indeterminate (excluded from PPb and mITT [a])
Streptococcus pyogenes isolated	Withdrawal but no new systemic antibacterial started	Not applicable	Unable to Evaluate	Indeterminate	Indeterminate (excluded from PPb and mITT [a])

New systemic antibacterial: Started prior to TOC or at TOC.
If a subject is discontinued at TOC and the investigator obtains a throat swab for culture prior to starting a new systemic antibacterial, the results of that TOC culture will be regarded as valid and included in the calculation of the bacteriological outcome at TOC.
Clinical response at TOC: Cure is not a valid clinical response for subjects who prematurely discontinued their participation in the study.
Subjects with a bacteriological outcome of 'Indeterminate' will be excluded from the mITT [a] analysis, but will be included as 'Unsatisfactory' in the mITT [b] co-primary efficacy analysis.
Subjects with a bacteriological response of 'Presumed Persistence' at TOC will be included in the PPb analysis if the subject is considered a 'Clinical Failure', has prematurely withdrawn from the study and has started a new systemic antibacterial for tonsillitis and/or pharyngitis or has died due to the indication. The bacteriological outcome in such cases will be regarded as 'Unsatisfactory'.
Data source: table 7.4.1-1 in study 302 statistical analysis plan.

3.1.1.2 Study 301

The design of study 301 was similar to the one of study 302 (for details, see sponsor's study protocols). The major difference between studies 301 and 302 was the APC-111 treatment duration: 7 day in study 301 and 10 days in study 302. Study 302 was conducted after study 301 was completed and failed to demonstrate non-inferiority of the 7-day APC-111 treatment to the 10-day Penicillin VK (250 mg PO QID) treatment.

In this study there were 253 and 260 randomized subjects in the APC-111 and Penicillin groups, respectively.

3.1.2 Subject Disposition, Demographic and Baseline Characteristics

3.1.2.1 Subject Disposition and Analysis Population

The summaries of subject disposition are presented in Table 3 for studies 301 and 302.

In study 302, there were 306 and 312 subjects randomized to the APC-111 and Penicillin groups, respectively. All randomized subjects were treated. Of these treated subjects, 251 (82.0%) and 249 (79.8%) completed the study in the APC-111 and Penicillin groups, respectively. A similar proportion of subjects were withdrawn from both treatment groups (18.0% for APC-111 and 20.2% for Penicillin). The most frequent reasons for withdrawal in both groups were "Insufficient therapeutic effect".

In study 301, there were 253 and 260 subjects randomized to the APC-111 and Penicillin groups, respectively. Three randomized subjects were not treated. Of the treated subjects, 214 (85.3%) and 224 (86.5%) completed the study the APC-111 and Penicillin groups, respectively. A similar proportion of subjects were withdrawn from both treatment groups (14.7% for APC-111 and 13.5% for Penicillin). The most frequent reasons for withdrawal in both groups were "Insufficient therapeutic effect".

The summaries of the analysis populations are presented in Table 4 for studies 301 and 302.

In study 302, the two treatment groups had similar distribution of mITT subjects (83.7% for APC-111 and 84.6% for Penicillin) and PPb subjects (76.1% for APC-111 and 73.4% for Penicillin).

In study 301, the two treatment groups had similar distribution of mITT subjects (75.9% for APC-111 and 78.1% for Penicillin) and PPb subjects (67.6% for APC-111 and 70.0% for Penicillin).

Table 3: Subject Disposition (Study 302)

Disposition	Number (%) of subjects		
	APC-111	Pen VK	Total
Subjects screened			673[a]
Subjects randomized[b]	306	312	618
Subjects treated	306	312	618
Subjects who completed study	251 (82.0)	249 (79.8)	500 (80.9)
Subjects who prematurely discontinued study	55 (18.0)	63 (20.2)	118 (19.1)
Reasons for premature discontinuation[c]			
Insufficient therapeutic effect	28 (9.2)	24 (7.7)	52 (8.4)
Subject lost to follow-up	14 (4.6)	11 (3.5)	25 (4.0)
Adverse event	10 (3.3)	14 (4.5)	24 (3.9)
Investigator's discretion due to negative basline culture for S. pyogenes	1 (0.3)	2 (0.6)	3 (0.5)
Consent withdrawn	0 (0)	3 (1.0)	3 (0.5)
Subject noncompliance	0 (0)	4 (1.3)	4 (0.6)
Protocol violations	0 (0)	1 (0.3)	1 (0.2)
Other	2 (0.7)	4 (1.3)	6 (1.0)

[a]One additional screen failure subject was identified at a site close out visit post data base lock. This subject was a screen failure based on a negative (b) (4) Strep A Test. The data base was not unlocked to include this subject and hence this subject was not included in the summary table.
[b]Two subjects (0288-3021 and 0454-3007) were randomized into the web-based interactive response system, but were withdrawn from the study prior to being dispensed study medication, and are not included in the number of subjects randomized. These two subjects are included in the number of subjects screened and were classified by the Investigators and Sponsor as screen failures. [c]Reasons for premature discontinuation are presented in decreasing order of frequency in the APC-111 column, with the exception of the "Other" category.
Data Source: Sponsor's CSR Table 10-1.

Table 3: Subject Disposition (continued) (Study 301)

Disposition	Number (%) of patients		
	APC-111	Pen VK	Total
Patients screened	–	–	617
Patients randomized	253	260	513
Patients treated	251 (100.0)	259 (100.0)	510 (100.0)
Patients who completed study	214 (85.3)	224 (86.5)	438 (85.9)
Patients who prematurely discontinued study	37 (14.7)	35 (13.5)	72 (14.1)
Reasons for premature discontinuationa			
Insufficient therapeutic effect	10 (4.0)	9 (3.5)	19 (3.7)
Adverse event	7 (2.8)	9 (3.5)	16 (3.1)
Patient lost to follow-up	7 (2.8)	5 (1.9)	12 (2.4)
Consent withdrawn	3 (1.2)	1 (0.4)	4 (0.8)
Patient noncompliance	1 (0.4)	1 (0.4)	2 (0.4)
Protocol violations	1 (0.4)	2 (0.8)	3 (0.6)
Other	8 (3.2)	8 (3.1)	16 (3.1)

[a] Reasons for premature discontinuation are presented in decreasing order of frequency in the APC-111 column, with the exception of the "Other" category.
Data Source: Sponsor's CSR Table 10-1.

Table 4: Analysis Population (Study 302)

Population	Number (%) of Subjects		
	APC-111	Pen VK	Total
Subjects randomized	306 (100.0)	312 (100.0)	618 (100.0)
ITT/Safety	302 (98.7)	306 (98.1)	608 (98.4)
mITT/mITT[b]	256 (83.7)	264 (84.6)	520 (84.1)
PPc1 [a]	273 (89.2)	263 (84.3)	536 (86.7)
PPc2	280 (91.5)	263 (84.3)	543 (87.9)
PPb1	228 (74.5)	229 (73.4)	457 (73.9)
PPb2/PPb	233 (76.1)	229 (73.4)	462 (74.8)

PPc1: Per-Protocol clinical analysis population with compliance calculated prior to treatment unblinding.
PPc2: Principal PPc analysis population with compliance calculated after unblinding based on active study medication.
PPb1: Per-Protocol bacteriological analysis population with compliance calculated prior to treatment unblinding.
PPb2: Co-primary PPb analysis population with compliance calculated after unblinding based on active study medication.
[a] Subject 0290-3002 was excluded from PPc1 prior to unblinding. Validity was re-assessed after unblinding and subject was included in the Principal PPc (PPc2) population as unable to evaluate.
Data Source: Sponsor's CSR Table 10-2.

