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)

1956 (Vol. 59-60)

1. D Gobesso & F Spera, "Tonsillopathy; rheumatic disease and phenoxymethyl penicillin; preliminary report" Clin. Pediat. 38:361-366 May 1956
2. BB Breese & FA Disney "penicillin V (phenoxymethyl penicillin) treatment of beta-hemolytic streptococcal infections in children" A.M.A.J.Dis.Child. 92:20-23 July 1956
3. LD Asay & GL Hartman "Therapy of acute purulent otitis media and purulent tonsillitis with dibenzylenediamine dipenicillin G (benzathine penicillin)" J. Pediat. 49:565-566 November 1956
4. PB Peacock "In Seskatchewan health region (including special reference to use of penicillin in streptococcal infections)" Canad. J. Pub. Health 46:486-496 December 1955
5. AM Diehl, TR Hamilton, & JS May "prevention of recurrent rheumatic fever: use of repository benzathine penicillin G" South. M.J. 49:250-259 March 1956
6. TJ Brooks Jr. &TI Moe "Use of benzathine penicillin G in carriers of group A beta-hemolytic streptococci" JAMA 160:162-165 January 21, 1956
7. DN Mohler, DG Wallin, EG Dreyfus, & HJ Bakst "home treatment of streptococcal disease; comparison of efficacy of oral administration of penicillin and intramuscular injection of benzathine penicillin in treatment of pharyngitis" New England J. Med. 254:45-50 January 12, 1956
8. H Hartenstein & HA Feldman "treatment of children with acute pharyngitis with single penicillin dose" J.Pediat. 48:318-322 March 1956
9. PAL Chapple et al. "treatment of acute sore throat in general practice; therapeutic trial, with observations on symptoms and bacteriology" Brit.M.J. 1:705-708 March 31, 1956

1955 (Vol. 57-58)

8. C Moore, CD Gibson Jr &LC Lindemann "comparison of intramuscular benzathine penicillin and oral sulfonamide in control of recurrences" J. Pediat. 47:450-460 October 1955
9. TB Hill "treatment (penicillin of streptococcal carrier state in a rural school" AMA J Dis Child 90:280-282 September 1955
10. M Markowitz & W Hemphill "comparison of oral benzathine penicillin G and ssulfonamidesfor prevention of streptococcal infections and recurrences of rheumatic fever" Pediatrics 15:509-514 May 1955
11. JR Seal "oral penicillin prophylaxis of streptococcal infections" Am J Pub Health 45:662-672 May (Part 1) 1955
12. GH Stollerman, JH Rusoff, & I Hirschfeld "prophylaxis against group A streptococci in rheumatic fever; use of single monthly injections of benzathine penicillin G" New England J Med 252:787-792 May 12, 1955
13. RA Tidwell "single approach (using benzathine penicillin) to streptococcic prophylaxis" Northwest Med. 54: 467-471 May 1955
14. RL Chancey et al. "prophylaxis; comparison of oral penicillin and benzathine penicillin" Am J M Sc 229:165-171 February 1955
15. BB Breese and FA Disney "successful treatment of beta hemolytic streptococcal infections inchildren with single injection of repository penicillin (benzathine penicillin G)" Pediatrics 15:516-520 May 1955

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16. R Chamovitz, FJ Catanzaro, CA Stetson, & CH Rammelkamp Jr. Rheum fever prevention "by treatment of previous streptococcal infections; evaluation of penicillin G" New England J Med 251:466-471 September 16, 1954
17. CB Perry & WA Gillespie "intramuscular benzathine penicillin in prophylaxis of streptococcal infection in rheumatic children" Brit Med J 2:729-730 September 25, 1954

