CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-678/SE1-003

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

DEC 17 1997

NDA:	50-678 / SE1-003
Generic Drug Name:	Dirithromycin
Drug Trade Name:	Dynabac™
Formulation:	Tablet
Drug Class:	
Applicant:	Eli Lilly and Company
Indications:	I. Acute Bacterial Exacerbation of Chronic Bronchitis II. Secondary Bacterial Infection of Acute Bronchitis III. Skin and Skin-Structure Infections
Documents Reviewed:	NDA volumes 1,35, 36,..., 62 of 84 dated December 20, 1996
Statistical Reviewer:	Li Ming Dong, Ph.D., HFD-725
Type of Review:	Clinical
Medical Reviewer:	Alma Davidson, M.D., HFD-520
Project Manager:	Mr. Jose Cintron, HFD-520

I. INTRODUCTION

This submission is to support the efficacy and safety of a shorter course of dirithromycin tablets: 500 mg/day once daily for 5 days for indications of acute exacerbation of chronic bronchitis (AECB), secondary bacterial infection of acute bronchitis (SBIAB), and skin and skin-structure (skin and soft tissue) infections. Dirithromycin at the same dosage for 7 days was previously approved through NDA 50-678 for indications including the above three indications. The proposed label including changes in dirithromycin duration from "7 days" to "5-7 days"; adding *H. Influenzae* for AECB, SBIAB, and *S. Pyogenes* for skin and skin-structure infections.

Erythromycin 250mg tablet every 6 hours was chosen as the comparator because it is the prototypical antibiotic for proposed indications on the label. It was chosen after a discussion with FDA.

Sponsor submitted eight clinical studies. Four studies were pivotal: studies B9ZMC AQAT and B9ZMC AQAW were conducted for the indication of AECB; studies B9ZMC AQAU and B9ZMC AQAX were conducted for the indication of skin and skin-structure infections. No studies were conducted among SBIAB patients. This review will focus on these four pivotal studies.

II. EVALUATION

II.A. Study B9ZMC AQAT

Title

Dirithromycin 5 Days vs. Erythromycin 7 Days in the Treatment of Acute Superimposed on Chronic Bronchitis

Objectives

To compare dirithromycin, administered once daily (500 mg/day) for 5 days, to erythromycin, administered every 6 hours (1000 mg/day) for 7 days, for effectiveness and safety in the treatment of acute superimposed on chronic bronchitis.

Design of the Study

This is a double-blind, double-dummy, randomized, multicenter study with two treatment arms.

The study drug was dirithromycin 500mg (two tablets, 250mg each) once daily taken with or immediately after a meal for 5 days. The comparator drug was erythromycin 250mg tablet every 6 hours, administered 1 hour before meal and at bedtime, for 7 days. About equal number of patients were assigned randomly to each treatment group. The blindness was maintained by giving patient placebo tablets resemble the dose, frequency and duration of the other study drug.

The protocol planned to enroll approximately 600-700 patients in this study in order to obtain a minimum of 140 clinically evaluable patients (70 per treatment group). Later the protocol was amended to target at 300 clinical evaluable patients (150 per treatment group) among 600-700 enrolled patients. If the true favorable response rates were 80% (case 1) or 90% (case 2) in both treatment groups, the sample size provided an 80% chance of ruling out a difference of 13% or greater (case 1) or 10% or greater (case 2) with 95% confidence (2-sided).

Enrolled patients were scheduled for four study visits: pretherapy, during therapy (study day 3-5), posttherapy (3-5 days after the end of study-drug therapy) and late posttherapy visits (10-14 days after the end of study-drug therapy). At pretherapy visit, complete history and physical examination were performed, a sputum culture was collected, and a X-ray was performed to rule out pneumonia. At subsequent visits, complete history and physical examination were repeated, and sputum cultures were done if clinically indicated.

Lab study were also done for safety monitoring.

Primary Endpoint

Efficacy evaluation was based on clinical (symptomatic) response and bacteriologic response.

Patient's clinical response fell into one of the five categories: cure, improvement, relapse, failure and unable to evaluate. Categories of cure and improvement were combined into one class named favorable response. Relapse and failure were combined into another class named unfavorable response. Dirithromycin was compared with erythromycin with respect to favorable response rate.

Bacteriologic response was evaluated by the sponsor, while blinded to patient's therapy. It had six categories if follow-up sputum culture was available: eradication, persistence, relapse, colonization, superinfection and eradication with reinfection. If patient's sputum culture was not available, bacteriologic response was assigned to one of the three categories: presumed eradication, presumed persistence or indeterminate.

Reviewer's comments: The sponsor did not explicitly specify primary endpoint as well as the test-of-cure visit in protocol and submission. FDA "Points to Consider" document recommends to use clinical success (cured or improved) rate among clinically evaluable patients at the test-of-cure visit as the primary efficacy endpoint. FDA Division of Anti-Infective Drug Product "Guidance for Industry (Feburary, 1997)" document recommends to consider visit 1 to 2 weeks after the completion of the therapy as the test-of-cure visit. Therefore clinical favorable response rate was considered as the primary endpoint by the medical reviewer at FDA. Confidence interval of the difference in the clinical favorable response rates was used to evaluate efficacy according to "Points to Consider" document.

Bacteriologic response was derived from results of sputum culture and clinical response.

Analysis Population

Sponsor's efficacy analysis was based on three patient groups: clinically evaluable, bacteriologically evaluable, and Intent-to-treat patients. Clinically evaluable patients included those who met inclusion/exclusion criteria; had appropriate pretherapy and posttherapy history and physical examination, had pretherapy X-ray which ruled out pneumonia infiltrate, had qualified pretherapy Gram's Stain, and met minimum compliance requirement. In order to be bacteriologically evaluable, patient must meet all criteria for clinically evaluable, plus having positive culture of pretherapy sputum for one of following respiratory pathogens:

Haemophilus influenzae	*Klebsiella pneumoniae*
Streptococcus pneumoniae	*Klebsiella species*
Moraxella catarrhalis	*Staphylococcus aureus*
Haemophilus parainfluenzae	Group A Streptococci.

The third analysis population was the intent-to-treat population which included all randomized patients, whether they received the study drugs or not.

Efficacy analysis used Pearson's $\chi 2$ test and 95% confidence interval to compare investigation drug and standard drug treatment.

Reviewer's Comments: The terms "qualified" and "evaluable" were used synonymously throughout the submission by the sponsor. Note also that sponsor's bacteriologically evaluable population is in fact both clinically and bacteriologically evaluable.

The sponsor determined patient evaluability based on information available at posttherapy visit. Evaluable population would be slightly smaller if it were based on late posttherapy visit.

Conduct of the Study

A total of 499 patients were enrolled and randomized through 30 principal investigators in US during the study period of November 1991 to August 1992. Among them 249 patients were randomly allocated to dirithromycin group, and 250 patients to erythromycin group.

The protocol was amended February 5, 1992 as the result of a discussion with FDA. Prior to the amendment, a patient whose pretherapy culture did not grow a pathogen or grew a pathogen resistant to one or both study drugs was to be discontinued from the study. After the amendment, the patient could remain in the study unless the patient was symptomatically relapsing or failing. There were 176 patients enrolled in this study prior to the protocol amendment

The sponsor reported clinical and microbiologic results at posttherapy visit (3-5 days after the end of study-drug therapy) and at termination. Patient responses, clinical or bacteriologic, at termination were determined according to the following: if a patient returned at the late post-therapy visit (10-14 days after the end of study-drug therapy), the patient responses at termination were the responses at this visit; if a patient did not return for late posttherapy visit, the patient responses at posttherapy visit were carried forward as responses at termination.

Reviewer's Comments: All failures and relapse at posttherapy visit were carried forward to late posttherapy visit, that is, they were considered as failures or relapses at late posttherapy visit. However, carrying forward responses of "cure" or "improvement" to late posttherapy visit potentially undercounted relapses 10-14 days after the therapy for both study drugs. As a result, the favorable response rates at termination might over estimate the favorable response rates at late posttherapy visit.

Definition of "response at termination" were not given in study protocol and amendments. It might be done retrospectively.

Demographic and Baseline Characteristics

Table A1 displayed the demographic characteristics as well as smoking and alcohol habits of all enrolled patients. Female comprised 55-58% of patients in each treatment group. Age ranged from years old, with mean ages of 49.05 in dirithromycin group and 47.70 years old in erythromycin group. As for ethnic origin, both groups were predominantly Caucasian (more than 92%). In each of the two treatment arms, over a half enrolled patients were smoker and had over one third patients had alcohol habit. The two treatment groups were well matched with respect to gender, age, ethnic origin, weight, height, as well as smoking and alcohol habits.

To compare treatment groups at baseline with respect to the severity of symptoms, the sponsor provided mean symptom score for bacteriologically evaluable patients as in Table A2. Results for clinically evaluable and Intent-To-Treat populations were comparable with results for bacteriologically evaluable patients. The mean symptom scores included scores from patients in whom the symptom was absent (score of 0) to patients in whom the symptom were severe (score of 4). As shown in Table A2, the baseline symptom scores for the two treatment group were comparable for bacteriologically evaluable patients.

Table A1 AQAT
Baseline Demographic Characteristics And Smoking Habits
All Patients

	DIRITHROMYCIN N = 249		ERYTHROMYCIN N = 250		TOTAL N = 499	
	n	(%)	n	(%)	n	(%)
MALE	105		112			
FEMALE	144		138			
MEAN AGE	49.05	(±17.84)	47.70	(±16.67)		
MEAN HEIGHT	169.10	(±12)	169.30	(±10)		
MEAN WEIGHT	76.96	(±18)	78.79	(±23)		
ORIGIN:						
CAUCASIAN	230	(92.4%)	236	(94.4%)		
BLACK	12	(4.8%)	13	(5.2%)		
HISPANIC	4	(1.6%)	1	(0.4%)		
NATIVE AMERICAN	1	(0.4%)	0			
ASIAN	1	(0.4%)	0			
OTHER	1	(0.4%)	0			
SMOKING	129	(51.8%)	141	(56.4%)	270	(54.1%)
ALCOHOL	90	(36.1%)	89	(35.6%)	179	(35.9%)
MEAN NO. OF YEARS SMOKED	25		25			

Source: Tables AQAT.2 and AQAT.5.6, page 15 and page 92, Vol. 42 of 84.

Table A2 AQAT
Mean Pretherapy Symptom Scores
Bacteriologically-Evaluable Patients

SYMPTOM	DIRITHROMYCIN N = 103	ERYTHROMYCIN N=108
Cough	2.282	2.269
Sputum production	2.165	2.102
Dyspnea	1.670	1.435
Tachypnea	0.553	0.546
Rales	0.670	0.676
Coarse rhonchi	1.592	1.411
Pleuritic Chest Pain	0.689	0.602
Chills	0.680	0.537
Temperature (oC)	37.237	37.169

Source: Table AQAT.6.52, page 200, Vol. 42 of 84.

The sponsor also reported that the two treatment groups were compared with respect to compliance. No statistically significant differences between the two study drug groups were reported as clinically relevant by the sponsor.

Reviewer's Comment: The sponsor provided tables which listed percentage distribution for categorical variables, mean and standard deviation for continuous variables. The sponsor stated that there were no statistically significant difference between the two treatment groups, but no p-values were provided.

Discontinuation/Completion Information

A total of 370 patients (74%) completed the study protocol. Among them 196 patients (78.7%) were in dirithromycin group, and 174 (69.6%) in the comparator group (Table A3). Lack of efficacy was the most common reason for early withdrawals for both treatment groups: 11.2% and 10% for dirithromycin and erythromycin respectively. Adverse events accounted for 2.4-4.8% withdrawals in each arm. Patient listed as ENTRY CRITERIA EXCLUSION included patient who discontinued due to pretherapy microbiology results before the protocol amendment.