Table 4: Analysis Population (continued) (Study 301)

Population	Number (%) of patients		
	APC-111	Pen VK	Total
Patients randomized	253 (100.0)	260 (100.0)	513 (100.0)
ITT/Safety	248 (98.0)	259 (99.6)	507 (98.8)
mITT/mITT[b]	192 (75.9)	203 (78.1)	395 (77.0)
PPc	218 (86.2)	227 (87.3)	445 (86.7)
PPb	171 (67.6)	182 (70.0)	353 (68.8)

Data Source: Sponsor's CSR Table 10-2.

3.1.2.2 Baseline Characteristics

The baseline demographic characteristics (Table 5) were comparable between the two treatment groups in the ITT population in both studies.

Table 5: Demographic Characteristics (ITT Population) (Studies 301 and 302)

	Study 302		Study 301	
	APC-111	**Pen VK**	**APC-111**	**Pen VK**
	(N =302)	**(N = 306)**	**(N =248)**	**(N = 259)**
Gender, n (%)				
Female	175 (57.9)	198 (64.7)	151 (60.9)	178 (68.7)
Male	127 (42.1)	108 (35.3)	97 (39.1)	81 (31.3)
Race, n (%)				
Caucasian	273 (90.4)	283 (92.5)	225 (90.7)	237 (91.5)
African American	13 (4.3)	9 (2.9)	9 (3.6)	6 (2.3)
Asian / Oriental	9 (3.0)	6 (2.0)	0 (0.0)	6 (2.3)
American Indian / Alaskan Native	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Other	7 (2.3)	7 (2.3)	14 (5.6)	10 (3.9)
Ethnicity, n (%)				
Hispanic	17 (5.6)	13 (4.2)	16 (6.5)	19 (7.3)
Non – Hispanic	285 (94.4)	293 (95.8)		
Age group*, n (%)				
12 to <19 years	70 (23.2)	69 (22.5)	68 (27.4)	74 (28.6)
19 to <30 years	75 (24.8)	103 (33.7)	62 (25.0)	59 (22.8)
30 to <40 years	101 (33.4)	72 (23.5)	59 (23.8)	64 (24.7)
≥40 years	56 (18.5)	62 (20.3)	59 (23.8)	62 (23.9)
Age (years)				
Mean (SD)	29.9 (12.07)	29.3 (12.43)	28.5 (12.90)	28.4 (12.92)
Median (range)	30.0 (12 – 67)	28.0 (12 – 72)	26.0 (12-73)	27.0 (12-77)
Weight (kg)				
N	301	305	247	258
Mean (SD)	79.34 (21.15)	76.66 (19.63)	80.60 (22.719)	76.08 (23.016)
Median (range)	76.48 (39.0 – 160.8)	73.94 (38.6 – 142.0)	78.47 (31.3-195.1)	72.58 (35.1-167.7)

* The corresponding age intervals used in study 301 were: 12 to <19 years; 19 to <28 years, 28 to <38 years, and ≥38 years.

Data source: Sponsor's CSR table 10-6 for study 302 and table 10-5 for study 301.

3.1.3 Statistical Methodology

Study 302

The primary hypothesis tested in the study was that APC-111 treatment would be non-inferior to the treatment of penicillin with respect to the efficacy measurement of proportion of subjects who had a satisfactory bacteriological outcome in both the mITT[b] and PPb populations. A non-inferiority margin of 10% was used in the primary hypothesis test. A two-sided 95% CI for the difference in the satisfactory bacteriological response rates between APC-111 and penicillin treatment groups was constructed. APC-111 was considered non-inferior to penicillin if the lower limit of the 95% confidence interval was greater than or equal to -10%.

Study 301

Regarding the difference in the statistical analysis plan between studies 301 and 302, the following was stated in section 4 "Rational for Addendum" of the sponsor's clinical study report of study 301:

> *Discussions with the Food and Drug Administration (FDA) on the subsequent Phase III study, Protocol 111.302, resulted in changes in the analysis of the primary and secondary efficacy variables. As outlined in the SAP for Protocol 111.302, the primary and secondary analyses were performed unadjusted for region by calculating the asymptotic point estimate and two-sided 95% confidence interval for the treatment difference in bacteriological 'Satisfactory Outcome' rates and for the treatment differences in clinical 'Success' rates.*
>
> *In addition, treatment compliance in Protocol 111.302 was calculated based on active study medication only.*
>
> *For consistency between the studies and to facilitate comparisons across the studies, treatment compliance and the primary and secondary efficacy variables for Protocol 111.301 were re-analyzed with the analysis methods used in Protocol 111.302.*

Justification of non-inferiority margin of 10%

As presented at the FDA anti-infective drugs advisory committee meeting in February 2002, an adequate non-inferiority margin should be the minimum of M1 and M2. Here M1 represents conservative estimate for the treatment effect of the active control over placebo and M2 represents the largest clinically acceptable difference between the test drug and the active control.

Estimate of M1 (penicillin treatment effect over placebo)

In order to evaluate the bacteriological effect of the penicillin treatment over placebo (M1) in the setting of APC-111 studies 301 and 302, the FDA medical team leader Dr. John Alexander has done a thorough literature search. Two lists from this search were provided: one for studies

published before 1957 in Index Medicus (see Appendix 1) and one for studies obtained from PubMed (see Appendix 2).

The majority of these studies from the first list (based on Index Medicus) demonstrated that penicillin treatment was effective in preventing and treating Group A streptococcal pharyngitis. It was difficult from these studies, however, to extrapolate the treatment effect of penicillin over placebo in the setting of APC-111 studies 301 and 302 due to the dissimilarity in the study design parameters such as study population, endpoint definition, and treatment regimen.

The studies from the second list (based on PubMed) compared the treatment effect of penicillin with other antibiotics, or compared different doses/frequencies/duration of penicillin. These studies reported that longer treatment duration of penicillin was associated with better bacteriological outcome. The oral penicillin treatment of 7 days or longer yielded a bacteriological eradication rate of 70% to 100%. The majority of these studies, however, were not placebo-controlled studies. From this list three placebo-controlled trials were identified that had at least one post-baseline bacteriological outcome measured. These studies are:

1. Krober MS et al., Streptococcal pharyngitis. Placebo-controlled double-blind evaluation of clinical response to penicillin therapy. JAMA. 1985 Mar 1; 253(9):1271-4.

2. Dagnelie CF et al., Do patients with sore throat benefit from penicillin? A randomized double-blind placebo-controlled clinical trial with penicillin V in general practice. Br J Gen Pract. 1996 Oct; 46(411):589-93.

3. Zwart S et al., Penicillin for acute sore throat: randomised double blind trial of seven days versus three days treatment or placebo in adults. BMJ. 2000 Jan 15; 320(7228):150-4.

Krober's paper studied the clinical response to 3-day penicillin V therapy (250 mg three times daily) compared with placebo in children with symptomatic pharyngitis and throat cultures positive for group A beta-hemolytic streptococci (GABHA). The bacteriological outcome at 24, 48, and 72 hours after randomization was measured in this study. The results related to the bacteriological outcome were reported as follows:

> "Of the 26 culture-positive patients, all 11 in the penicillin-treated group had negative throat cultures at 24, 48, and 72 hours. Nearly all of the throat cultures taken at these time intervals from the 15 patients who had taken the placebo remained culture positive for GABHS."