18. AM Diehl, TR Hamilton, IC Keeling, & JS May “long acting repository penicillin (benzathine ppenicillin G) in prophylaxis of recurrent rheumatic fever” JAMA 155:1466-1470 August 21, 1954
19. LA Scuro & L Ortona “use of dibenzylethylenediamine penicillin in prophylaxis of streptococcic infection in rheumatic disease” Minerva Med 1:1835-1839 June 27, 1954
20. JR Seal, WJ Mogabgab, GJ Friou, & JE Banta “penicillin prophylaxis of epidemic streptococcal infections; effects of small and large doses of oral penicillin on epidemic streptococcal infection s and on carriers of group A streptococci” J Lab & Clin Med 44:831-859 December 1954
21. JR Seal, WJ Mogabgab, GJ Friou, & JE Banta “penicillin prophylaxis of epidemic streptococcal infections; epidemic and effects ofprophylaxis on clinical manifestations of acute streptococcal and nonstreptococcal respiratory infections” J Lab & Clin Med 44:727-753 November 1954
22. CZ Berry & J Ferber “reactions to penicillin administered orally form as prophylaxis” US Armed Forces MJ 5:1137-1149 August 1954
23. SH Bernstein et al. “observations in air force recruits of streptococcal diseases and their control withorally administered penicillin” J Lab & Clin Med 44:1-13 July 1954
24. RA Tidwell “control of streptococcal upper respiratory infection (with special reference to benzathine penicillin) in cardiac andrheumatic fever patients and their siblings: preliminary report” Northwest Med 53:470-476 May 1954
25. HL Drezner “current concepts (with special reference to treating streptococcal infections with penicillin” J M Soc. New Jersey 50: 538-541 December 1953
26. E Craige Rheum Fever “prevention (special reference to penicillin therapy of streptococcic infections)” North Carolina M J 14:593-596 December 1953
27. SH Bernstein, HA Feldman, OF Harper Jr, & WH Klingensmith Streptococci, infections “mass oral penicillin prophylaxis in control” AMA Arch Int Med 93:894-898 June 1954
28. HA Feldman, SH Bernstein, & HB Williams “treatment of acute streptococcic infection with penicillin (panbiotic, penicillin preparation)” JAMA 155:109-111 May 8, 1954; correction in 155:660 June 12, 1954

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29. AG Kuttner “prevention (by use of sulfonamides and penicillin) of rheumatic fever and rheumatic heart disease” Postgrad Med 14:429-432 November 1953
30. LW Wannamaker et al, “effect of penicillin prophylaxis on carrier state” New England J Med 249:1-7 July 2, 1953
31. MA Smith “community program for prevention of recurrence (with special reference to penicillin)” Pub. Health Rep. 68:16-19 January 1953
32. Committee on prevention of Rheumatic Fever appointed by Council on Rheumatic Fever and Congenital Heart Disease of American Heart Association “Prevention of Rheumatic Fever Lancet 1:285-286 February 7, 1953 (?also in JAMA 151:141-143 January 10, 1953
33. KH Kohn, A Milzer, & H MacLean “prophylaxis of recurrences with penicillin given orally; final report of 5 year study” JAMA 151:347-351 January 31, 1953
34. B Feinberg “sulfonamides and penicillin in control of children” Rhode Island M J 36:138-140 March 1953
35. E Roberts “use of sulfonamides and penicillin to prevent recurrence; 12 year study” AMA Am J Dis. Child 85: 643-647 June 1953
36. FW Denny Jr, LW Wannamaker, & EO Hahn “comparative effects of penicillin, aureomycin, and terramycin on streptococcal tonsillitis and pharyngitis” Pediatrics 11:7-13 January 1953
37. H Eagle, R Fleischman & M Levy ‘“continuous” vs. “discontinuous” therapy with penicillin; effect of interval between injections on therapeutic efficacy’ New England J Med 248:481-488 March 19, 1953
38. BB Breese “treatment of beta-hemolytic streptococcic infections in home; relative value of available methods (with special regard to benzylethylenediamine penicillin)” JAMA 152:10-14 May 2, 1953
39. L Finberg, L Leventer, & A Tramer “treatment of pneumococcus pneumonia and B hemolytic streptococcus infections with oral penicillin suspension” Antibiotics & Chemother. 3:353-356 April 1953