Table A3 AQAT
Reasons Patients Discontinued
All Patients

	DIRITHROMYCIN N = 249		ERYTHROMYCIN N = 250	
REASON STUDY DRUG DISCONTINUED	n	(%)	n	(%)
PROTOCOL COMPLETE	196	(78.7%)	174	(69.6%)
LACK OF EFFICACY	28	(11.2%)	25	(10.0%)
LOST TO FOLLOW-UP	4	(1.6%)	8	(3.2%)
PATIENT DECISION	2	(0.8%)	3	(1.2%)
ENTRY CRITERIA EXCLUSION	12	(4.8%)	24	(9.6%)
PROTOCOL VIOLATION	1	(0.4%)	4	(1.6%)
ADVERSE EVENT	6	(2.4%)	12	(4.8%)

Source: Table AQAT.5.14, page 141, Vol. 42 of 84.

Efficacy Results

Of the 249 patients who received dirithromycin, 164 (65.9%) were clinically evaluable and 85 (34.1%) were not clinically evaluable. Of the 164 clinically evaluable patients, 103 (41.4% of all 249 patients) were also bacteriologically evaluable. Of the 250 patients who received erythromycin, 159 (63.6%) patients were clinically evaluable, and 91 (34.4%) patients were not clinically evaluable. Among 159 clinically evaluable patients, 108 patients (43.2% of all 250 patients) were also bacteriologically evaluable and 51 patients were clinically evaluable but not bacteriologically evaluable.

Reviewer's Comment: The sponsor used the posttherapy visit (3-5 days after the completion of the therapy) as the test-of-cure visit in study report. Patient evaluability was decided based on information obtained at this visit rather than the late posttherapy visit (10-14 days after the completion of the therapy). If a patient was lost to follow-up at the posttherapy visit, the patient was considered unevaluable. If a patient had posttherapy visit but did not return for late posttherapy visit, the patients was still considered as evaluable by the sponsor. The patient's clinical/bacteriological evaluation at previous visit (posttherapy visit) was carried forward and defined as clinical/bacteriologic response at "termination" by the sponsor. However, according to FDA DAIDP "Points-To-Consider" document, late postherapy visit in this study is recommended as the test-of-cure visit. Therefore, FDA efficacy evaluation was based on results at termination.

Clinical Results Table A4 showed the clinical responses for the two treatment groups. The distributions of the clinical ~~respon~~ses among four categories (cure, improvement, relapse and failure) were similar between the dirithromycin and erythromycin groups. Among 164 clinically evaluable patients treated with dirithromycin, 54.9% (90) patients were cured and 22.6% (37) were improved. For 159 clinically evaluable patients treated with erythromycin, 59.1% (94) were cured and 20.8% (33) patients were improved. There was 14.6% (24) patients failed the dirithromycin treatment, and 12.6% (20) patients failed the erythromycin treatment. The relapse rates for the two groups were both slightly below 8%. As shown in Table A5, 77.5% dirithromycin patients achieved favorable clinical response (cure or improvement), compared with 79.9% erythromycin patients achieved favorable clinical response. The 95% confidence interval for the difference (dirithromycin - erythromycin) in favorable clinical response rates was [-11.5%, 6.7%].

Table A4 AQAT
Clinical Response Summary by Therapy Group
Clinically-Evaluable Patients at Termination

	DIRITHROMYCIN		ERYTHROMYCIN		TOTAL	
RESPONSE	n	(%)	n	(%)	n	(%)
EVALUABLE	164		159		323	
CURE	90	(54.9%)	94	(59.1%)	184	(57.0%)
IMPROVEMENT	37	(22.6%)	33	(20.8%)	70	(21.7%)
RELAPSE	13	(7.9%)	12	(7.5%)	25	(7.7%)
FAILURE	24	(14.6%)	20	(12.6%)	44	(13.6%)
UNEVALUABLE	85		91		176	
TOTAL	249		250		499	

Source: Table AQAT.6.29, page 174, Vol. 42 of 84.

TABLE A5 AQAT: SUMMARY OF SPONSOR'S EFFICACY RESULTS AT TERMINATION

n=499	Favorable Response Rate		95% Confidence Interval
Analysis Population	Dirithromycin 5-day (n=249)	Erythromycin 7-day (n=250)	Dirithromycin vs. Erythromycin
Clinical efficacy in clinically evaluable patients	77.4% (127/164)	79.8% (127/159)	[-11.5%, 6.7%]
Bacteriological efficacy in bacteriologically evaluable patients	73.7% (76/103)	79.6% (86/108)	[-17.5%, 5.8%]
Intent-to-treat patients	79.1% (197/249)	77.6% (194/250)	[-5.9%, 8.9%]

Clinical favorable response: cure / improvement
Clinical unfavorable response: failure / relapse
Bacteriologic favorable response: eradication / presumptive eradication
Bacteriological unfavorable response: persistence / presumed microbiology persistence / relapse / eradication with reinfection

Reviewer's Comment: The sponsor calculated 95% confidence intervals without correction for continuity. If the calculation were done with the correction for continuity, the 95% confidence interval for the difference in favorable clinical response rates between the two groups (dirithromycin minus erythromycin) would be [-12.0%, 7.1%]. Other confidence intervals would be slightly wider than reported if calculated with the correction for continuity. This applies throughout this submission.

In sponsor's data, clinical response of patient (investigator 116) was recorded as "relapse" at posttherapy visit, "improvement" at late posttherapy visit. However, the clinical response of this patient at late posttherapy visit should be considered as "relapse" because of earlier relapse.

Please note that a patient may be cured without being clinically evaluable. Please note also that sponsor's bacteriologically evaluable population was in fact both clinically and bacteriologically evaluable by definition. This comment applies to all four pivotal studies.

Microbiologic Results For bacteriologically evaluable patients, pretherapy pathogen(s) were eradicated or presumptively eradicated for 73.8% (76/103) dirithromycin treated patients. For erythromycin treated patients, pretherapy pathogen(s) were eradicated or presumptively eradicated for 79.6% (86/108) patients. Table A6 showed the break-down of bacteriologic response. It was observed that most of bacteriologically favorable responses were presumptive eradication.

Table A 6 AQAT
Bacteriologic Response Summary by Therapy Group
Bacteriologically-Evaluable Patients at Termination

	DIRITHROMYCIN N = 103		ERYTHROMYCIN N = 108		TOTAL N = 211	
RESPONSE	n	(%)	n	(%)	n	(%)
ERADICATION	4	(3.9%)	4	(3.7%)	8	(3.8%)
PRESUMPTIVE ERADICATION	72	(69.9%)	82	(75.9%)	154	(73.0%)
ERADICATION WITH REINFECTION	3	(2.9%)	1	(0.9%)	4	(1.9%)
RELAPSE	1	(1.0%)	0		1	(0.5%)
PRESUMED MICROBIOLOG PERSISTENCE	19	(18.4%)	17	(15.7%)	36	(17.1%)
PERSISTENCE	4	(3.9%)	4	(3.7%)	8	(3.8%)

Source: Table AQAT.6.35, page 180, Vol. 42 of 84.

The following table present rates of eradication or presumptive eradication by pathogen for patients who were bacteriologically evaluable. For pretherapy pathogen, *H Influenzae* were eradicated or presumptively eradicated for 78.2% (18/23) dirithromycin patients, compared with 60.0% (21/35) eradication or presumptive eradication for erythromycin patients.

Table A7 AQAT
Bacteriologic Eradication or Presumptive Eradication Rate by Pathogen
Bacteriologically-Evaluable at Termination

PATHOGENS	DIRITHROMYCIN n=103	ERITHROMYCIN n=108
H INFLUENZAE	78.2% (18/23)	60.0% (21/35)
M CATARRHALIS	87.5% (7/8)	87.5% (7/8)
STR PNEUMONIAE	50.0% (3/6)	80.0% (4/5)
ST AUREUS	80.0% (4/5)	100.0% (11/11)
H PARAINFLUENZAE	66.6% (18/27)	89.6% (26/29)
K PNEUMONIAE	60.0% (3/5)	75.0% (3/4)
STR GRP A	100.0% (2/2)	
MULTIPLE ORGANISMS	77.7% (21/27)	86.6% (13/15)
KLEBSIELLA SP		100.0% (1/1)

Source: Tables AQAT.6.36 and AQAT.6.38, pages 181 and 185, Vol. 42 of 84.

Reviewer's Comment: Rate in table A7 represented results only for patients with single organism. For patients with multiple organisms, the breakdowns for three major pathogens were as following table. The combined results are in section III. Reviewer's Summary.

Pathogens	Dirithromycin	Erythromycin
H. Influenzae	78.6% (11/14)	77.8% (7/9)
M. Catarrhalis	66.7% (2/3)	85.7% (6/7)
S. Pneumoniae	81.8% (9/11)	100.0% (3/3)

Source: Tables AQAT.6.37 and AQAT.6.39, pages 182 and 186, Vol. 42 of 84.

TABLE A8 AQAT: SUMMARY OF SPONSOR'S EFFICACY RESULTS AT POSTTHERAPY

n=499	Favorable Response Rate		95% Confidence Interval
Analysis Population	Dirithromycin 5-day (n=249)	Erythromycin 7-day (n=250)	Dirithromycin vs. Erythromycin
Clinical efficacy in clinically evaluable patients	81.1% (133/164)	86.2% (137/159)	[-13.3%, 3.1%]
Bacteriological efficacy in bacteriologically evaluable patients	73.8% (76/103)	81.5% (88/108)	[-19.1%, 3.8%]
Intent-to-treat patients	82.8% (206/249)	83.2% (208/250)	[-7.2%, 6.3%]

Clinical favorable response: cure / improvement
Clinical unfavorable response: failure / relapse
Bacteriologic favorable response: eradication / presumptive eradication
Bacteriological unfavorable response: persistence / presumed microbiology persistence / relapse / eradication with reinfection

Table A8 summarized the sponsor's results at posttherapy. The general trend was similar to results at termination.

Safety

The data presented in this section are based on information obtained from all patients. All events were recorded regardless of suspected relationship to study drug. Signs and symptoms related to the disease process, including parameters considered to be disease diagnostic criteria, were recorded as events if they were not present on admission and appeared later in the study, or if they were present on admission and worsened during the study.

One death (the result of a car accident 8 weeks after study discontinuation) was reported. Eleven patients (3 in the dirithromycin group and 8 in the erythromycin group) experienced events which were reported as serious. One erythromycin-treated patient who experienced G.I. hemorrhage met the criteria of an alert report (i.e., serious, unexpected, and possibly causally related).

Six dirithromycin-treated patients and 12 erythromycin-treated patients discontinued early due to adverse events. Three of the 6 dirithromycin-treated patients and 4 of the 7 erythromycin-treated patients experienced adverse events related to the gastrointestinal system. These gastrointestinal events resulting in discontinuation were possibly related to study-drug administration. Three dirithromycin-treated patients and 4 erythromycin-treated patient had adverse events resulting in discontinuation that were not thought to be related to study drug.