The results from Krober's paper demonstrated that the 3-day penicillin V therapy was very effective in eradicating GABHS compared with placebo. However, given the difference in the duration of the penicillin treatment (3 days in Krober's study vs. 10 days in APC-111 studies 301 and 302) and the timing at which the bacteriological outcome was measured (≤3 days in Krober's study vs. 14-18 days in APC-111 studies 301 and 302), the results from this study were not directly used to extrapolate the penicillin treatment effect in APC-11 studies 301 and 302.

Dagnelie's paper assessed the efficacy of 10-day penicillin V on the clinical course and bacteriological response. The bacteriological outcome at day 2 after randomization was

measured in this study. Again, this study demonstrated that the penicillin treatment was very effective in eradicating GABHS compared with placebo. The bacteriological eradication rate was 75% (41/55) for penicillin and 4% (2/56) for placebo. The point estimate for the difference in the bacteriological eradication rates at day 2 between the 10-day penicillin and placebo treatments was 70% with a 95% CI of (58%, 84%). These results indicated that the bacteriological eradication rate at day 2 with 10-day penicillin treatment was 58% higher compared with placebo.

This study didn't collect bacteriological outcome data after day 2 post-randomization. Could the difference in the bacteriological eradication rate at the end of the 10-day treatment between the penicillin and placebo groups be as good as the one observed on day 2 during therapy? The statistical reviewer could not conclude this. If this can be concluded, then one could use 58% as an estimate for the penicillin treatment effect over placebo in APC-11 studies 301 and 302.

Zwart's paper evaluated the effectiveness of two penicillin treatment regimens compared with placebo in patients (aged 15-60 years) with sore throat and other pharyngitis symptoms. The study treatment groups were: (1) placebo for 7 days; (2) two 250 mg capsules of penicillin V three times daily for 3 days followed by placebo for 4 days; (3) two 250 mg capsules of penicillin V three times daily for 7 days. The bacteriological eradication rate at day 14 after randomization was 7% (5/70) for the placebo treatment, 41% (36/87) for the 3-day penicillin treatment, and 72% (57/79) for the 7-day penicillin treatment. Thus, the point estimate for the difference in the bacteriological eradication rates between the 7-day penicillin treatment and the placebo treatment was 65% with an asymptotic 95% CI of (53%, 77%). Consequently, a reasonable estimate for the bacterial eradication rate of 7-day penicillin treatment could be 53% higher than placebo.

It is noted that the duration of the penicillin treatment was 7 days in Zwart's study. If a 10-day regimen had been used, one could likely obtain a similar or even better bacteriological outcome at day 14 as demonstrated in a paper by Schwartz 1981 (Appendix 2). In addition, as mentioned above, the results from the other two placebo-controlled studies were also supportive of the results from Zwart's study. Thus it is reasonable to use 53% as an estimate for M1 (the treatment effect of bacteriological eradication at day 14 for a 10-day penicillin treatment compared with placebo).

It is also noted that one could obtain a more conservative estimate for M1 when taking into account for potential uncertainties with respect to constancy of the control effect, heterogeneity in the patient population and trial to trial variability.

Selection of an appropriate non-inferiority margin

If an estimate of 53% for the bacteriological effect of penicillin over placebo (M1) is used, and if 10% is the largest clinical acceptable difference between the test drug and penicillin (M2), then a non-inferiority margin of 10% is acceptable for AP-111 studies 301 and 302.

The sponsor's rationale for the selection of the non-inferiority margin of 10% was based on the results presented in Zwart's paper.

Sensitivity Analyses of Primary Efficacy Endpoint

The primary efficacy analysis for the primary efficacy endpoint was performed in the mITT[b] and PPb populations. To examine the sensitivity of the primary efficacy results in study 302, the statistical reviewer has performed an analysis for the primary efficacy endpoint in the PPb1 population in the same manner as the sponsor did in the mITT[b] and PPb populations.

According to the sponsor's SAP, the PPb1 population was determined prior to study unblinding and included all mITT subjects who had no major study protocol violations, including compliance with blinded study medications. The PPb population was determined after study unblinding, based on compliance with the actual study medication received. The only difference between the PPb and PPb1 populations was related to the determination of study medication compliance after unblinding and before unblinding. A subject who was non-compliant with placebo medication but compliant with active study medication could be included in the PPb population, if otherwise valid.

3.1.4 Results and Conclusions

3.1.4.1 Study 302

Primary Efficacy Endpoint: Bacteriological Outcome at TOC

The bacteriological outcome at TOC was the primary efficacy endpoint. The primary efficacy analysis of this endpoint was performed in the PPb and mITT [b] co-primary populations. The results of the primary efficacy analysis, bacteriological outcome, and associated bacteriological responses at the TOC visit in the PPb and mITT [b] are presented in Table 6.

In the mITT[b] population, the percentage of subjects with a satisfactory bacteriological outcome at the TOC visit was comparable between the APC-111 treatment group (82.4%) and the penicillin VK treatment group (78.4%). The 95% lower confidence bound for the difference in the percentage of subjects with a satisfactory bacteriological outcome between the APC-111 and penicillin VK treatment groups at the TOC visit was -2.8%, which was greater than the non-inferiority margin of -10%.

The results of the primary efficacy analysis in the co-primary PPb population corroborated the findings observed in the mITT[b] population. The percentages of PPb subjects with a satisfactory bacteriological outcome at the TOC visit were 85.0% and 83.4% in the APC-111 and penicillin VK treatment groups, respectively. As observed in the mITT[b] population, APC-111 QD for 10 days consistently demonstrated non-inferiority to penicillin VK QID for 10 days in terms of the rate of satisfactory bacteriological outcome in the PPb population at the TOC visit. In the PPb population, the 95% lower confidence bound for the difference between the APC-111 and penicillin VK treatment groups in percentage of subjects with a satisfactory bacteriological outcome at the TOC visit was -5.1%, which was greater than the non-inferiority margin of -10%.

As part of the sensitivity analysis, this reviewer also performed the analysis of the primary efficacy endpoint in the PPb1 population. The results of the analysis are presented in Table 7. They corroborated the findings observed in the mITT[b] and PPb populations.

In conclusion, study 302 demonstrated that 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 using a 10% non-inferiority margin.

Secondary Efficacy Endpoints: Bacteriological Outcome at LPT, Clinical Outcome at TOC, and Clinical Outcome at LPT

The efficacy analysis results of the bacteriological outcome at LPT are presented in Table 8.
The efficacy analysis results of the clinical outcome at TOC are presented in Table 9.
The efficacy analysis results of the clinical outcome at LPT are presented in Table 10.

The results of these secondary efficacy endpoints are consistent with the results of the primary efficacy analyses, demonstrating that the treatment of APC-111 is non-inferior to the penicillin treatment.

3.1.4.2 Study 301

Primary Efficacy Endpoint: Bacteriological Outcome at TOC

The results of the primary efficacy analysis of the bacteriological outcome, and associated bacteriological responses at the TOC visit in the PPb and mITT [b] populations are presented in Table 6.