40. HM Gezon, JS Cook Jr, RL Magoffin, & CH Miller "use of penicillin and sulfadiazine (sulfonamide) as prophylactic agents against streptococcal and non-specific respiratory infections among recruits at naval training center" Am J Hyg 57:71-100 January 1953
41. LL Coriell, RM McAllister, E Preston III, & AD Hunt "scarlet fever and mixed infections of throat and nasopharynx treated orally with dibenzylethylenediamine dipenicillin G (Bicillin)" Antibiotics & Chemother. 3:357-367 April 1953

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42. AH Gale, WA Gillespie, & CB Perry "oral penicillin in prophylaxis of streptococcal infection in rheumatic children" Lancet 2:61-63 July 12, 1952
43. GH Stollerman & JH Rusoff "prophylaxis against group A streptococcal infections in patients; use of new repository penicillin preparation (dibenzylethylenediamine penicillin)" JAMA 150:1571-1575 December 20, 1952
44. E Bengtsson & G Birke "complications in penicillin-treated acute throat infections caused by beta-hemolytic streptococci and among carriers of hemolytic streptococci" Acta Med. Scandinav. 143:120-128 1952
45. MA Smith, D Skinner, & L Erickson "prophylactic effect of penicillin tablets on throat flora" Am J Clin Path 22:948-951 October 1952

1951 (Vol. 49-50)
46. BF Massell "present status of penicillin prophylaxis (by treating streptococcic infections)" Mod. Concepts Cardiovasc. Dis. 20:108-109 September 1951
47. BF Massell et al. "prevention by prompt penicillin therapy of hemolytic streptococcic respiratory infections; progress report" JAMA 146:1469-1474 August 18, 1951
48. A Ravina "role of penicillin in prophylaxis of acute articular rheumatism" Presse Med. 59:976-977 July 7, 1951
49. MM Maliner "Oral penicillin in prophylaxis of recurrent rheumatic fever" J. Pediatr. 37: 858-861 December 1950
50. "Prevention of rheumatic fever (use of penicillin therapy for streptococcal infections)" US Armed Forces M J 2:607-613 April 1951
51. LW Wannamaker et al. "Prophylaxis of acute rheumatic fever by treatment of preceding streptococcal infection with various amounts of depot penicillin" Am J Med 10:673-695 June 1951
52. WR Brink, CH Rammelkamp Jr, FW Denny, & LW Wannamaker "effect of penicillin and aureomycin on natural course of streptococcal tonsillitis and pharyngitis" Am J Med 10:300-308 March 1951
53. D Wheatley ""Acute follicular tonsillitis treated with oral penicillin" Practitioner 166:166-168 February 1951
54. T Bennike et al. "Penicillin therapy in acute tonsillitis and phlegmonous tonsillitis" Acta Med Scandinav 139:253-274 1951

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55. M Brick et al. "oral penicillin prophylaxis" Canad M A J 63:255-258 September 1950
56. IAP Evans "Discussion of management of rheumatic fever and its early complications; oral penicillin in prophylaxis of streptococcal infections and rheumatic relapse" Proc Roy Soc Med 43: 206-208 March 1950
57. KH Kohn, A Milzer, & H MacLean "Oral penicillin prophylaxis of recurrences (by reducing hemolytic streptococcal infections in throat); interim report on method after 3 year study" JAMA 142: 20-25 January 7, 1950
58. FW Denny "Prevention of rheumatic fever; treatment of preceding streptococcic infection" JAMA 143:151-153 May 13, 1950

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59. JW Hofer – Rheumatic Fever, cardiac complications "Oral penicillin for children" J Pediat 35:135-144 August 1949

60. MM Maliner, SD Amsterdam & CC Arreche "Further studies on oral penicillin in prophylaxis of recurrent rheumatic fever" J Pediat 35:145-150 August 1949
61. KW Schneider – Rheumatic Fever, therapy "penicillin" Med Klin 44:764-767 June 17, 1949 (Foreign Language Article?????????)
62. RL Jackson "Treatment of acute rheumatic fever and prevention of recurrences" JAMA 141:439-445 October 15, 1949