Table A9 AQAT
Frequency of Patients Experiencing Adverse Events: All Events
All Patients

	DIRITHROMYCIN N = 249		ERYTHROMYCIN N = 250	
EVENT CLASSIFICATION TERM	n	(%)	n	(%)
PATIENTS WITH AT LEAST ONE EVENT	125	(50.2%)	133	(53.2%)
PATIENTS WITH NO EVENT	124	(49.8%)	117	(46.8%)
HEADACHE	24	(9.6%)	18	(7.2%)
NAUSEA	17	(6.8%)	13	(5.2%)
DIARRHEA	16	(6.4%)	23	(9.2%)
ABDOMINAL PAIN	14	(5.6%)	13	(5.2%)
ASTHMA	14	(5.6%)	13	(5.2%)
DYSPEPSIA	12	(4.8%)	7	(2.8%)
LUNG DISORDER	12	(4.8%)	13	(5.2%)
RHINITIS	12	(4.8%)	19	(7.6%)
CHEST PAIN	9	(3.6%)	9	(3.6%)
DIZZINESS	9	(3.6%)	6	(2.4%)
DYSPNEA	9	(3.6%)	11	(4.4%)
PAIN	9	(3.6%)	12	(4.8%)
ASTHENIA	7	(2.8%)	5	(2.0%)
BACK PAIN	5	(2.0%)	3	(1.2%)
PHARYNGITIS	4	(1.6%)	6	(2.4%)
CHILLS	3	(1.2%)	6	(2.4%)
INSOMNIA	3	(1.2%)	6	(2.4%)

Source: Tables AQAT.12, page 21, Vol. 42 of 84.

Adverse events reported at a rate of greater than or equal to two percent for either treatment group for the total population are listed in Table A9. One or more adverse events were reported from 125 (50.2%) of dirithromycin-treated patients compared with 133 (53.2%) of the erythromycin-treated patients (p=0.503). Headache and nausea were the most often reported adverse events among dirithromycin treated patients. Headache occurred in 24 (9.6%) dirithromycin patients, and nausea occurred in 17 (6.8%) patients. In comparison, 18 (7.2%) erythromycin patients experienced headache and 13 (5.2%) patients experienced nausea. When event classification terms were analyzed individually, there was a statistically significant difference between treatment groups in the proportion of patients reporting hyperventilation; 4 (1/6%) erythromycin treated and no dirithromycin-treated patients reported hyperventilation (p=.045).

To examine the potential effects of drug therapy on laboratory test results for the total population, an analysis was performed to examine the changes in the mean values for each population for each analyte. The mean changes were determined from the difference between the average posttherapy and pretherapy measurements using data from all patients having laboratory data for the specific analyte available from both visits.

No statistically significant difference between the treatment groups was seen; however, statistically significant changes within groups were seen for several analytes. In the absence of untreated control patients, statistically significant differences within the two treatment groups are impossible to ascribe to drug treatment. None of the mean changes for any analyte approached a level that would be considered of clinical significance.

II.B. Study B9ZMC AQAW

Title

Dirithromycin 5 Days vs. Erythromycin 7 Days in the Treatment of Acute Superimposed on Chronic Bronchitis

Reviewer's Comments: Study B9ZMC AQAW, referred to as study AQAW in this review, was similar to study B9ZMC AQAT. In fact, protocol for study AQAW was identical to the protocol for study AQAT. For summary of the design of this study, see first part of section II.A.. Reviewer's comments on the design of study AQAT also apply to study AQAW.

Conduct of the Study

A total of 558 patients were enrolled through 47 principal investigators in US and were randomly allocated to two treatment groups during the study period from January 1992 to November 1992. Among them 282 patients were randomly allocated to dirithromycin group, and 276 patients to erythromycin group.

The protocol was amended February 5, 1992 as the result of a discussion with FDA. Prior to the amendment, a patient whose pretherapy culture did not grow a pathogen or grew a pathogen resistant to one or both study drugs was to be discontinued from the study. After the amendment, the patient could remain in the study unless the patient was symptomatically relapsing or failing. There were 33 patients enrolled in this study prior to the protocol amendment

Reviewer's Comment: A patient whose pretherapy culture did not grow a pathogen or grew a pathogen resistant to one or both study drugs still remained in the study after protocol amendment. However, such patient was excluded from per protocol analysis (considered as unevaluable). Intent-to-treat and safety analysis included such patient.

The sponsor reported clinical and microbiologic results at posttherapy visit (3-5 days after the end of

study-drug therapy) and at termination. Patient responses, clinical or bacteriologic, at termination were determined according to the following: if a patient returned at the late post-therapy visit (10-14 days after the end of study-drug therapy), the patient responses at termination were the responses at this visit; if a patient did not return for late posttherapy visit, the patient responses at posttherapy visit were carried forward as responses at termination.

Reviewer's Comments: As in study AQAT, all failures and relapse at posttherapy visit were carried forward to late posttherapy visit, that is, they were considered as failures or relapses at late posttherapy visit. However, carrying forward responses of "cure" or "improvement" to late posttherapy visit potentially undercounted relapses for both study drugs. As a result, the favorable response rates at late posttherapy might be over estimated by the favorable response rate at termination.

Demographic and Baseline Characteristics

Table B1 displayed the demographic characteristics as well as smoking and alcohol habits of all enrolled patients. Female comprised 50.4% – 49.6 % of patients in each treatment group. Age ranged from

years old, with mean ages of 54.78 in dirithromycin group and 55.53 years old in erythromycin group. As for ethnic origin, both groups were predominantly Caucasian (more than 85%). In each of the two treatment arms, over 40.4% and 41.3% enrolled patients were smoker. The average number of years of smoking was 29 years for both groups. Each group had over one third patients with alcohol habit. The two treatment groups were well matched with respect to gender, age, ethnic origin, weight, height, as well as smoking and alcohol habits.

To compare treatment groups at baseline with respect to the severity of symptoms, the sponsor provided mean symptom score for bacteriologically evaluable patients as in Table B2. Results for clinically evaluable and Intent-To-Treat populations were comparable with results for bacteriologically evaluable patients. The mean symptom scores included scores from patients in whom the symptom was absent (score of 0) to patients in whom the symptom were severe (score of 4). As shown in Table B2, the baseline symptom scores for dirithromycin and erythromycin groups were comparable for bacteriologically evaluable patients.

The sponsor also reported that the two treatment groups were compared with respect to compliance. No statistically significant differences between the two study drug groups were reported as clinically relevant by the sponsor.

Reviewer's Comment: The sponsor provided tables which listed percentage distribution for categorical variables, mean and standard deviation for continuous variables. The sponsor stated that there were no statistically significant difference between the two treatment groups, but no p-values were provided.

Table B1 AQAW
Baseline Demographic Characteristics And Smoking Habits
All Patients

	DIRITHROMYCIN N = 282		ERYTHROMYCIN N = 276		TOTAL N = 558	
	n	(%)	n	(%)	n	(%)
MALE	140		139			
FEMALE	142		137			
MEAN AGE	54.78 (±15.93)		55.53 (±15.38)			
MEAN HEIGHT	169.52 (±9)		170.14 (±10)			
MEAN WEIGHT	78.46 (±19)		78.82 (±21)			
ORIGIN:						
CAUCASIAN	241	(85.5%)	252	(91.3%)		
BLACK	21	(7.4%)	14	(5.1%)		
HISPANIC	14	(5.0%)	6	(2.2%)		
NATIVE AMERICAN	1	(0.4%)	0			
ASIAN	3	(1.1%)	3	(1.1%)		
OTHER	2	(0.7%)	1	(0.4%)		
SMOKING	114	(40.4%)	114	(41.3%)	228	(40.9%)
ALCOHOL	108	(38.3%)	98	(35.5%)	206	(36.9%)
MEAN NO. OF YEARS SMOKED	29		29			

Source: Tables AQAW.2 and AQAW.5.6, page 7 and page 93, Vol. 45 of 84.

Table B2 AQAW
Mean Pretherapy Symptom Scores
Bacteriologically-Evaluable Patients

SYMPTOM	DIRITHROMYCIN N =125	ERYTHROMYCIN N=108
Cough	2.168	2.065
Sputum production	1.968	1.963
Dyspnea	1.280	1.269
Tachypnea	0.432	0.315
Rales	0.416	0.398
Coarse rhonchi	1.408	1.176
Pleuritic Chest Pain	0.504	0.370
Chills	0.320	0.259
Temperature (oC)	36.821	36.870

Source: Table AQAW.6.52, page 188, Vol. 45 of 84.

Discontinuation/Completion Information

A total of 444 patients (80%) completed the study protocol. Among them 232 patients (82.3%) were in dirithromycin group, and 212 (76.8%) in the comparator group (Table B3). Lack of efficacy was the most common reason for early withdrawls:8.5% (24/282) in dirithromycin treated group and 10.8% (30/276) in

erythromycin treated group. Adverse events accounted for 2.5% withdrawals in dirithromycin arm and 5.8% withdrawals in erythromycin arm.

Table B3 AQAW
Reasons Patients Discontinued
All Patients

REASON STUDY DRUG DISCONTINUED	DIRITHROMYCIN N = 282 n	(%)	ERYTHROMYCIN N = 276 n	(%)
PROTOCOL COMPLETE	232	(82.3%)	212	(76.8%)
LACK OF EFFICACY - PAT	2	(0.7%)	3	(1.1%)
LACK OF EFFICACY - PHYS	5	(1.8%)	4	(1.4%)
LACK OF EFFICACY - BOTH	17	(6.0%)	23	(8.3%)
UNABLE TO CONTACT	3	(1.1%)	5	(1.8%)
PATIENT DECISION-PERSONL	1	(0.4%)	1	(0.4%)
PATIENT DECISION-OTHER	1	(0.4%)	2	(0.7%)
ENTRY CRITERIA NOT MET	9	(3.2%)	7	(2.5%)
PROTOCOL VARIANCE	5	(1.8%)	3	(1.1%)
ADVERSE EVENT	7	(2.5%)	16	(5.8%)

Source: Table AQAW.5.14, page 130, Vol. 45 of 84.

Efficacy Results

Of the 282 patients who were randomized to dirithromycin group, 190 (67.4%) were clinically evaluable and 92 (32.6%) were not clinically evaluable. Of the 190 clinically evaluable patients, 125 patients were also bacteriologically evaluable. This was about 44.3% of all 282 dirithromycin patients. Of the 276 patients who were randomized to erythromycin group, 177 (64.1%) patients were clinically evaluable, and 99 (35.9%) patients were not clinically evaluable. Of the 177 clinically evaluable patients, 108 patients were also bacteriologically evaluable. This was about 39.1% of all 276 erythromycin patients. Fifty one erythromycin patients were clinically evaluable only.

Clinical Results Table B4 showed the clinical responses for the two treatment groups at termination. Distributions of the clinical responses among four categories (cure, improvement, relapse and failure) were similar between the dirithromycin and erythromycin groups. Among 190 clinically evaluable patients treated with dirithromycin, 57.6% (109) patients were cured and 19.5% (37) were improved. For 177 clinically evaluable patients treated with erythromycin, 52.0% (92) were cured and 13.6% (24) patients were improved. There was 9.5% (18) patients failed the dirithromycin treatment, and 16.4% (29) patients failed the erythromycin treatment. The relapse rates were 13.7% (26/190) for dirithromycin patients and 18.1% (32/177) for the comparator. As shown in Table B5, 76.8% (146/190) dirithromycin treated patients achieved favorable clinical response (cure or improvement), compared with 65.5% (116/177) erythromycin treated patients achieved favorable clinical response. The 95% confidence interval for the difference (dirithromycin - erythromycin) in favorable clinical response rates was [2.1%, 20.5%].

Reviewer's Comment: The sponsor calculated the confidence interval without the correction for continuity. With the correction for continuity, the 95% confidence interval for the difference in favorable response rates would be [1.5%, 21.1%]. Other confidence intervals would be slightly wider than reported if calculated with the correction for continuity.