In the mITT[b] population, the percentage of subjects with a satisfactory bacteriological outcome at the TOC visit was greater in the penicillin VK treatment group (83.7%) compared with the APC-111 treatment group (71.9%). Furthermore, the 95% upper confidence bound for the difference in mean percentages of subjects with a satisfactory bacteriological outcome between the APC-111 and penicillin VK treatment groups at the TOC visit was below zero, demonstrating the lower performance of APC-111 QD for 7 days compared with penicillin VK QID for 10 days in terms of the bacteriological outcome at TOC. The 95% lower confidence bound for the difference in the proportions of subjects with a satisfactory bacteriological outcome between the APC-111 and penicillin VK treatment groups at the TOC visit was less than -10% (The 95% lower confidence bound was -20%). Therefore, APC-111 775 mg QD for 7 days failed to demonstrate non-inferiority to penicillin VK 250 mg QID for 10 days with respect to the treatment of tonsillitis and/or pharyngitis at the TOC visit.

In the PPb population, the efficacy results corroborated the findings in the mITT[b] population. They failed to demonstrate non-inferiority of APC-111 QD for 7 days to penicillin VK QID for 10 days in terms of the rate of satisfactory bacteriological outcome at the TOC visit. The proportion of PPb subjects with a satisfactory bacteriological outcome at the TOC visit was greater in the penicillin VK treatment group (88.5%) compared with the APC-111 treatment

group (76.6%). Furthermore, the 95% upper confidence bound for the difference in the proportions of subjects with a satisfactory bacteriological outcome between the APC-111 and penicillin VK treatment groups at the TOC visit did not encompass zero, again demonstrating the lower performance of APC-111 QD for 7 days compared with penicillin VK QID for 10 days in terms of the bacteriological outcome at TOC. The 95% lower confidence bound for the difference in the proportions of subjects with a satisfactory bacteriological outcome between the APC-111 and penicillin VK treatment groups at the TOC visit was -19.7%, which was less than -10%. Therefore, APC-111 775 mg QD for 7 days failed to demonstrate non-inferiority to penicillin VK 250 mg QID for 10 days with respect to the treatment of tonsillitis and/or pharyngitis at the TOC visit.

Secondary Efficacy Endpoints: Bacteriological Outcome at LPT, Clinical Outcome at TOC, and Clinical Outcome at LPT

The efficacy analysis results of the bacteriological outcome at LPT are presented in Table 8.
The efficacy analysis results of the clinical outcome at TOC are presented in Table 9.
The efficacy analysis results of the clinical outcome at LPT are presented in Table 10.

The results of these secondary efficacy endpoints are consistent with the results of the primary efficacy analyses, demonstrating that the treatment of APC-111 is not non-inferior to the penicillin treatment.

Table 6: Bacteriological Outcome at the TOC Visit

	Number of subjects (%)							
	Study 302				Study 301			
	PPb[a]		mITT [b][b]		PPb[a]		mITT [b][b]	
Bacteriological outcome/ Bacteriological response	APC-111 (10 Days)	Pen VK (10 Days)	APC-111 (10 Days)	Pen VK (10 Days)	APC-111 (7 Days)	Pen VK (10 Days)	APC-111 (7 Days)	Pen VK (10 Days)
N	233	229	256	264	171	182	192	203
Satisfactory	198 (85.0)	191 (83.4)	211 (82.4)	207 (78.4)	131 (76.6)	161 (88.5)	138 (71.9)	170 (83.7)
Eradication	198 (85.0)	191 (83.4)	204 (79.7)	206 (78.0)	131 (76.6)	161 (88.5)	138 (71.9)	169 (83.3)
Presumed Eradication			7 (2.7)	1 (0.4)			0 (0.0)	1 (0.5)
Unsatisfactory	35 (15.0)	38 (16.6)	45 (17.6)	57 (21.6)	40 (23.4)	21 (11.5)	54 (28.1)	33 (16.3)
Persistence	30 (12.9)	32 (14.0)	30 (11.7)	37 (14.0)	37 (21.6)	20 (11.0)	40 (20.8)	21 (10.3)
Presumed Persistence	5 (2.1)	6 (2.6)	7 (2.7)	8 (3.0)	3 (1.8)	1 (0.5)	5 (2.6)	1 (0.5)
Indeterminate	-	-	8 (3.1)	12 (4.5)	-	-	9 (4.7)	11 (5.4)
Comparison[c]								
Difference (95% CI)	1.6 (-5.1, 8.2)		4.0 (-2.8, 10.8)		-11.9% (-19.7, -4.0)		-11.9% (-20.0, -3.7)	

[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] 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. Difference between treatment groups: calculated as (APC-111 – penicillin). Two-sided 95% confidence interval.

Data source: Tables 2.7.3-12 & 13 in Sponsor's m5\clincstat\clinsum.pdf.

Table 7: Bacteriological Outcome at the TOC Visit (Study 302) for PPb1 Population

	Number of subjects (%)		
Bacteriological outcome/ Bacteriological response	APC-111 (10 Days)	Pen VK (10 Days)	Difference (95% CI)
N	228	229	
Satisfactory	195 (85.5)	191 (83.4)	2.1% (-4.5%, 8.8%)
Eradication	195 (85.5)	191 (83.4)	
Presumed Eradication			
Unsatisfactory	33 (14.5)	38 (16.6)	
Persistence	28 (12.3)	32 (14.0)	
Presumed Persistence	5 (2.1)	6 (2.6)	
Indeterminate	-	-	

Table 8: Bacteriological Outcome at the LPT Visit

	Number of subjects (%)							
	Study 302				Study 301			
	PPb[a]		mITT [b][b]		PPb[a]		mITT [b][b]	
Bacteriological outcome/ Bacteriological response	**APC-111 (10 Days)**	**Pen VK (10 Days)**	**APC-111 (10 Days)**	**Pen VK (10 Days)**	**APC-111 (7 Days)**	**Pen VK (10 Days)**	**APC-111 (7 Days)**	**Pen VK (10 Days)**
N	219	217	256	264	165	177		
Satisfactory	169 (77.2%)	164 (75.6%)	179 (69.9%)	179 (67.8%)	118 (71.5)	141 (79.7)		
Eradication	169 (77.2%)	164 (75.6%)	175 (68.4%)	175 (66.3%)	118 (71.5)	141 (79.7)		
Presumed Eradication	-	-	4 (1.6%)	4 (1.5%)				
Unsatisfactory	50 (22.8%)	53 (24.4%)	77 (30.1%)	85 (32.2%)	47 (28.5)	36 (20.3)		
Unsatisfactory at TOC[c]	34 (15.5%)	38 (17.5%)	45 (17.6%)	57 (21.6%)	37 (22.4)	21 (11.9)		
Persistence	29 (13.2%)	32 (14.7%)	29 (11.3%)	37 (14.0%)				
Presumed Persistence	5 (2.3%)	6 (2.8%)	7 (2.7%)	8 (3.0%)				
Indeterminate	-	-	9 (3.5%)	12 (4.5%)				
Satisfactory at TOC with secondary failure at LPT	16 (7.3%)	15 (6.9%)	32 (12.5%)	28 (10.6%)	10 (6.1)	15 (8.5)		
Carrier/Re-colonization	2 (0.9%)	7 (3.2%)	4 (1.6%)	8 (3.0%)	6 (3.6)	5 (2.8)		
Recurrence	1 (0.5%)	1 (0.5%)	2 (0.8%)	1 (0.4%)	0 (0.0)	2 (1.1)		
Presumed Recurrence	11 (5.0%)	6 (2.8%)	13 (5.1%)	8 (3.0%)	4 (2.4)	8 (4.5)		
Reinfection	2 (0.9%)	1 (0.5%)	2 (0.8%)	1 (0.4%)				
Indeterminate	-	-	11 (4.3%)	10 (3.8%)				
Comparison								
Difference (95% CI) [d]	1.6 (-6.4, 9.6)		2.1 (-5.8, 10.1)		-8.1 (-17.2, 0.9)			

[a] The PPb population consisted of all subjects with a positive baseline visit throat swab for *S. pyogenes*, an evaluable throat swab at TOC or were clinical failures who withdrew early from the study and started a new antimicrobial for the treatment of tonsillitis and/or pharyngitis, and had no major protocol violations.
[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 as unsatisfactory bacteriological outcome.
[c] Subject 0466-3001 had a bacteriological response of persistence at TOC (PPb population) and indeterminate at LPT (mITT [b] population).
[d] Comparison between treatment groups: asymptotic point estimate and 95% confidence interval for the difference in satisfactory bacteriological outcome rates.
[e] Difference between treatment groups: calculated as (APC-111 – penicillin). Two-sided 95% confidence interval.
Data source: Tables 2.7.3-14 & 15 in Sponsor's m5\clincstat\clinsum.pdf.