1948 (Vol. 43-44)
63. BF Massell, JW Dow & TD Jones "orally administered penicillin in patients with rheumatic fever" JAMA 138:1030-1036 December 4, 1948
64. HG Nelson et al. "Tonsillar carriers of hemolytic streptococci; effect of tonsillectomy and administration of penicillin on rheumatic and nonrheumatic fever patients" J Infec Dis 83:138-146 September-October 1948
65. A Milzer, KH Kohn & H MacLean "oral prophylaxis with penicillin; resistant hemolytic streptococci" JAMA 136:536-538 February 21, 1948
66. B Schuster Throat, infections "- bismuth vs. penicillin" U S Nav M Bull 48:61-65 January-February 1948
67. E Jawetz Throat, infections "- dynamics of action of penicillin: time dose relationship in human streptococcic disease" Arch Int Med 81:203-208 February 1948
68. WI Daggett Throat, infections "-present status of penicillin and sulfonamides" Practitioner 159:442-445 December 1947

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69. MM Maliner & SD Amsterdam "Oral penicillin in prophylaxis of recurrent rheumatic fever" J Pediat 31:658-661 December 1947
70. JR Goerner, BF Massell, & TD Jones "use of penicillin in treatment of carriers of beta-hemolytic streptococci among patients with rheumatic fever" New England J Med 237:576-580 October 16, 1947
71. GR Royston Throat, infections "- Penicillin by intraoral drip" Brit M J 2:454-455 September 20, 1947
72. PJ Burke RF, prevention "- penicillin prophylaxis" Lancet 1:255-256 February 15, 1947
73. R Jennings & ED DeLamater Streptococci, carriers "- penicillin therapy" Am J Med 2:1-22 January 1947
74. LA Rantz Throat, infections "antibiotics (penicillin and sulfonamides) in treatment of hemolytic streptococcus sore throat" California Med 66:66 February 1947
75. RE Faucett, MP Thomas & JC Ruddock Throat, infections "- Treatment of acute infections, with special reference to use of penicillin" California Med 65: 218-224 November 1946

1946 (Vol. 39-40)
76. S Davison Throat, infections "-use of penicillin in acute sore throat" JAMA 131:1050-1052 July 27, 1946
77. ES Hopp Tonsils, infections "-penicillin in oral therapy of acute follicular tonsillitis" Arch Otolaryng 44:409-413 October 1946
78. LA Rantz, WW Spink & PJ Boisvert "chemotherapy (with penicillin and sulfonamide) and hemolytic streptococcus carrier state" Bull. US Army M Dept 5:662-666 June 1946
79. M Hamburger Jr & HM Lemon "Problem of dangerous carrier of hemolytic streptococci; chemotherapeutic control (with calcium penicillin and sulfadiazine, sulfonamide) of nasal carriers" JAMA 130:836-841 March 30, 1946
80. LA Rantz, PJ Boisvert & WW Spink "hemolytic streptococcal sore throat; antibody response following treatment with penicillin, sulfadiazine (sulfonamide) and salicylates" Science 103:352-353 March 22, 1946
81. WW Spink, LA Rantz, PJ Boisvert & H Cogeshall "sulfadiazine (sulfonamide) and penicillin for hemolytic streptococcal infections of upper respiratory tract; evaluation in tonsillitis, nasopharyngitis, and scarlet fever" Arch Int Med 77:260-294 March 1946
82. P Ashley "treatment (especially using convalescent serum and penicillin) of scarlet fever" JAMA 130:771-774, March 23, 1946

1945 (Vol. 37-38)

83. LA Rantz, WW Spink, PJ Boisvert & H Cogeshall Rheumatic Fever, therapy "-penicillin" J Pediat 26:576-582 June 1945
84. M Meads, ME Flipse Jr, MW Barnes & M Finland Throat, bacteriology "of scarlet fever patients treated intramuscularly or by spray with penicillin and comparison with sulfadiazine (sulfonamide)" JAMA 129:785-789 November 17, 1945
85. R Robinson Throat, bacteriology "hemolytic streptococcal infections; complications and sequels with special reference to penicillin treatment" Brit M J 2:213-214 August 18, 1945
86. JD Keith et al. "penicillin in hemolytic streptococcal infections" Canad M A J 53:471-478 November 1945
87. N Plummer et al. "penicillin therapy in hemolytic streptococcal pharyngitis and tonsillitis" JAMA 127:369-374 February 17, 1945