Table B4 AQAW
Clinical Response Summary by Therapy Group
Clinically-Evaluable Patients at Termination

RESPONSE	DIRITHROMYCIN n	(%)	ERYTHROMYCIN n	(%)	TOTAL n	(%)
EVALUABLE	190		177		367	
CURE	109	(57.4%)	92	(52.0%)	201	(54.8%)
IMPROVEMENT	37	(19.5%)	24	(13.6%)	61	(16.6%)
FAILURE	18	(9.5%)	29	(16.4%)	47	(12.8%)
RELAPSE	26	(13.7%)	32	(18.1%)	58	(15.8%)
UNEVALUABLE	92		99		191	
TOTAL	282		276		558	

Source: Table AQAW.6.29, page 163, Vol. 45 of 84.

TABLE B5 AQAW: SUMMARY OF SPONSOR'S EFFICACY RESULTS AT TERMINATION

n=558	Favorable Response Rate		95% Confidence Interval
Analysis Population	Dirithromycin 5-day (n=282)	Erythromycin 7-day (n=276)	Dirithromycin vs. Erythromycin
Clinical efficacy in clinically evaluable patients	76.8% (146/190)	65.5% (116/177)	[2.1%, 20.5%]
Bacteriological efficacy in bacteriologically evaluable patients	76.0% (95/125)	68.5% (74/108)	[-4.0%, 19.0%]
Intent-to-treat patients	69.5% (196/282)	65.9% (182/276)	[-4.2%, 11.3%]

Clinical favorable response: cure / improvement
Clinical unfavorable response: failure / relapse
Bacteriologic favorable response: eradication / presumptive eradication
Bacteriological unfavorable response: persistence / presumed microbiology persistence / relapse / eradication with reinfection

Microbiologic Results For bacteriologically evaluable patients, pretherapy pathogen(s) were eradicated or presumptively eradicated for 76.0% (95/125) dirithromycin treated patients. For erythromycin treated patients, pretherapy pathogen(s) were eradicated or presumptively eradicated for 68.5% (74/108) patients. Table B6 showed the break-down of bacteriologic response. It was observed that most of bacteriologically favorable responses were presumptive eradication.

Table B 6 AQAW
Bacteriologic Response Summary by Therapy Group
Bacteriologically-Evaluable Patients at Termination

RESPONSE	DIRITHROMYCIN N = 125 n	(%)	ERYTHROMYCIN N = 108 n	(%)	TOTAL N = 233 n	(%)
ERADICATION	3	(2.4%)	5	(4.6%)	8	(3.4%)
PRESUMPTIVE ERADICATION	92	(73.6%)	69	(63.9%)	161	(69.1%)
ERADICATION WITH REINFECTION	3	(2.4%)	1	(0.9%)	4	(1.7%)
RELAPSE	1	(0.8%)	0		1	(0.4%)
PRESUMED MICROBIOLOG PERSISTENCE	23	(18.4%)	29	(26.9%)	52	(22.3%)
PERSISTENCE	3	(2.4%)	4	(3.7%)	7	(3.0%)

Source: Table AQAW.6.35, page 169, Vol. 45 of 84.

The following table present rates of eradication or presumptive eradication by pathogen. For pretherapy pathogen, *H Influenzae* were eradicated or presumptively eradicated for 72.9% (27/37) dirithromycin patients, compared with 70.2% (26/37) eradication or presumptive eradication for erythromycin patients.

Table B7 AQAW
Bacteriologic Eradication or Presumptive Eradication Rate by Pathogen
Bacteriologically-Evaluable at Termination

PATHOGENS	DIRITHROMYCIN n=125	ERITHROMYCIN n=108
H INFLUENZAE	72.9% (27/37)	70.2% (26/37)
M CATARRHALIS	100.0% (7/7)	60.0% (6/10)
STR PNEUMONIAE	83.3% (10/12)	66.6% (4/6)
ST AUREUS	50.0% (1/2)	33.3%(1/3)
H PARAINFLUENZAE	76.5% (36/47)	72.6% (24/33)
K PNEUMONIAE	100.0% (1/1)	0.0% (0/3)
STR GRP A	(0/0)	100.0% (1/1)
MULTIPLE ORGANISMS	76.4% (13/17)	76.8% (10/13)
KLEBSIELLA SP	0.0% (0/1)	100.0%(2/2)
K OXYTOCA	0.0% (0/1)	

Source: Tables AQAW.6.36 and AQAW.6.38, pages 170 and 173, Vol. 45 of 84.

Reviewer's Comment: Rate in table B7 represented results only for patients with single organism. For patients with multiple organisms, the breakdowns for three major pathogens were as in the following table. The combined results are in section III. Reviewer's Summary.

Pathogens	Dirithromycin	Erythromycin
H. Influenzae	90.0%(10/11)	83.3% (5/6)
M. Catarrhalis	100.0% (4/4)	50.0% (2/4)
S. Pneumoniae	100.0%(10/10)	100.0% (6/6)

Source: Tables AQAW.6.37 and AQAW.6.39, pages 171 and 174, Vol. 45 of 84.

Sponsor's results at posttherapy was summarized in Table B8. The general trend was similar to results at termination.

TABLE B8 AQAW: SUMMARY OF SPONSOR'S EFFICACY RESULTS AT POSTTHERAPY

n=558	Favorable Response Rate		95% Confidence Interval
Analysis Population	Dirithromycin 5-day (n=282)	Erythromycin 7-day (n=276)	Dirithromycin vs. Erythromycin
Clinical efficacy in clinically evaluable patients	86.8% (165/190)	75.1% (133/177)	[3.7%, 19.7%]
Bacteriological efficacy in bacteriologically evaluable patients	81.6% (102/125)	75.9% (82/108)	[-4.9%, 16.2%]
Intent-to-treat patients	77.7% (219/282)	74.6% (206/276)	[-4.0%, 10.1%]

Clinical favorable response: cure / improvement
Clinical unfavorable response: failure / relapse
Bacteriologic favorable response: eradication / presumptive eradication
Bacteriological unfavorable response: persistence / presumed microbiology persistence / relapse / eradication with reinfection

Safety

The data presented in this section are based on information obtained from all patients. All events were recorded regardless of suspected relationship to study drug. Signs and symptoms related to the disease process, including parameters considered to be disease diagnostic criteria, were recorded as events if they were not present on admission and appeared later in the study, or if they were present on admission and worsened during the study.

No deaths were reported for any patients in this study. Eleven patients (6 in the dirithromycin group and 5 in the erythromycin group) experienced events that were reported as serious. No patient experienced an event that met the criteria of an alert report (i.e., serious, unexpected, and possibly causally related).

Seven dirithromycin-treated patients and 16 erythromycin-treated patients discontinued early due to adverse events. One dirithromycin-treated patient and 8 erythromycin-treated patients had events considered probably related to the study drug. Three dirithromycin-treated patients and 3 erythromycin-treated patients had events considered possibly related to study drug. Three dirithromycin-treated patients and 5 erythromycin-treated patients had adverse events resulting in discontinuation that were not thought to be related to study drug.

Two of the 7 dirithromycin-treated patients and 6 of the 16 erythromycin-treated patients experienced adverse events related to the gastrointestinal system. All of the gastrointestinal events resulting in discontinuation of erythromycin-treated patients were considered probably related to study-drug administration. Of the gastrointestinal events affecting patients treated with dirithromycin, one was considered possibly related to study drug and one was not related. Two patients in the dirithromycin

treatment group experienced events related to the body as a whole, one of which was considered probably related to study drug and the other was considered possibly related to study drug. Two patients in the erythromycin treatment group had events related to the body as a whole, both of which were considered probably related to study drug. One dirithromycin-treated patient had an event affecting the cardiovascular system, 2 erythromycin-treated patients reported events affecting the skin and appendages, and 1 erythromycin-treated patient reported an event affecting the nervous system, all of which were considered possibly related to study drug.

Adverse events reported at a rate of greater than or equal to two percent for either treatment group for the total population are listed in Table B9. One or more adverse events were reported from 138 of 282 (48.9%) dirithromycin-treated patients compared with 156 of 276 (56.5%) erythromycin-treated patients (p=.073). When event classification terms were analyzed individually, there was a statistically significant difference between treatment groups in the proportion of patients reporting hypertension (4 [1.4%] dirithromycin-treated and no erythromycin-treated patients reported hypertension [p=.047]) and in the proportion of patients reporting asthenia (5 [1.8%] erythromycin-treated patients and no dirithromycin-treated patients reported asthenia [p=.023]).

Table B9 AQAW
Frequency of Patients Experiencing Adverse Events: All Events
All Patients

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 282 n	(%)	ERYTHROMYCIN N = 276 n	(%)
PATIENTS WITH AT LEAST ONE EVENT	138	(48.9%)	156	(56.5%)
PATIENTS WITH NO EVENT	144	(51.1%)	120	(43.5%)
DIARRHEA	19	(6.7%)	27	(9.8%)
NAUSEA	19	(6.7%)	28	(10.1%)
ABDOMINAL PAIN	17	(6.0%)	19	(6.9%)
HEADACHE	15	(5.3%)	23	(8.3%)
DYSPEPSIA	13	(4.6%)	9	(3.3%)
LUNG DISORDER	11	(3.9%)	17	(6.2%)
PAIN	9	(3.2%)	5	(1.8%)
CHEST PAIN	7	(2.5%)	6	(2.2%)
DYSPNEA	7	(2.5%)	3	(1.1%)
PHARYNGITIS	7	(2.5%)	9	(3.3%)
RHINITIS	6	(2.1%)	11	(4.0%)
DIZZINESS	5	(1.8%)	8	(2.9%)

Source: Tables AQAW.12, page 21, Vol. 45 of 84.

One or more adverse events starting during therapy were reported by 97 (34.4%) patients treated with dirithromycin and by 117 (42.4%) patients treated with erythromycin (p=.052). There were 150 during-therapy events reported by dirithromycin-treated patients and 194 events reported by erythromycin-treated patients. Of all the adverse events, 62.8% of events reported by patients in the dirithromycin group and 72.1% of events reported by patients in the erythromycin group had onset during the period of study-drug therapy. When event terms were analyzed individually, there was a statistically significant difference between the treatment groups for asthenia beginning during therapy (4 [1.4%] erythromycin-treated patients and no dirithromycin-treated patients reported asthenia [p=.042]).

To examine the potential effects of drug therapy on laboratory test results for the total population, an analysis was performed to examine the changes in the mean values for each population for each analyte.

The mean changes were determined from the difference between the average posttherapy and pretherapy measurements using data from all patients having laboratory data for the specific analyte available from both visits.

A statistically significant difference between the treatment groups was seen for the analyte calcium (p=.032). The mean changes for each treatment group were small and were not clinically significant. Statistically significant changes within groups were seen for several analytes. In the absence of untreated control patients, statistically significant differences within the two treatment groups are impossible to ascribe to drug treatment. Categorical analysis of numeric and non-numeric laboratory results revealed a statistically significant difference between treatment groups for the analyte phosphorus, with zero dirithromycin-treated patients having phosphorus values changing from normal or high at admission to low at posttherapy compared with 5 erythromycin-treated patients. None of the mean changes for any analyte approached a level that would be considered of clinical significance.

II.C. Study B9ZMC AQAU

Title
Dirithromycin 5 Days versus Erythromycin Base 7 Days in the Treatment of Skin and Soft Tissue Infections

Objectives
To compare dirithromycin, administered once daily (500 mg/day) for 5 days, to erythromycin, administered every 6 hours (1000 mg/day) for 7 days, for effectiveness and safety in the treatment of skin and soft tissue infections.