Table 9: Clinical Outcome at the TOC Visit

	Number of Subjects (%)							
	Study 302				Study 301			
	PPb[a]		mITT [b][b]		PPb[a]		mITT [b][b]	
Bacteriological outcome/ Bacteriological response	APC-111 (10 Days)	Pen VK (10 Days)	APC-111 (10 Days)	Pen VK (10 Days)	APC-111 (7 Days)	Pen VK (10 Days)	APC-111 (7 Days)	Pen VK (10 Days)
N	233	229	256	264	171	182	192	203
Success	213 (91.4)	212 (92.6)	226 (88.3)	228 (86.4)	149 (87.1)	168 (92.3)	155 (80.7)	177 (87.2)
Clinical cure	213 (91.4)	212 (92.6)	226 (88.3)	228 (86.4)	149 (87.1)	168 (92.3)	155 (80.7)	177 (87.2)
Non-Success	20 (9.6)	17 (7.4)	30 (11.7)	36 (13.6)	22 (12.9)	14 (7.7)	37 (19.3)	26 (12.8)
Clinical Failure	18 (7.7)	15 (6.6)	20 (7.8)	21 (8.0)	13 (7.6)	9 (4.9)	19 (9.9)	10 (4.9)
Unable to Evaluate	2 (0.9)	2 (0.9)	8 (3.1)	10 (3.8)				
Indeterminate					9 (5.3)	5 (2.7)	11 (5.7)	7 (3.4)
Missing	-	-	2 (0.8)	5 (1.9)	-	-	7 (3.6)	9 (4.4)
Comparison[c]								
Difference (95% CI)	-1.2 (-6.1, 3.8)		1.9 (-3.8, 7.6)		-5.2% (-11.5, 1.2)		-6.5% (-13.7, 0.8)	

Data source: Tables 14.2.1/5 in Sponsor's clinical study reports of study 302 and Tables 5-7 & 5-9 in clinical study report addendum of study 301.

Table 9: Clinical Outcome at the TOC Visit (continued) (PPc Population)

	Number of Subjects (%)			
	Study 302		Study 301	
Bacteriological outcome/ Bacteriological response	APC-111 (10 Days)	Pen VK (10 Days)	APC-111 (7 Days)	Pen VK (10 Days)
N	280	263	218	227
Success	257 (91.8)	246 (93.5)	186 (85.3)	211 (93.0)
Clinical cure	257 (91.8)	246 (93.5)	186 (85.3)	211 (93.0)
Non-Success	23 (8.2)	17 (6.5)	32 (14.7)	16 (7.0)
Clinical Failure	20 (7.1)	15 (5.7)	17 (7.8)	10 (4.4)
Unable to Evaluate	3 (1.1)	2 (0.8)		
Indeterminate			15 (6.9)	6 (2.6)
Comparison between APC-111 and Pen VK				
Difference (95% CI)	-1.8 (-6.1, 2.6)		-7.6% (-13.4, -1.9)	

Data source: Tables 2.7.3-16-17 in Sponsor's m5\clinistat\clinisum.pdf.

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Table 10: Clinical Outcome at the LPT Visit (PPc Population)

	Number of Subjects (%)			
	Study 302		Study 301	
Bacteriological outcome/ Bacteriological response	APC-111 (10 Days)	Pen VK (10 Days)	APC-111 (7 Days)	Pen VK (10 Days)
N	280	263	218	227
Success	222 (79.3)	216 (82.2)	168 (77.1)	189 (83.3)
Clinical cure	222 (79.3)	216 (82.2)	168 (77.1)	189 (83.3)
Non-Success	58 (20.7)	47 (17.9)	50 (22.9)	38 (16.7)
Clinical Failure	42 (15.0)	33 (12.5)	36 (16.5)	23 (10.1)
Unable to Evaluate	10 (3.6)	8 (3.0)		
Indeterminate			9 (4.1)	7 (3.1)
Missing	6 (2.1)	6 (2.3)	5 (2.3)	8 (3.5)
Comparison between APC-111 and Pen VK				
Difference (95% CI)	-2.8 (-9.5, 3.8)		-6.2% (-13.6, 1.2)	

Data source: Tables 2.7.3-18 * 19 in Sponsor's m5\clinistat\clinisum.pdf.

3.2 Evaluation of Safety

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor has performed subgroup analyses for the primary efficacy endpoint to assess the consistency of treatment effects across demographic and current infection characteristics (see Tables 11-12 for study 302). In general, the rate of satisfactory bacteriological outcome at the TOC visit across demographic characteristics and current infection characteristics was consistent with results for the primary efficacy population.

Table 11: Satisfactory Bacteriological Outcome at the TOC Visit by Demographic Subgroup in Protocol 111.302 – PPb Population[a]

	Number (%) of Subjects					
	APC-111 (N = 233)		Penicillin VK (N = 229)		Comparison[b]	
Demographic subgroup	**N**	**Satisfactory**	**N**	**Satisfactory**	**Difference (%)[c]**	**95% CI[d]**
Gender						
Female	137	116 (84.7)	145	123 (84.8)	-0.2	-8.6, 8.2
Male	96	82 (85.4)	84	68 (81.0)	4.5	-6.5,15.4
Age group						
12 to <19 years	47	40 (85.1)	47	37 (78.7)	6.4	-9.1, 21.9
19 to <30 years	61	53 (86.9)	79	65 (82.3)	4.6	-7.3, 16.6
30 to <40 years	81	63 (77.8)	57	47 (82.5)	-4.7	-18.1, 8.7
≥40 years	44	42 (95.5)	46	42 (91.3)	4.2	-6.1, 14.4
Race						
Caucasian	212	180 (84.9)	215	179 (83.3)		
African American	10	9 (90.0)	5	4 (80.0)		
Asian/Oriental	6	4 (66.7)	4	3 (75.0)		
American Indian / Alaska Native	0	0 (0.0)	1	1 (100.0)		
Other	5	5 (100.0)	4	4 (100.0)		
Ethnicity						
Hispanic	12	10 (83.3)	10	6 (60.0)		
Non-Hispanic	221	188 (85.1)	219	185 (84.5)		
Weight						
<40 kg	3	2 (66.7)	3	3 (100.0)		
40 to <80 kg	124	105 (84.7)	136	114 (83.8)	0.9	-8.0, 9.7
80 to <120 kg	93	80 (86.0)	84	70 (83.3)	2.7	-8.0, 13.3
120 to <160 kg	12	10 (83.3)	6	4 (66.7)		
≥160 kg	1	1 (100.0)	0	0 (0.0)		

[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] Comparison between treatment groups: asymptotic point estimate and 95% confidence interval for the difference in satisfactory bacteriological outcome rates.
[c] Difference between treatment groups: calculated as (APC-111 – penicillin).
[d] Two-sided 95% confidence interval.