1944 (Vol. 35-36)

88. JR Twiss RF, therapy "-penicillin" US Nav M Bull 43:1001-1009 November 1944
89. RF Watson, S Rothbard & HF Swift RF, therapy "-penicillin" JAMA 126:274-280 September 30, 1944
90. FP Foster et al. "Penicillin treatment of acute rheumatic fever" JAMA 126:281-282 September 30, 1944

1943 (Vol. 33-34) – No Articles

Other Interesting Titles

1. HM Wallace & H Rich "changing status of rheumatic fever and rheumatic heart disease in children and youth" AMA J Dis Child 89:7-14 January 1955
2. GH Stollerman "symposium on rheumatic fever and rheumatic heart disease: use of antibiotics" Am J Med 17: 757-767 December 1954
3. "rheumatism and arthritis; review of American and English literature of recent years (tenth rheumatism review)" Ann Int Med 39:498-618 September 1953
4. SH Walker "possible interference of chloramphenicol with penicillin in acute streptococcal pharyngitis" Antibiotics & Chemother. 3:677-680 July 1953
5. MA Smith et al "Rheumatic fever prophylaxis; community program through private physician" JAMA 149:636-649 June 14, 1952
6. EF Bland & TD Jones "Rheumatic fever and rheumatic heart disease; 20 year report on 1000 patients followed since childhood" Circulation 4:836-843 December 1951
7. TC Maddonald & IH Watson "sulfonamides and acute tonsillitis; controlled experiment in Royal air force community" Brit M J 1:323-326 February 17, 1951
8. L Weinstein, L Bachrach & NH Boyer "development of rheumatic fever and glomerulonephritis in cases of scarlet fever treated with penicillin" New England J Med 242:1002-1010 June 29, 1950
9. MG Wilson & R Lubschez "longevity in rheumatic fever, based on experience of 1042 children observed over period of 30 years" JAMA 138: 794-798 November 13, 1948
10. H Heiman "Pathogenesis and prophylaxis of acute rheumatic fever in children" Arch Pediat 65:266-271 May 1948 (Reprint, 1901)
11. Special report from Committee on School Health and Committee on Rheumatic Fever "Rheumatic Fever and school child: Statement to guide School Health Association" Pediatrics 2:321-323 September 1948
12. AT Martin "rheumatic fever and American Academy of Pediatrics – general purpose and scope" J Pediat 26: 209-210 March 1945
13. L Kuskin & M Siegel "The Changing Pattern of Rheumatic Heart Disease" J Pediat 49:574-582 November 1956

Appendix 2: PubMed List of Refences

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

1. Plaut ME et al., Cefamandole vs. procaine penicillin for treatment of pneumonia due to Streptococcus pneumoniae: a random trial.
   J Infect Dis. 1978 May;137 Suppl:S133-S138.
   PMID: 349092 [PubMed - indexed for MEDLINE]

2. Massell BF, Prophylaxis of streptococcal infections and rheumatic fever: a comparison of orally administered clindamycin and penicillin.
   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]

5. Muller O et al., Loracarbef versus penicillin V in the treatment of streptococcal pharyngitis and tonsillitis.
   Infection. 1992 Sep-Oct;20(5):301-8.
   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]

7. Disney FA et al., Loracarbef (LY163892) vs. penicillin VK in the treatment of streptococcal pharyngitis and tonsillitis.
   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]

10. Mc Carty J, Loracarbef versus penicillin VK in the treatment of streptococcal pharyngitis and tonsillitis in an adult population.

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

11. Fyllingen G et al., Phenoxymethylpenicillin two or three times daily for tonsillitis with beta-haemolytic streptococci group A: a blinded, randomized and controlled clinical study.
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)

17. Milatovic D, Evaluation of cefadroxil, penicillin and erythromycin in the treatment of streptococcal tonsillopharyngitis.
Pediatr Infect Dis J. 1991 Oct;10(10 Suppl):S61-3. No abstract available.
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