Design of the Study
The study design, dosage administration and scheduled visits were the same as study B9ZMC AQAT. The only difference was that the specimen for culture in this study were obtained at the skin infection site (swab or aspirate). The protocol planned to enroll approximately 300 patients in this study in order to obtain a minimum of 140 clinically evaluable patients (70 per treatment group). Later the protocol was amended to target at 300 clinical evaluable patients (150 per treatment group) among 300-400 enrolled patients.

Lab study on blood and urine sample were also done for safety monitoring. Abnormal changes in lab test results was to be reported as adverse events.

Primary Endpoint

Reviewer's comments: Categories of clinical and bacteriologic responses were the same as in study B9ZMC AQAT. Only the definition of each category was different (see clinical review of this submission for the definition). Responses at termination were constructed the same way as in study AQAT. As before, favorable (cure or improvement) clinical response rates among clinical evaluable patients at termination (late posttherapy or posttherapy visits) was considered as the primary endpoint for the evaluation of efficacy by the medical reviewer at FDA. Please note that for patients with multiple infected sites, investigators made their clinical assessment on the basis of all of the patient's infection sites simultaneously.

Analysis Population
Sponsor's efficacy analysis was based on three patient groups: clinically evaluable, bacteriologically evaluable, and Intent-to-treat patients. Clinically evaluable patients included those who met inclusion/exclusion criteria; had appropriate pretherapy and posttherapy history and physical examination,

and met minimum compliance requirement. In order to be bacteriologically evaluable, patient must meet all criteria for clinically evaluable, plus having positive culture for the following pathogens:

Staphylococcus aureus,	*Staphylococcus epidermidis* ,
Streptococcus pyogenes,	*Streptococcus agalactiae*,
Other β-hemolytic streptococci,	*Enterococcus* species,
Haemophilus influenzae,	*Escherichia coli,*
Proteus mirabilis,	*Klebsiella pneumoniae,*
Pseudomonas aeruginosa,	Other Enterobacteriaceae,

The third analysis population was the intent-to-treat population which included all randomized patients, whether they received the study drugs or not.

Conduct of the Study

The study was conducted in the US from December 1991 to August 1992. A total of 439 patients with a diagnosis of bacterial skin or soft tissue infection were enrolled by 12 investigators. Among them 220 patients were randomly allocated to dirithromycin treatment group, and 219 patients to erythromycin treatment group.

Protocol amendment became effective on March 3, 1992 as the result of a discussion with FDA. Prior to the amendment, a patient whose pretherapy culture did not grow a pathogen or grew a pathogen resistant to one or both study drugs was to be discontinued from the study. After the amendment, the patient could remain in the study unless the patient was symptomatically relapsing or failing. There were 144 patients enrolled in this study prior to the protocol amendment.

Demographic and Baseline Characteristics

Table C1 displayed the demographic characteristics of all enrolled patients. Female comprised 44-48% of patients in each treatment group. The mean age was 42.2 years old in dirithromycin group and 41.5 years old in erythromycin group. As for ethnic origin, about 80% patients were Caucasian in both groups, Black comprised about 10% of the patients, and Hispanic comprised 7.3% in dirithromycin group and 11.4% of patients in erythromycin group. There were nine types disease diagnosis. Their distributions are presented in Table C2.

Sponsor reported that the two treatment groups were well matched with respect to demographics including gender, age, ethnic origin, weight and height, smoking, alcohol habits, types of diagnosis and clinical condition at diagnosis.

Reviewer's Comment: Tables with percentage distributions for categorical variables, mean and standard deviation for continuous variables were reported by the sponsor. No p-values were provided. The two treatment groups appear to be balanced with respect to baseline variables mentioned above.

Table C1 AQAU
Baseline Demographic Characteristics
All Patients

	DIRITHROMYCIN N = 220		ERYTHROMYCIN N = 219		TOTAL N = 439	
	n	(%)	n	(%)	n	(%)
MALE	123		113			
FEMALE	97		106			
MEAN AGE	42.23	(±17.69)	41.46	(±17.10)		
MEAN HEIGHT	170.62	(±11)	170.95	(±12)		
MEAN WEIGHT	78.58	(±20)	79.53	(±21)		
ORIGIN:						
CAUCASIAN	176	(80.0%)	168	(76.7%)		
BLACK	26	(11.8%)	20	(9.1%)		
HISPANIC	16	(7.3%)	25	(11.4%)		
NATIVE AMERICAN	1	(0.5%)	3	(1.4%)		
ASIAN	1	(0.5%)	2	(0.9%)		
OTHER	0		1	(0.5%)		

Source: Tables AQAU.2, page 15, Vol. 48 of 84.

Table C2 AQAU
Presenting Diagnosis
All Patients

	DIRITHROMYCIN N = 220		ERYTHROMYCIN N = 219		TOTAL N = 439	
	n	(%)	n	(%)	n	(%)
ABSCESS, SUBCUTANEOUS	110	(50.0%)	114	(52.1%)	224	(51.0%)
CELLULITIS	28	(12.7%)	26	(11.9%)	54	(12.3%)
ERYSIPELAS	0		1	(0.5%)	1	(0.2%)
IMPETIGO	11	(5.0%)	15	(6.8%)	26	(5.9%)
INFECTION, POSTOPERATIVE WOUND	14	(6.4%)	9	(4.1%)	23	(5.2%)
INFECTION, TRAUMATIC WOUND	24	(10.9%)	31	(14.2%)	55	(12.5%)
LYMPHANGITIS	1	(0.5%)	2	(0.9%)	3	(0.7%)
PYODERMA	30	(13.6%)	15	(6.8%)	45	(10.3%)
SKIN, ULCER INFECTED	2	(0.9%)	6	(2.7%)	8	(1.8%)

Source: Tables AQAU.5.13, page 137, Vol. 48 of 84.

Discontinuation/Completion Information

A total of 343 patients (78%) completed the study protocol. Among them 168 patients (76.4%) were in dirithromycin group, and 175 (79.9%) in the comparator group (Table C3). Lack of efficacy was the most

common reason for early withdrawals for both treatment groups: 8.6% and 6.8% for dirithromycin and erythromycin respectively. Adverse events accounted for 3.2% withdrawals in both arms. Patient listed as ENTRY CRITERIA EXCLUSION included patient who discontinued due to pretherapy microbiology results before the protocol amendment.

Table C3 AQAU
Reasons Patients Discontinued
All Patients

REASON STUDY DRUG DISCONTINUED	DIRITHROMYCIN N = 220 n	(%)	ERYTHROMYCIN N = 219 n	(%)
PROTOCOL COMPLETE	168	(76.4%)	175	(79.9%)
LACK OF EFFICACY	19	(8.6%)	15	(6.8%)
LOST TO FOLLOW-UP	5	(2.3%)	3	(1.4%)
PATIENT DECISION	4	(1.8%)	2	(0.9%)
ENTRY CRITERIA EXCLUSION	15	(6.8%)	13	(5.9%)
PROTOCOL VIOLATION	2	(0.9%)	4	(1.8%)
ADVERSE EVENT	7	(3.2%)	7	(3.2%)

Source: Table AQAU.5.15, page 139, Vol. 48 of 84.

Efficacy Results

Of the 220 patients who received dirithromycin, 187 (85.0%) were clinically evaluable. Among them, 100 (45.4% of all 220 patients) were also bacteriologically evaluable. Of the 219 patients who received erythromycin, 184 (84.0%) patients were clinically evaluable. Of the 184 clinically evaluable patients, 111 patients (50.6% of all 219 patients) were also bacteriologically evaluable.

Reviewer's Comment: The sponsor presented efficacy results at two time points: posttherapy visit (3-5 days after the completion of the therapy) and at termination. The posttherapy visit was treated as the test-of-cure visit in study report. As in studies B9ZMC AQAT and B9ZMC AQAW, results at termination were considered the primary basis for efficacy evaluation.

Clinical Results Among 187 clinically evaluable patients treated with dirithromycin, favorable clinical response (cure or improvement) was observed in 84.5% (158) patients. Among 184 clinically evaluable patients treated with eythromycin, favorable clinical response(cure or improvement) was observed in 81.5% (150) patients. Table C4 showed the breakdown of clinical responses for the two treatment groups. The 95% confidence interval for the difference (dirithromycin - erythromycin) between favorable clinical response rates of the two groups was [-4.8%, 10.8%].

Table C4 AQAU
Clinical Response Summary by Therapy Group
Clinically-Evaluable Patients at Termination

RESPONSE	DIRITHROMYCIN n	(%) N=220	ERYTHROMYCIN n	(%) N=219	TOTAL n	(%) N=439
CURE	133	(71.1%)	140	(76.1%)	273	(73.6%)
IMPROVEMENT	25	(13.4%)	10	(5.4%)	35	(9.4%)
RELAPSE	13	(7.0%)	23	(12.5%)	36	(9.7%)
FAILURE	16	(8.6%)	11	(6.0%)	27	(7.3%)
TOTAL	187		184		371	

Source: Table AQAU.6.23, page 165, Vol. 48 of 84.

Reviewer's Comment: The sponsor calculated 95% confidence intervals without correction for continuity. If the calculation were done with the correction for continuity, 95% confidence intervals would be slightly wider than reported.

TABLE C5 AQAU: SUMMARY OF SPONSOR'S EFFICACY RESULTS AT TERMINATION

n=439	Favorable Response Rate		95% Confidence Interval
Analysis Population	Dirithromycin 5-day (n=220)	Erythromycin 7-day (n=219)	Dirithromycin vs. Erythromycin
Clinical efficacy in clinically evaluable patients	84.5% (158/187)	81.5% (150/184)	[-4.8%, 10.8%]
Bacteriological efficacy in clinically and bacteriologically evaluable patients	85.0% (85/100)	80.2% (89/111)	[-5.6%, 16.2%]
Intent-to-treat patients	85.0% (187/220)	80.8% (177/219)	[-3.0%, 11.4%]

Clinical favorable response: cure / improvement
Clinical unfavorable response: failure / relapse
Bacteriologic favorable response: eradication / presumptive eradication
Bacteriological unfavorable response: persistence / presumed microbiology persistence / relapse / eradication with reinfection

Reviewer's Comments: A patient may be cured without being clinically evaluable, that is why favorable clinical response rate for intent-to-treat population may be higher than that for clinically evaluable population.

Please note also that sponsor's bacteriologically evaluable population was in fact both clinically and bacteriologically evaluable by definition.

Microbiologic Results For bacteriologically evaluable patients, pretherapy pathogen(s) were eradicated or presumptively eradicated for 85.0% (85/100) dirithromycin treated patients. For 111 erythromycin treated patients who were bacteriologically evaluable, pretherapy pathogen(s) were eradicated or presumptively eradicated for 80.2% (89/111) patients. Table C6 showed the break-down of bacteriologic response. Most of bacteriologically favorable responses were presumptive eradication.

Table C 6 AQAU
Bacteriologic Response Summary by Therapy Group
Bacteriologically-Evaluable Patients at Termination

RESPONSE	DIRITHROMYCIN N = 100 n	(%)	ERYTHROMYCIN N = 111 n	(%)	TOTAL N = 211 n	(%)
ERADICATION	4	(4.0%)	0		4	(1.9%)
PRESUMPTIVE ERADICATION	81	(81.0%)	89	(80.2%)	170	(80.6%)
PRESUMED MICROBIOLOG PERSISTENCE	11	(11.0%)	14	(12.6%)	25	(11.8%)
PERSISTENCE	4	(4.0%)	8	(7.2%)	12	(5.7%)

Source: Table AQAU.6.29, page 171, Vol. 48 of 84.