Data source: Sponsor's Table 2.7 3-23 in m5\clincstat\clinsum.pdf.

Table 12: Satisfactory Bacteriological Outcome at the TOC Visit by Characteristics of Current Infection and Key Factors in Protocol 111.302 – PPb Population[a]

		Number (%) of subjects						
		APC-111 (N = 233)		Penicillin VK (N = 229)			Comparison[b]	
Characteristics of current infection and key factors		**N**	**Satisfactory**	**N**	**Satisfactory**		**Difference (%)[c]**	**95% CI[d]**
Previous antimicrobial within 30 days:								
Yes		2	2 (100.0)	2	0	(0.0)		
No		231	196 (84.8)	227	191	(84.1)	0.7	-5.9, 7.3
Number of tonsillitis/pharyngitis episodes within 36 months:								
0		194	164 (84.5)	170	139	(81.8)	2.8	-4.9, 10.5
1		24	21 (87.5)	42	38	(90.5)	-3.0	-18.9,13.0
2		13	11 (84.6)	10	7	(70.0)		
3		2	2 (100.0)	5	5	(100.0)		
4		0	0 (0.0)	1	1	(100.0)		
>4		0	0 (0.0)	1	1	(100.0)		
Signs and symptoms (Absent/Present):								
Sore throat	absent	0	0 (0.0)	0	0	(0.0)		
	present	233	198 (85.0)	229	191	(83.4)	1.6	-5.1, 8.2
Odynophagia	absent	3	3 (100.0)	5	4	(80.0)		
	present	230	195 (84.8)	224	187	(83.5)	1.3	-5.4, 8.0
Fever	absent	152	126 (82.9)	144	120	(83.3)	-0.4	-9.0, 8.1
	present	81	72 (88.9)	85	71	(83.5)	5.4	-5.1, 15.8
History of fever[e]	absent	87	71 (81.6)	77	59	(76.6)	5.0	-7.5, 17.5
	present	146	127 (87.0)	152	132	(86.8)	0.1	-7.5, 7.8

[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 or died due to tonsillitis and/or pharyngitis.
[b] Comparison between treatment groups: asymptotic point estimate and 95% confidence interval for the difference in satisfactory bacteriological outcome rates.
[c] Difference between treatment groups: calculated as (APC-111 – penicillin).
[d] Two-sided 95% confidence interval.
[e] History of fever: 24-48 hours from onset of symptoms.
Data source: Sponsor's Table 2.7 3-24 in m5\clincstat\clinsum.pdf.

Table 13: Satisfactory Bacteriological Outcome at the TOC Visit by Characteristics of Current Infection and Key Factors in Protocol 111.302 PPb Population[a] (Continued)

Characteristics of current infection and key factors		Number (%) of subjects: APC-111 (N = 233) N	APC-111 (N = 233) Satisfactory	Penicillin VK (N = 229) N	Penicillin VK (N = 229) Satisfactory	Comparison[b] Difference (%)[c]	Comparison[b] 95% CI[d]
Chills	absent	64	53 (82.8)	64	50 (78.1)	4.7	-9.0, 18.4
	present	169	145 (85.8)	165	141 (85.5)	0.3	-7.2, 7.9
Strawberry tongue	missing	0	0 (0.0)	1	0 (0.0)		
	absent	183	156 (85.2)	188	156 (83.0)	2.3	-5.2, 9.7
	present	50	42 (84.0)	40	35 (87.5)	-3.5	-17.9, 10.9
Uvular edema	absent	69	60 (87.0)	71	57 (80.3)	6.7	-5.5, 18.9
	present	164	138 (84.1)	158	134 (84.8)	-0.7	-8.6, 7.2
Pharyngeal erythema	absent	0	0 (0.0)	1	1 (100.0)		
	present	233	198 (85.0)	228	190 (83.3)	-1.6	-5.0, 8.3
Pharyngeal exudates	absent	98	84 (85.7)	95	75 (78.9)	6.8	-4.0, 17.5
	present	135	114 (84.4)	134	116 (86.6)	-2.1	-10.5, 6.3
Adenopathy of head and neck	absent	19	15 (78.9)	18	13 (72.2)	6.7	-20.9, 34.4
	present	214	183 (85.5)	211	178 (84.4)	1.2	-5.6, 8.0
Tender lymph nodes	absent	23	20 (87.0)	26	22 (84.6)	2.3	-17.2, 21.9
	present	210	178 (84.8)	203	169 (83.3)	1.5	-5.6, 8.6

[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 or died due to tonsillitis and/or pharyngitis.
[b] Comparison between treatment groups: asymptotic point estimate and 95% confidence interval for the difference in satisfactory bacteriological outcome rates.
[c] Difference between treatment groups: calculated as (APC-111 – penicillin).
[d] Two-sided 95% confidence interval.
[e] History of fever: 24-48 hours from onset of symptoms
Data source: Sponsor's Table 2.7 3-24 in m5\clincstat\clinsum.pdf.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no major statistical issues identified in this review.

The primary efficacy analysis consisted of testing the hypothesis of non-inferiority of the APC-111 treatment to the penicillin treatment based on the percentage of subjects with a satisfactory bacteriological outcome at the TOC visit in each treatment group. A non-inferiority margin of 10% was used in the non-inferiority testing. The treatment group differences in satisfactory bacteriological outcome rates were compared by calculating the point estimate and its asymptotic two-sided 95% confidence intervals for the difference in the satisfactory bacteriological outcome rates. If the lower confidence bound was greater than -10%, the APC-111 treatment was considered non-inferior to the penicillin treatment. The unadjusted analysis was performed using the mITT[b] and PPb co-primary populations, and was regarded as the primary efficacy analysis.

Justification of non-inferiority margin of 10%

As presented at the FDA anti-infective drugs advisory committee meeting in February 2002, an adequate non-inferiority margin should be the minimum of M1 and M2. Here M1 represents conservative estimate for the treatment effect of the active control over placebo and M2 represents the largest clinically acceptable difference between the test drug and the active control.

Estimate of M1 (penicillin treatment effect over placebo)

In order to evaluate the bacteriological effect of the penicillin treatment over placebo (M1) in the setting of APC-111 studies 301 and 302, the FDA medical team leader Dr. John Alexander has done a thorough literature search. Two lists from this search were provided: one for studies published before 1957 in Index Medicus (see Appendix 1) and one for studies obtained from PubMed (see Appendix 2).

The majority of these studies from the first list (based on Index Medicus) demonstrated that penicillin treatment was effective in preventing and treating Group A streptococcal pharyngitis. It was difficult from these studies, however, to extrapolate the treatment effect of penicillin over placebo in the setting of APC-111 studies 301 and 302 due to the dissimilarity in the study design parameters such as study population, endpoint definition, and treatment regimen.

The studies from the second list (based on PubMed) compared the treatment effect of penicillin with other antibiotics, or compared different doses/frequencies/duration of penicillin. These studies reported that longer treatment duration of penicillin was associated with better bacteriological outcome. The oral penicillin treatment of 7 days or longer yielded a bacteriological eradication rate of 70% to 100%. The majority of these studies, however, were not placebo-controlled studies. From this list three placebo-

controlled trials were identified that had at least one post-baseline bacteriological outcome measured. These studies are:

1. Krober MS et al., Streptococcal pharyngitis. Placebo-controlled double-blind evaluation of clinical response to penicillin therapy. JAMA. 1985 Mar 1; 253(9):1271-4.