Microbiological results by pathogen for patients who were bacteriologically evaluable were presented in Table C7. Pathogen *S. Pyogenes* (Listed as *STR GRP A* in table C7) was eradicated or presumptively eradicated for 100% (5/5) patients for both dirithromycin and erythromycin groups.

Table C7 AQAU
Bacteriologic Eradication or Presumptive Eradication Rate by Pathogen
Bacteriologically-Evaluable at Termination

PATHOGENS	DIRITHROMYCIN n=103	ERITHROMYCIN n=108
S AUREUS	78.4% (44/56)	91.4% (54/59)
MULTIPLE ORGANISMS	88.8% (16/18)	88.8% (24/27)
STR GRP D	100.0% (3/3)	100.0% (3/3)
STR GRP C	100.0% (1/1)	
ST EPIDERMIDIS	100.0% (8/8)	100.0% (13/13)
STR GRP A	100.0% (5/5)	100.0% (5/5)
STR GRP G	100.0% (2/2)	100.0% (1/1)
PS AERUGINOSA	100.0% (2/2)	
E AGGLOMERANS	100.0% (1/1)	
S MARCESCENS	100.0% (1/1)	
H INFLUENZAE	100.0% (1/1)	
STR GRP B	100.0% (1/1)	100.0% (2/2)
PR MIRABILIS	100.0% (1/1)	
K PNEUMONIAE		100.0% (1/1)

Source: Tables AQAU.6.30 and AQAU.6.32, pages 172 and 175, Vol. 48 of 84.

Reviewer's Comment: As in studies AQAT and AQAW, rates in table C7 were only for patients with single organism. For patients with multiple organisms, the breakdowns for two major pathogens were as in the following table. The combined results by pretherapy pathogen are in section III. Reviewer's Summary.

Pathogens	Dirithromycin	Erythromycin
S. Aureus	85.7%(12/14)	68.8% (11/16)
S. Pyogenes (Str Grp A)	100.0%(3/3)	85.7% (6/7)

Source: Tables AQAU.6.31 and AQAU.6.33, pages 173 and 176, Vol. 48 of 84.

TABLE C8 AQAU: SUMMARY OF SPONSOR'S EFFICACY RESULTS AT POSTTHERAPY

n=439	Favorable Response Rate		95% Confidence Interval
Analysis Population	Dirithromycin 5-day (n=220)	Erythromycin 7-day (n=219)	Dirithromycin vs. Erythromycin
Clinical efficacy in clinically evaluable patients	86.6% (162/187)	90.8% (167/184)	[-10.7%, 2.4%]
Bacteriological efficacy in clinically and bacteriologically evaluable patients	87.0% (87/100)	85.6% (95/111)	[-8.1%, 10.9%]
Intent-to-treat patients	86.8% (191/220)	88.5% (194/219)	[-8.0%, 4.5%]

Clinical favorable response: cure / improvement
Clinical unfavorable response: failure / relapse
Bacteriologic favorable response: eradication / presumptive eradication
Bacteriological unfavorable response: persistence / presumed microbiologic persistence / relapse / eradication with reinfection

Table C8 summarized the sponsor's results at posttherapy. The general trend was similar to results at termination. The favorable response rates were slightly higher than those at termination. The reason was that some cured or improved patients at posttherapy visit relapsed at late postterapy visit.

This study examined nine skin and soft-tissue infection diagnoses: subcutaneous abscess (including paronychia, furuncle, or carbuncle), impetigo, pyoderma, infected skin ulcer; post-surgical wound infection, traumatic wound infection, cellulitis, erysipelas, and lymphangitis. Clinical and bacteriologic response for each of the three patient data sets (all patients, clinically evaluable patients, and bacteriologically evaluable patients) by diagnosis at posttherapy were presented by sponsor. Results across different types of infection were consistent with pooled results.

Patients whose infections required incision and drainage in addition to study drug treatment were analyzed both separately and in combination with all other patients meeting the skin and soft tissue diagnostic criteria. Cochran-Mantel-Haenszel tests were performed by the sponsor to test the difference between treatment groups with respect to favorable response rates, after adjusting for the effects of incision and drainage procedure. No statistically significant differences were found.

Safety

Safety evaluation was based on reports of adverse events and abnormal laboratory results. Same rule as in study B9ZMC AQAT in determining adverse events were applied.

No deaths were reported during the course of this study. Four patients, 2 in each treatment group, experienced events which were reported as serious; however, none met the criteria of an alert report (ie, serious, unexpected, and possibly causally related). None of the events were considered related to study-drug administration.

Seven dirithromycin-treated patients and 7 erythromycin-treated patients discontinued early due to adverse events. Three of the 7 dirithromycin-treated patients and 4 of the 7 erythromycin-treated patients experienced adverse events related to the gastrointestinal system. These gastrointestinal events resulting in discontinuation were presumed to be related to study-drug administration. Additionally, one dirithromycin-treated patient discontinued because of a rash which was presumed to be related to study drug. Three dirithromycin-treated patients and 3 erythromycin-treated patient had adverse events resulting in discontinuation that were not thought to be related to study drug.

Adverse events reported at a rate of greater than or equal to two percent for either treatment group for the total population are listed in Table C9. When the entire study period was considered, at least one adverse event was reported from 92 of 220 (41.8%) patients treated with dirithromycin compared to 96 of 219 (43.8%) treated with erythromycin (p=0.669). When event classification terms were analyzed individually, there was a statistically significant difference between treatment groups in the proportion of all patients reporting nausea; 8 dirithromycin-treated patients reported nausea compared with 20 erythromycin-treated patients (p=0.018).

Table C9 AQAU
Frequency of Patients Experiencing Adverse Events: All Events
All Patients

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 220 n	(%)	ERYTHROMYCIN N = 219 n	(%)	PVALUE
PATIENTS WITH AT LEAST ONE EVENT	92	(41.8%)	96	(43.8%)	0.669
PATIENTS WITH NO EVENT	128	(58.2%)	123	(56.2%)	0.669
ABDOMINAL PAIN	20	(9.1%)	19	(8.7%)	0.879
HEADACHE	17	(7.7%)	15	(6.8%)	0.723
DIARRHEA	15	(6.8%)	21	(9.6%)	0.29
DYSPEPSIA	11	(5.0%)	6	(2.7%)	0.22
NAUSEA	8	(3.6%)	20	(9.1%)	0.018
SURGICAL PROCEDURE	8	(3.6%)	3	(1.4%)	0.129
PAIN	7	(3.2%)	9	(4.1%)	0.604
INFECTION	3	(1.4%)	5	(2.3%)	0.471
RHINITIS	3	(1.4%)	5	(2.3%)	0.471

Source: Tables AQAU.12, page 22, Vol. 48 of 84.

No statistically significant difference between the treatment groups was seen; however, statistically significant changes within groups were seen for several analytes. In the absence of untreated control patients, statistically significant differences within the two treatment groups are impossible to ascribe to

drug treatment. None of the mean changes for any analyte approached a level that would be considered of clinical significance.

II.D. Study B9ZMC AQAX

Study B9ZMC AQAX design was identical to that of study B9ZMC AQAU.

Conduct of the Study

A total of 368 patients with a diagnosis of bacterial skin or soft tissue infection were enrolled by 21 investigators in the US from February 1992 to January 1993.. Among them 181 patients were randomly allocated to dirithromycin treatment group, and 187 patients to erythromycin treatment group.

Protocol amendment became effective on March 3, 1992.

Demographic and Baseline Characteristics

Table D1 displayed the demographic characteristics of all enrolled patients. Female comprised 42.5% of patients in dirithromycin group and 52.9% of patients in erythromycin group. The mean age was 41.6-42.4 years old in two groups. As for ethnic origin, more than 80% patients were Caucasian in both groups, Black and Hispanic took less than 10% of all patients. There were nine types disease diagnosis. Their distributions were presented in Table D2.

Sponsor reported that the two treatment groups were well matched with respect to demographics including gender, age, ethnic origin, weight and height, smoking, alcohol habits, types of diagnosis and clinical condition at diagnosis.

Table D1 AQAX
Baseline Demographic Characteristics
All Patients

	DIRITHROMYCIN N = 181		ERYTHROMYCIN N = 187	
	n	(%)	n	(%)
MALE	104		88	
FEMALE	77		99	
MEAN AGE	41.63	(±16.84)	42.24	(±17.97)
MEAN HEIGHT	171.17	(±10)	170.19	(±10)
MEAN WEIGHT	83.43	(±21)	80.64	(±21)
ORIGIN:				
CAUCASIAN	156	(86.2%)	155	(82.9%)
BLACK	11	(6.1%)	18	(9.6%)
HISPANIC	13	(7.2%)	12	(6.4%)
NATIVE AMERICAN	0		2	(1.1%)
ASIAN	1	(0.6%)	0	

Source: Tables AQAX.2, page 173, Vol. 50 of 84.

Table D2 AQAX
Presenting Diagnosis
All Patients

	DIRITHROMYCIN N = 181		ERYTHROMYCIN N = 187		TOTAL N = 368	
	n	(%)	n	(%)	n	(%)
ABSCESS, SUBCUTANEOUS	100	(55.2%)	95	(50.8%)	195	(53.0%)
CELLULITIS	8	(4.4%)	11	(5.9%)	19	(5.2%)
ERYSIPELAS	0		1	(0.5%)	1	(0.3%)
IMPETIGO	25	(13.8%)	23	(12.3%)	48	(13.0%)
INFECTION, POSTOPERATIVE WOUND	6	(3.3%)	6	(3.2%)	12	(3.3%)
INFECTION, TRAUMATIC WOUND	24	(13.3%)	22	(11.8%)	46	(12.5%)
PYODERMA	15	(8.3%)	25	(13.4%)	40	(10.9%)
SKIN, ULCER INFECTED	3	(1.7%)	4	(2.1%)	7	(1.9%)

Source: Tables AQAX.5.13, page 137, Vol. 50 of 84.

Discontinuation/Completion Information

A total of 312 patients (85%) completed the study protocol. Among them 154 patients (85.1%) were in dirithromycin group, and 158 (84.5%) in the comparator group (Table D3). Lack of efficacy was a common reason for early withdrawals for both treatment groups: 7.2% and 4.8% for dirithromycin and erythromycin respectively. Three (1.7%) patients in dirithromycin group withdrew from the study due to adverse events, while 11 patients in erythromycin group withdrew for the same reason.

Table D3 AQAX
Reasons Patients Discontinued
All Patients

REASON STUDY DRUG DISCONTINUED	DIRITHROMYCIN N = 181		ERYTHROMYCIN N = 187	
	n	(%)	n	(%)
PROTOCOL COMPLETE	154	(85.1%)	158	(84.5%)
LACK OF EFFICACY - PHYS	7	(3.9%)	6	(3.2%)
LACK OF EFFICACY - BOTH	6	(3.3%)	3	(1.6%)
UNABLE TO CONTACT	4	(2.2%)	4	(2.1%)
PATIENT DECISION-PERSONAL	2	(1.1%)	0	
PATIENT DECISION-OTHER	1	(0.6%)	1	(0.5%)
ENTRY CRITERIA NOT MET	3	(1.7%)	1	(0.5%)
PROTOCOL VARIANCE	1	(0.6%)	3	(1.6%)
ADVERSE EVENT	3	(1.7%)	11	(5.9%)

Source: Table AQAX.5.15, page 294, Vol. 50 of 84.

Efficacy Results

Of the 181 patients who were randomized to dirithromycin, 161 (90%) were clinically evaluable. Among 161 clinically evaluable patients, 104 patients (57% of all 181 patients) were also bacteriologically evaluable. Of the 187 patients who were randomized to erythromycin, 151 patients (81%) were clinically evaluable. Of the 151 clinically evaluable patients, 82 patients (44% of all 187 patients) were also bacteriologically evaluable.

Table D4 AQAX
Clinical Response Summary by Therapy Group
Clinically-Evaluable Patients at Termination

RESPONSE	DIRITHROMYCIN n (%) N=181		ERYTHROMYCIN n (%) N=187		TOTAL n (%) N=368	
CURE	113	(70.2%)	107	(70.9%)	220	(70.5%)
IMPROVEMENT	26	(16.1%)	23	(15.2%)	49	(15.7%)
RELAPSE	8	(5.0%)	14	(9.3%)	22	(7.1%)
FAILURE	14	(8.7%)	7	(4.6%)	21	(6.7%)
TOTAL	161		151		312	

Source: Table AQAX.6.23, page 321, Vol. 50 of 84.

TABLE D5 AQAX: SUMMARY OF SPONSOR'S EFFICACY RESULTS AT TERMINATION

n=368	Favorable Response Rate		95% Confidence Interval
Analysis Population	Dirithromycin 5-day (n=181)	Erythromycin 7-day (n=187)	Dirithromycin vs. Erythromycin
Clinical efficacy in clinically evaluable patients	86.3% (139/161)	86.1% (130/151)	[-7.4%, 7.9%]
Bacteriological efficacy in clinically and bacteriologically evaluable patients	85.6% (89/104)	86.6% (71/82)	[-11.0%, 9.0%]
Intent-to-treat patients	85.1% (154/181)	85.6% (160/187)	[-7.7%, 6.8%]

Clinical favorable response: cure / improvement
Clinical unfavorable response: failure / relapse
Bacteriologic favorable response: eradication / presumptive eradication
Bacteriological unfavorable response: persistence / presumed microbiologic persistence / relapse / eradication with reinfection

Clinical Results Among 161 clinically evaluable patients treated with dirithromycin, favorable clinical response (cure or improvement) was observed in 86.3% (139) patients. Among 151 clinically evaluable

patients treated with erythromycin, favorable clinical response(cure or improvement) was observed in 86.1% (130) patients. The 95% confidence interval for the difference (dirithromycin - erythromycin) between favorable clinical response rates was [-7.4%, 7.9%]. Table D4 showed the breakdown of clinical responses for the two treatment groups.

Reviewer's Comment: The above 95% confidence interval for difference meets the criteria for equivalence. This suggests that dirithromycin is equivalent to erythromycin in efficacy.

Microbiologic Results For bacteriologically evaluable patients, pretherapy pathogen(s) were eradicated or presumptively eradicated for 85.6% (89/104) dirithromycin treated patients. For 82 erythromycin treated patients who were bacteriologically evaluable, pretherapy pathogen(s) were eradicated or presumptively eradicated for 86.6% (71/82) patients. Table D6 showed the break-down of bacteriologic response. Most of bacteriologically favorable responses were presumptive eradication.

Table D 6 AQAX
Bacteriologic Response Summary by Therapy Group
Bacteriologically-Evaluable Patients at Termination

RESPONSE	DIRITHROMYCIN N = 104 n	(%)	ERYTHROMYCIN N = 82 n	(%)	TOTAL N = 186 n	(%)
ERADICATION	1	(1.0%)	1	(1.2%)	2	(1.1%)
PRESUMPTIVE ERADICATION	88	(84.6%)	70	(85.4%)	158	(84.9%)
ERADICATION WITH REINFECTION	0		1	(1.2%)	1	(0.5%)
PRESUMED MICROBIOLOG PERSISTENCE	13	(12.5%)	6	(7.3%)	19	(10.2%)
PERSISTENCE	2	(1.9%)	4	(4.9%)	6	(3.2%)

Source: Table AQAX.6.29, page 327, Vol. 50 of 84.

Table D7 AQAX
Bacteriologic Eradication or Presumptive Eradication Rate by Pathogen
Bacteriologically-Evaluable at Termination

PATHOGENS	DIRITHROMYCIN n=104		ERITHROMYCIN n=82	
MULTIPLE ORGANISMS	84.0%	(21/25)	81.2%	(13/16)
ST AUREUS	86.0%	(43/50)	91.1%	(31/34)
ST EPIDERMIDIS	88.2%	(15/17)	77.7%	(7/9)
ENTEROBACTER SP	75.0%	(3/4)	75.0%	(3/4)
E COLI	50.0%	(1/2)	100.0%	(3/3)
PR MIRABILIS	100.0%	(2/2)	66.6%	(2/3)
STR GRP A	100.0%	(2/2)	100.0%	(3/3)
K PNEUMONIAE	100.0%	(1/1)	100.0%	(1/1)
STR GRP B	100.0%	(1/1)	100.0%	(1/1)
STR GRP C			100.0%	(1/1)
STR GRP D			100.0%	(6/6)
H INFLUENZAE			100.0%	(1/1)

Source: Tables AQAX.6. and AQAX.6.32, pages 328 and 332, Vol. 50 of 84.

Microbiological results by pathogen for patients who were bacteriologically evaluable were presented in Table D7. Pathogen *S. Pyogenes* (Listed as *STR GRP A* in table D7) was eradicated or presumptively eradicated for 100% (2/2) dirithromycin patients and 100% (3/3) erythromycin.

Reviewer's Comment: Rates in table D7 were only for patients with single organism. For patients with multiple organisms, the breakdowns for two major pathogens were as in the following table. The combined results by pretherapy pathogen are in section III. Reviewer's Summary.

Pathogens	Dirithromycin	Erythromycin
S. Aureus	85.7% (18/21)	90.9% (10/11)
S. Pyogenes (Str Grp A)	100.0% (4/4)	100.0% (5/5)

Source: Tables AQAX.6.31 and AQAX.6.33, pages 329 and 333, Vol. 50 of 84.

Table D8 summarized the sponsor's results at posttherapy. The general trend was similar to results at termination.

As in study B9ZMC AQAU, this study examined efficacy results by eight infection diagnoses: subcutaneous abscess (including paronychia, furuncle, or carbuncle), cellulitis, erysipelas, impetigo, post-surgical wound infection, traumatic wound infection, pyoderma, and infected skin ulcer. Results (at posttherapy) across different types of infection were consistent with pooled results.

For the subgroup of patients whose infections required incision and drainage in addition to study drug treatment, Cochran-Mantel-Haenszel tests were performed by the sponsor to test the difference between treatment groups with respect to favorable bacteriologic response rate, after adjusting for the effects of incision and drainage procedure. No statistically significant differences were found.

TABLE D8 AQAX: SUMMARY OF SPONSOR'S EFFICACY RESULTS AT POSTTHERAPY

n=368	Favorable Response Rate		95% Confidence Interval
Analysis Population	Dirithromycin 5-day (n=181)	Erythromycin 7-day (n=187)	Dirithromycin vs. Erythromycin
Clinical efficacy in clinically evaluable patients	90.1% (145/161)	93.4% (141/151)	[-9.4%, 2.8%]
Bacteriological efficacy in clinically and bacteriologically evaluable patients	88.5% (92/104)	90.2% (74/82)	[-10.7%, 7.1%]
Intent-to-treat patients	88.4% (160/181)	92.5% (173/187)	[-10.1%, 1.9%]

Clinical favorable response: cure / improvement
Clinical unfavorable response: failure / relapse
Bacteriologic favorable response: eradication / presumptive eradication
Bacteriological unfavorable response: persistence / presumed microbiologic persistence / relapse / eradication with reinfection

Safety

Safety evaluation was based on reports of adverse events and abnormal laboratory results. Same rule in determining adverse events were applied as in study B9ZMC AQAT.

No deaths were reported during the course of this study. Three patients, 2 in the dirithromycin treatment group and 1 in the erythromycin treatment group, experienced events that were reported. These events were abscess, chest pain, and allergic reaction, respectively. A report was also made to the FDA on a fourth patient who experienced postsurgical wound infection and chronic obstructive pulmonary disease (COPD); the infection was not considered to be an adverse event by the study investigator because it was the primary study condition, and the COPD was not diagnosed until after the patient was discontinued from the study for the reason lack of efficacy. The serious adverse event of chest pain, which was experienced by dirithromycin-treated patient 118-7327, met the criteria for an alert report (ie, serious, unexpected, and possibly causally related). The esophagitis, duodenitis, and esophageal dysmotility that occurred in this patient were more likely to be related to an underlying esophageal motility; however, a causal relationship to study drug could not be excluded.

Adverse events reported at a rate of greater than or equal to two percent for either treatment group for the total population are listed in Table D9. When the entire study period was considered, at least one adverse event was reported by 69 of 181 (38.1%) patients treated with dirithromycin compared with 81 of 187 (43.3%) patients treated with erythromycin (p=.311). When event classification terms were analyzed individually, no statistically significant differences were found between treatment groups in the proportion of all patients reporting any adverse event. One unintended pregnancy was reported by a patient in the erythromycin treatment group. The patient had a negative urine pregnancy test at study enrollment, but results of a repeat urine pregnancy test at posttherapy were positive. The patient experienced an uneventful pregnancy and delivered a healthy baby boy.

Table D9 AQAX
Frequency of Patients Experiencing Adverse Events: All Events
All Patients

EVENT CLASSIFICATION TERM	DIRITHROMYCIN N = 181 n	(%)	ERYTHROMYCIN N = 187 n	(%)	PVALUE
PATIENTS WITH AT LEAST ONE EVENT	69	(38.1%)	81	(43.3%)	0.311
PATIENTS WITH NO EVENT	112	(61.9%)	106	(56.7%)	0.311
HEADACHE	16	(8.8%)	15	(8.0%)	0.777
ABDOMINAL PAIN	15	(8.3%)	7	(3.7%)	0.066
DIARRHEA	12	(6.6%)	17	(9.1%)	0.381
NAUSEA	11	(6.1%)	20	(10.7%)	0.111
RASH	8	(4.4%)	5	(2.7%)	0.364
INFECTION	5	(2.8%)	4	(2.1%)	0.699
FLATULENCE	1	(0.6%)	4	(2.1%)	0.189
RHINITIS	1	(0.6%)	6	(3.2%)	0.062
VOMITING	1	(0.6%)	6	(3.2%)	0.062

Source: Tables AQAX.12, pages 179, Vol. 50 of 84.

When the subset of events that were reported to start during the course of study-drug therapy were analyzed, at least one event was reported by 47 (26.0%) patients treated with dirithromycin and by 62

(33.2%) patients treated with erythromycin (p=.131). When event classification terms were analyzed individually, no statistically significant differences were found between treatment groups in the proportion of all patients reporting any adverse event with onset during therapy.

A statistically significant difference between the treatment groups was seen for mean cell volume (MCV), with the MCV increasing for patients in the dirithromycin treatment group and decreasing for patients in the erythromycin group (p=.018). Statistically significant changes within groups were seen for several analytes. In the absence of untreated control patients, statistically significant differences within the two treatment groups are impossible to ascribe to drug treatment. None of the mean changes for any analyte approached a level that would be considered of clinical significance. Categorical analysis of numeric and non-numeric laboratory results revealed a statistically significant difference between treatment groups for urine analysis of ketones, with 15 patients in the dirithromycin treatment group changing from normal to abnormal compared with 5 erythromycin patients (p=.017). This change in urine ketone status was not thought to be clinically significant.