2. Dagnelie CF et al., Do patients with sore throat benefit from penicillin? A randomized double-blind placebo-controlled clinical trial with penicillin V in general practice. Br J Gen Pract. 1996 Oct; 46(411):589-93.

3. Zwart S et al., Penicillin for acute sore throat: randomised double blind trial of seven days versus three days treatment or placebo in adults. BMJ. 2000 Jan 15; 320(7228):150-4.

Krober's paper studied the clinical response to 3-day penicillin V therapy (250 mg three times daily) compared with placebo in children with symptomatic pharyngitis and throat cultures positive for group A beta-hemolytic streptococci (GABHA). The bacteriological outcome at 24, 48, and 72 hours after randomization was measured in this study. The results related to the bacteriological outcome were reported as follows:

> "Of the 26 culture-positive patients, all 11 in the penicillin-treated group had negative throat cultures at 24, 48, and 72 hours. Nearly all of the throat cultures taken at these time intervals from the 15 patients who had taken the placebo remained culture positive for GABHS."

The results from Krober's paper demonstrated that the 3-day penicillin V therapy was very effective in eradicating GABHS compared with placebo. However, given the difference in the duration of the penicillin treatment (3 days in Krober's study vs. 10 days in APC-111 studies 301 and 302) and the timing at which the bacteriological outcome was measured (≤3 days in Krober's study vs. 14-18 days in APC-111 studies 301 and 302), the results from this study were not directly used to extrapolate the penicillin treatment effect in APC-11 studies 301 and 302.

Dagnelie's paper assessed the efficacy of 10-day penicillin V on the clinical course and bacteriological response. The bacteriological outcome at day 2 after randomization was measured in this study. Again, this study demonstrated that the penicillin treatment was very effective in eradicating GABHS compared with placebo. The bacteriological eradication rate was 75% (41/55) for penicillin and 4% (2/56) for placebo. The point estimate for the difference in the bacteriological eradication rates at day 2 between the 10-day penicillin and placebo treatments was 70% with a 95% CI of (58%, 84%). These results indicated that the bacteriological eradication rate at day 2 with 10-day penicillin treatment was 58% higher compared with placebo.

This study didn't collect bacteriological outcome data after day 2 post-randomization. Could the difference in the bacteriological eradication rate at the end of the 10-day treatment between the penicillin and placebo groups be as good as the one observed on

day 2 during therapy? The statistical reviewer could not conclude this. If this can be concluded, then one could use 58% as an estimate for the penicillin treatment effect over placebo in APC-11 studies 301 and 302.

Zwart's paper evaluated the effectiveness of two penicillin treatment regimens compared with placebo in patients (aged 15-60 years) with sore throat and other pharyngitis symptoms. The study treatment groups were: (1) placebo for 7 days; (2) two 250 mg capsules of penicillin V three times daily for 3 days followed by placebo for 4 days; (3) two 250 mg capsules of penicillin V three times daily for 7 days. The bacteriological eradication rate at day 14 after randomization was 7% (5/70) for the placebo treatment, 41% (36/87) for the 3-day penicillin treatment, and 72% (57/79) for the 7-day penicillin treatment. Thus, the point estimate for the difference in the bacteriological eradication rates between the 7-day penicillin treatment and the placebo treatment was 65% with an asymptotic 95% CI of (53%, 77%). Consequently, a reasonable estimate for the bacterial eradication rate of 7-day penicillin treatment could be 53% higher than placebo.

It is noted that the duration of the penicillin treatment was 7 days in Zwart's study. If a 10-day regimen had been used, one could likely obtain a similar or even better bacteriological outcome at day 14 as demonstrated in a paper by Schwartz 1981 (Appendix 2). In addition, as mentioned above, the results from the other two placebo-controlled studies were also supportive of the results from Zwart's study. Thus it is reasonable to use 53% as an estimate for M1 (the treatment effect of bacteriological eradication at day 14 for a 10-day penicillin treatment compared with placebo).

It is also noted that one could obtain a more conservative estimate for M1 when taking into account for potential uncertainties with respect to constancy of the control effect, heterogeneity in the patient population and trial to trial variability.

Selection of an appropriate non-inferiority margin

If an estimate of 53% for the bacteriological effect of penicillin over placebo (M1) is used, and if 10% is the largest clinical acceptable difference between the test drug and penicillin (M2), then a non-inferiority margin of 10% is acceptable for AP-111 studies 301 and 302.

The sponsor's rationale for the selection of the non-inferiority margin of 10% was based on the results presented in Zwart's paper.

Sensitivity Analyses of Primary Efficacy Endpoint

The primary efficacy analysis for the primary efficacy endpoint was performed in the mITT[b] and PPb populations. To examine the sensitivity of the primary efficacy results in study 302, the statistical reviewer has performed an analysis for the primary efficacy endpoint in the PPb1 population in the same manner as the sponsor did in the mITT[b] and PPb populations.

According to the sponsor's SAP, the PPb1 population was determined prior to study unblinding and included all mITT subjects who had no major study protocol violations, including compliance with blinded study medications. The PPb population was determined after study unblinding, based on compliance with the actual study medication received. The only difference between the PPb and PPb1 populations was related to the determination of study medication compliance after unblinding and before unblinding. A subject who was non-compliant with placebo medication but compliant with active study medication could be included in the PPb population, if otherwise valid.

The results of this sensitivity analysis were consistent with the findings observed in the mITT[b] and PPb populations.

5.2 Conclusions and Recommendations

In this NDA submission the sponsor, under the provisions specified in the Federal Food, Drug and Cosmetic Act, Section 505(b) (2), seeks approval of a once-a-day, pulsatile-release, multiparticulate tablet formulation of amoxicillin, APC-111 MP Tablet, 775 mg for a 10-day regimen for the treatment of tonsillitis and/or pharyngitis (b) (4) to *Streptococcus pyogenes* (*S. pyogenes*) in adolescents and adults.

This submission included data from two pivotal studies (studies 301 and 302) in patients with acute streptococcal tonsillitis and/or pharyngitis. Both studies were randomized, double blind, double-dummy, multi-center, and non-inferiority trials with penicillin VK 250 mg PO QID for 10 days as the active comparator. The primary efficacy endpoint was the bacteriological outcome at the Test-of-Cure (TOC) visit (day 14-18). A 10% of non-inferiority margin was used.

Study 301 failed to demonstrate the non-inferiority of APC-111 775 mg QD for 7 days compared with penicillin VK 250 mg QID for 10 days in terms of the rate of the satisfactory bacteriological outcome at TOC.

Study 302 demonstrated the non-inferiority of APC-111 775 mg QD for 10 days compared with penicillin VK 250 mg QID for 10 days in terms of the rate of the satisfactory bacteriological outcome at TOC. This study demonstrated that the 10-day APC-111 775 mg QD regimen was effective for the treatment of tonsillitis and/or pharyngitis due to *S. pyogenes* in adolescents and adults.

Based on existing supportive evidence of efficacy of amoxicillin and the efficacy results observed in the current NDA submission, it is recommended that this NDA receive an approval action.

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Appendix 1: Index Medicus List of Group A Streptococcus/Penicillin References (Studies from before 1957)

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Appendix 2: PubMed List of Refences

Search of articles for Group A Streptococcus and penicillin, limited to English language articles of clinical trials

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   J Infect Dis. 1978 May;137 Suppl:S133-S138.
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   JAMA. 1979 Apr 13;241(15):1589-94.
   PMID: 372593 [PubMed - indexed for MEDLINE]

3. Bass JW et al., Streptococcal pharyngitis in children. A comparison of four treatment schedules with intramuscular penicillin G benzathine.
   JAMA. 1976 Mar 15;235(11):1112-6.
   PMID: 765515 [PubMed - indexed for MEDLINE]

Four treatment regimens of benzathine penicillin +/- procaine penicillin given as a single dose.

4. Randolph MF et al., Streptococcal pharyngitis: posttreatment carrier prevalence and clinical relapse in children treated with clindamycin palmitate or phenoxymethyl penicillin.
   Clin Pediatr (Phila). 1975 Feb;14(2):119-22. No abstract available.
   PMID: 803421 [PubMed - indexed for MEDLINE]

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   PMID: 1428189 [PubMed - indexed for MEDLINE]

6. Schrock CG, Clarithromycin vs penicillin in the treatment of streptococcal pharyngitis.
   J Fam Pract. 1992 Dec;35(6):622-6.
   PMID: 1453146 [PubMed - indexed for MEDLINE]

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   Pediatr Infect Dis J. 1992 Aug;11(8 Suppl):S20-6.
   PMID: 1513608 [PubMed - indexed for MEDLINE]

8. Ramet J et al., Comparative study of cefetamet pivoxil and penicillin V in the treatment of group A beta-hemolytic streptococcal pharyngitis.
   Chemotherapy. 1992;38 Suppl 2:33-7.
   PMID: 1516463 [PubMed - indexed for MEDLINE]

9. Mc Carty J et al., Loracarbef versus penicillin VK in the treatment of streptococcal pharyngitis and tonsillitis in adults.
   Clin Ther. 1992 Jan-Feb;14(1):30-40.
   PMID: 1576624 [PubMed - indexed for MEDLINE]

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Am J Med. 1992 Jun 22;92(6A):74S-79S.
PMID: 1621750 [PubMed - indexed for MEDLINE]

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Scand J Infect Dis. 1991;23(5):553-8.
PMID: 1767251 [PubMed - indexed for MEDLINE]

Phenoxymethyl penicillin was given 2 or 3 times daily for 7 days.

12. Levenstein JH, Clarithromycin versus penicillin in the treatment of streptococcal pharyngitis.
J Antimicrob Chemother. 1991 Feb;27 Suppl A:67-74.
PMID: 1827104 [PubMed - indexed for MEDLINE]

13. Bachrand RT Jr., A comparative study of clarithromycin and penicillin VK in the treatment of outpatients with streptococcal pharyngitis.
J Antimicrob Chemother. 1991 Feb;27 Suppl A:75-82.
PMID: 1827105 [PubMed - indexed for MEDLINE]

14. Pichichero ME et al., A comparison of cephalosporins and penicillins in the treatment of group A beta-hemolytic streptococcal pharyngitis: a meta-analysis supporting the concept of microbial copathogenicity.
Pediatr Infect Dis J. 1991 Apr;10(4):275-81.
PMID: 1829514 [PubMed - indexed for MEDLINE]

15. Stein GE et al., Comparative study of clarithromycin and penicillin V in the treatment of streptococcal pharyngitis.
Eur J Clin Microbiol Infect Dis. 1991 Nov;10(11):949-53.
PMID: 1838978 [PubMed - indexed for MEDLINE]

16. el-Daher NT et al., Immediate vs. delayed treatment of group A beta-hemolytic streptococcal pharyngitis with penicillin V.
Pediatr Infect Dis J. 1991 Feb;10(2):126-30.
PMID: 1905799 [PubMed - indexed for MEDLINE]

Placebo trial (Placebo given for 48-52 hours)

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PMID: 1945599 [PubMed - indexed for MEDLINE]

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PMID: 1990041 [PubMed - indexed for MEDLINE]

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PMID: 2052057 [PubMed - indexed for MEDLINE]

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PMID: 2124962 [PubMed - indexed for MEDLINE]

Penicillin given at same total daily dose, but varying frequency (1000 mg once daily, 500 mg twice daily, or 250 mg four times daily)

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Eur J Clin Microbiol Infect Dis. 1989 Apr;8(4):282-8.
PMID: 2496998 [PubMed - indexed for MEDLINE]

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Arch Otolaryngol Head Neck Surg. 1989 Jul;115(7):856-9.
PMID: 2500139 [PubMed - indexed for MEDLINE]

24. Brook I, Treatment of patients with acute recurrent tonsillitis due to group A beta-haemolytic streptococci: a prospective randomized study comparing penicillin and amoxycillin/clavulanate potassium.
J Antimicrob Chemother. 1989 Aug;24(2):227-33.
PMID: 2676941 [PubMed - indexed for MEDLINE]

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J Pediatr. 1988 Dec;113(6):1089-94.
PMID: 3057159 [PubMed - indexed for MEDLINE]

Placebo trial (Placebo given for 48 hours – followed by antibiotic treatment of GAS positive patients)

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Pediatr Infect Dis. 1986 Nov-Dec;5(6):649-54.
PMID: 3099268 [PubMed - indexed for MEDLINE]

27. Gerber MA et al., Five vs ten days of penicillin V therapy for streptococcal pharyngitis.
Am J Dis Child. 1987 Feb;141(2):224-7.
PMID: 3101484 [PubMed - indexed for MEDLINE]

Difference in bacteriological outcome for 5 vs. 10 days of PCN reported

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J Pediatr. 1987 May;110(5):777-82.
PMID: 3106607 [PubMed - indexed for MEDLINE]

Evaluation of penicillin tolerance as a factor in bacteriological persistence of GAS in penicillin treatment failures. Dicloxacillin was more effective than penicillin in eliminating GAS in patients who had already failed treatment with 10 days of penicillin.

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Clin Pediatr (Phila). 1987 Sep;26(9):453-8.
PMID: 3113804 [PubMed - indexed for MEDLINE]

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Scand J Infect Dis. 1988;20(1):37-46.
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J Pediatr. 1988 Aug;113(2):400-3. No abstract available.
PMID: 3135377 [PubMed - indexed for MEDLINE]

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Pediatr Infect Dis J. 1987 Jul;6(7):635-43.
PMID: 3302916 [PubMed - indexed for MEDLINE]

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J Pediatr. 1987 May;110(5):783-7.
PMID: 3553513 [PubMed - indexed for MEDLINE]

35. Brook I et al., Treatment of patients with a history of recurrent tonsillitis due to group A beta-hemolytic streptococci. A prospective randomized study comparing penicillin, erythromycin, and clindamycin.
Clin Pediatr (Phila). 1985 Jun;24(6):331-6.
PMID: 3888491 [PubMed - indexed for MEDLINE]

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J Pediatr. 1985 Jun;106(6):876-80.
PMID: 3889257 [PubMed - indexed for MEDLINE]

37. Kaplan EL, Benzathine penicillin G for treatment of group A streptococcal pharyngitis: a reappraisal in 1985.
Pediatr Infect Dis. 1985 Sep-Oct;4(5):592-6. No abstract available.
PMID: 3900950 [PubMed - indexed for MEDLINE]

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JAMA. 1985 Mar 1;253(9):1271-4.
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Am J Dis Child. 1974 Oct;128(4):457-60. No abstract available.
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Am J Dis Child. 1969 Jun;117(6):663-7. No abstract available.
PMID: 4890507 [PubMed - indexed for MEDLINE]

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J Hyg (Lond). 1971 Sep;69(3):355-60. No abstract available.
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