III. REVIEWER'S SUMMARY

Studies AQAT and AQAW

Studies AQAT and AQAW were designed to evaluate the efficacy and safety of dirithromycin taken for 5 days in the treatment of acute superimposed on chronic bronchitis. The study was a double-blind, double-dummy, randomized, multicenter study with two treatment arms. Erythromycin 250mg tablet every 6 hours was the active control drug. The two studies used the same design, disease diagnosis criteria, evaluation criteria as well as data analysis methods.

Sponsor submitted clinical and bacteriologic results at two time points: posttherapy visit (3-5 days after the completion of the therapy) and termination. Patient response at termination was obtained by carrying the last observation available from either late posttherapy visit (10-14 days after the completion of the therapy) or posttherapy visit. In any case, failure or relapse at posttherapy visit were always carried forward. Sponsor used posttherapy visit as the test-of-cure visit to define patient's evaluability status and final results. However, medical reviewer at FDA considered results at termination as the results at test-of-cure visit. The primary endpoint was the favorable clinical response (cure or improvement) rate.

A total of 1057 patients were randomized to two treatment arms in these two studies, among them 499 patients were in study AQAT and 558 patients were in study AQAW. Either study had adequate number of evaluable patients. Sponsor reported that for each of the study, the two treatment groups were well matched with respect to age, gender, height, weight, origin, smoking and alcohol habits, presenting clinical condition, and historical diagnosis. The patient characteristics were also similar between the two studies.

Efficacy results for individual study as well as the two studies pooled were summarized in the following table. The clinical favorable responses (cure or improvement) were achieved in 77.4% (127/164) dirithromycin-treated patients in study AQAT, compared with 79.8% (127/159) in erythromycin treated patients. In study AQAW, favorable clinical response rate was 76.8% (146/190) for dirithromycin-treated patients, and 65.5% (116/177) for erythromycin treated patients. Result of this study showed that dirithromycin is slightly better in efficacy than erythromycin. Overall 77.1% dirithromycin-treated patients achieved favorable clinical response, which was 4.8% higher than that of erythromycin-treated. The 95% confidence interval (95% CI) was calculated (without correction for continuity) for the difference between response rates of the two groups. Whether for individual study or for the two studies combined, the lower bounds of the 95% CIs were all above the FDA "Points to Consider" document recommended cut-off points, which demonstrates the therapeutic equivalence of the two drugs.

Efficacy Results: Favorable Response Rates at Termination AQAT and AQAW				
Studies	Dirithromycin	Erythromycin	95% CI[3]	Cut-off [4]
Clinical response[1]				
AQAT (n=499)	77.4% (127/164)	79.8% (127/159)	[-11.5%, 6.7%]	-20%
AQAW (n=558)	76.8% (146/190)	65.5% (116/177)	[2.1%, 20.5%]	-20%
AQAT+AQAW(n=1057)	77.1% (273/354)	72.3% (243/336)	[-1.7%, 11.3%]	-20%
Microbiological response[2]				
AQAT	73.7% (76/103)	79.6% (86/108)	[-17.5%, 5.8%]	
AQAW	76.0% (95/125)	68.5% (74/108)	[-4.0%, 19.0%]	
AQAT+AQAW	75.0% (171/228)	74.1% (160/216)	[-7.2%, 9.0%]	

[1] Among clinically evaluable patients.
[2] Among clinically and bacteriologically evaluable patients.
[3] Confidence interval for the difference in favorable response rates: dirithromycin-erythromycin
[4] FDA "Points to Consider" document recommended cut-off for the lower bound of 95% CI.

Microbiological eradication or presumptive eradication rates for the subset of both clinically and bacteriologically evaluable population supported the clinical results. Correlation between bacteriologic response and clinical response were shown by the sponsor. However, it was in part due to the fact that most of the favorable bacteriologic responses (eradication or presumptive eradication) were presumptive eradications, which were derived from clinical response of cure or improvement.

The following table displayed microbiological results by three major organisms for the indication of acute exacerbation of chronic bronchitis. The total isolates included patients with single or multiple pretherapy pathogens. *H. Influenzae* was the pathogen that sponsor proposed to be added on to the label. There were a total of 85 patients with *H. Influenzae* treated with dirithromycin in two studies, and 66 (78%) of them were eradicated or presumptively eradicated. For erythromycin treated patients, pretherapy *H. Influenzae* was eradicated or presumptively eradicated for 59 of 87 (68%) isolates. The eradication/presumptive eradication rates for other two pathogens were also similar between two groups for the two studies combined. Overall dirithromycin had a 19% higher eradication/presumptive eradication rate for *M. Catarrahalis* than erythromycin, but it was not statistically significant (p=0.157, Fisher's Test).

Eradication or Presumptive Eradication Rates[1] at Termination of Three Major Pathogens AQAT and AQAW						
	AQAT		AQAW		AQAT+AQAW	
Pathogen	Dirithro.	Erythro.	Dirithro.	Erythro.	Dirithro.	Erythro.
H. Influenzae	78% (29/37)	64% (28/44)	77% (37/48)	72% (31/43)	78% (66/85)	68% (59/87)
S. Pneumoniae	71% (12/17)	88% (7/8)	91% (20/22)	83% (10/12)	82% (32/39)	85% (17/20)
M. Catarrahalis	82% (9/11)	87% (13/15)	100% (11/11)	57% (8/14)	91% (20/22)	72% (21/29)

[1] Among clinically and bacteriologically evaluable patients.

Studies AQAU and AQAX

Studies AQAU and AQAX were a pair of studies designed to evaluate the efficacy and safety of dirithromycin (same dose) in the treatment of (uncomplicated) skin and skin-structure (sometimes referred to as skin and soft tissue infections by the sponsor) infections. The study was a double-blind, double-dummy, randomized, multicenter study with two treatment arms. Erythromycin was the active control drug as in studies AQAT and AQAW. The two studies used the same design, disease diagnosis criteria,

evaluation criteria as well as statistical methods. In addition, this pair of studies were conducted and analyzed in a similar fashion as bronchitis studies, except the criteria for diagnosis and evaluation were different. The specimen for culture in these two studies was obtained at infection sites by swab or aspiration, while in studies AQAT and AQAW sputum was collected for culture.

As in studies for bronchitis, sponsor used posttherapy visit as the test-of-cure visit to define patient's evaluability status and final results. However, medical reviewer at FDA considered results at termination as the results at test-of-cure visit. The primary endpoint was the favorable clinical response (cure or improvement) rate.

A total of 807 patients were randomized to two treatment arms in these two studies, among them 439 patients were in study AQAU and 368 patients were in study AQAX. The number of evaluable patients in either study was adequate. Patient population for these two studies included nine subgroups of skin and skin structure infections (disease diagnosis), slightly more than a half of them were subcutaneous abscess. Sponsor reported that the patient population of the two studies were similar in age, gender distribution, and origin. The two treatment groups were well matched with respect to age, gender, height, weight, origin, and presenting clinical condition for each study as well as for both studies combined.

The following table summarized efficacy results of studies AQAU and AQAX as well as the two studies combined. In study AQAU, clinical favorable responses (cure or improvement) were observed among 84.5% (158/187) dirithromycin-treated patients, while it was observed among 81.5% (150/184) erythromycin treated patients. In study AQAX, favorable clinical response rate was 86.3% (139/161) for dirithromycin-treated patients, and 86.1% (130/151) for erythromycin treated patients. Results of the two treatment group were very similar in both studies, which yielded an overall 85.3% (297/348) favorable clinical response rates for dirithromycin group and 83.6% (280/335) for erythromycin group. The 95% confidence intervals for the three sets of patients all satisfy criteria for therapeutic equivalence.

Microbiological results were consistent with the clinical results. Percentages of eradication or presumptive eradication of pretherapy pathogen(s) for the subset of both clinically and bacteriologically evaluable population were all above 80%. Correlation between bacteriologic response and clinical response were shown by the sponsor. As pointed out earlier, it was partly because that microbiological response was derived from clinical response.

Efficacy Results: Favorable Response Rates at Termination AQAU and AQAX				
Studies	Dirithromycin	Erythromycin	95% CI	Cut-off
Clinical response				
AQAU (n=439)	84.5% (158/187)	81.5% (150/184)	[-4.8%, 10.8%]	-15%
AQAX (n=368)	86.3% (139/161)	86.1% (130/151)	[-7.4%, 7.9%]	-15%
AQAU+AQAX(n=807)	85.3% (297/348)	83.6% (280/335)	[-3.7%, 7.2%]	-15%
Microbiological response				
AQAU	85.0% (85/100)	80.2% (89/111)	[-5.6%, 16.2%]	
AQAX	85.6% (89/104)	86.6% (71/82)	[-11.0%, 9.0%]	
AQAU+AQAX	85.3% (174/204)	82.9% (160/193)	[-5.3%, 10.1%]	

The following table displayed microbiological results by two pathogens that the sponsor wants to have on the label for the indication of skin and skin structure infections. The total isolates included patients with single or multiple pretherapy pathogens. *S. Pyogenes* (referred as "Group A streptococci" by sponsor) was the pathogen that sponsor proposed to be added on to the label. For AQAU and AQAX combined, a total of 34 *S. Pyogenes* isolates were found. Among them 14 were in dirithromycin group and 20 were in erythromycin group. All the isolates in dirithromycin group were eradicated or presumptively eradicated, 19/20 (95%) of *S. Pyogenes* isolates in erythromycin group were eradicated or presumptively eradicated.

The eradication/presumptive eradication rates for *S. Aureus* were similar between two treatment groups, 83% (117/141) for and 88% (106/120) erythromycin for combined studies.

Eradication or Presumptive Eradication Rates by Two Pathogens at Termination AQAU and AQAX						
	AQAU		AQAX		AQAU+AQAX	
Pathogen	Dirithro.	Erythro.	Dirithro.	Erythro.	Dirithro.	Erythro.
S. Pyogenes	100% (8/8)	92% (11/12)	100% (6/6)	100% (8/8)	100% (14/14)	95% (19/20)
S. Aureus	80% (56/70)	87% (65/75)	86% (61/71)	91% (41/45)	83% (117/141)	88% (106/120)

Conclusions

In conclusion, both pivotal studies (AQAT and AQAW) met the criteria specified in FDA "Points to Consider" document for equivalence of dirithromycin 5-day regimen with erythromycin 7-day regimen for the indication of acute bacterial exacerbation of chronic bronchitis (AECB). The two studies also showed that dirithromycin is effective to eradicate *H. Influenzae* organism. Please note that dirithromycin has been approved for AECB indication for a 7-day treatment course, and sponsor requested to change the label from "7 days" to "5-7 days" in the duration of treatment using evidences provided by these two 5-day studies.

Sponsor also requested approval of dirithromycin 5-day regimen for the treatment of secondary bacterial infections of acute bronchitis (SBIAB), but no study was conducted on SBIAB patients in this submission. Since SBIAB is considered as a different disease entity, approval for SBIAB is questionable.

For the indication of skin and skin-structure infections, both pivotal studies (AQAU and AQAX) met the criteria specified in FDA "Points to Consider" document for equivalence of dirithromycin 5-day regimen with erythromycin 7-day regimen. The two studies also showed evidence of effectiveness of dirithromycin in eradicating *S. Pyogenes* organism.

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cc:
Archival: NDA 50678/SE 1-003
HFD-520/Chikami
HFD-520/Albuerne
HFD-520/Davidson
HFD-520/Cintron
HFD-725/Huque
HFD-725/Lin
HFD-725/Dong
HFD-344/Thomas
Chron.