

**Table 12. Sponsor Assessment of Clinical Cure and Bacteriologic Eradication at TOC by Baseline Pathogen - Bacteriologic Per Protocol Population**

Baseline Pathogen	Clinical Cure Rates No. Subjects Cured/No. Subjects with Pathogen (%)				Bacteriologic Eradication Rates No. Pathogens Eradicated/No. Pathogens Isolated (%)			
	Azithromycin SR		Comparator		Azithromycin SR		Comparator	
<b>Study A0661075 – Comparator: Clarithromycin ER</b>								
Total Subjects with Pathogens	100		127					
Total No. Pathogens	134		169		134		169	
<i>H. influenzae</i>	14/15	(93.3)	23/26	(88.5)	14/15	(93.3)	23/26	(88.5)
β lactamase +	3/3	(100)	4/4	(100)	3/3	(100)	4/4	(100)
β lactamase -	11/12	(91.7)	19/22	(86.4)	11/12	(91.7)	19/22	(86.4)
<i>M. catarrhalis</i>	8/8	(100)	3/5	(60.0)	8/8	(100)	3/5	(60.0)
β lactamase +	6/6	(100)	2/4	(50.0)	6/6	(100)	2/4	(50.0)
β lactamase -	2/2	(100)	1/1	(100)	2/2	(100)	1/1	(100)
<i>S. pneumoniae</i>	17/19	(89.5)	25/27	(92.6)	17/19	(89.5)	26/29	(89.7)
Penicillin Susceptible	11/12	(91.7)	17/18	(94.4)	11/12	(91.7)	18/20	(90.0)
Penicillin Intermediate	6/6	(100)	7/8	(87.5)	6/6	(100)	7/8	(87.5)
Penicillin Resistant	0/1	(0.0)	1/1	(100)	0/1	(0.0)	1/1	(100)
<i>C. pneumoniae</i>	19/21	(90.5)	29/31	(93.5)	19/21	(90.5)	29/31	(93.5)
<i>M. pneumoniae</i>	25/26	(96.2)	20/21	(95.2)	25/26	(96.2)	20/21	(95.2)
<b>Study A0661103 - Comparator: Levofloxacin</b>								
Total Subjects with Pathogens	91		104					
Total No. Pathogens	107		130		107		130	
<i>H. influenzae</i>	14/15	(93.3)	8/8	(100)	14/15	(93.3)	8/8	(100)
β lactamase +	3/3	(100)	0/0		3/3	(100)	0/0	
β lactamase -	11/12	(91.7)	8/8	(100)	11/12	(91.7)	8/8	(100)
<i>M. catarrhalis</i>	7/7	(100)	2/2	(100)	7/7	(100)	2/2	(100)
β lactamase +	5/5	(100)	1/1	(100)	5/5	(100)	1/1	(100)
β lactamase -	2/2	(100)	0/0		2/2	(100)	0/0	
<i>S. pneumoniae</i>	11/14	(78.6)	10/12	(83.3)	12/14	(85.7)	10/12	(83.3)
Penicillin Susceptible	8/9	(88.9)	7/8	(87.5)	8/9	(88.9)	7/8	(87.5)
Penicillin Intermediate	3/4	(75.0)	3/4	(75.0)	4/4	(100)	3/4	(75.0)
Penicillin Resistant	0/1	(0.0)	0/0		0/1	(0.0)	0/0	
<i>C. pneumoniae</i>	18/19	(94.7)	21/22	(95.5)	18/19	(94.7)	21/22	(95.5)
<i>M. pneumoniae</i>	5/7	(71.4)	18/18	(100)	5/7	(71.4)	18/18	(100)

Subjects may have had more than one pathogen.

Eradication = Eradication + Presumed Eradication, Persistence = Persistence + Presumed Persistence.

TOC = Test of Cure

***In vitro* susceptibility of baseline isolates from Study A0661075.** Three hundred seventy-three isolates representing 20 species of bacteria (one group was identified to the genus level only) were recovered at baseline from all treated patients in both arms (A0661075 Table 2.7). The pathogens and their susceptibility to azithromycin and clarithromycin for all randomized subjects are listed in A0661075 Table 5.6 (n = 207 isolates). The β-lactamase characteristics for *H. influenzae* and *M. catarrhalis* and susceptibility to oxacillin for *S. aureus* or to penicillin for *S. pneumoniae* isolated from all treated subjects

are listed in A0661075 Table 2.7. Some characteristics of the six most prevalent pathogens isolated from all randomized subjects across both arms of the study are listed here.

- 1) The *most prevalent pathogen* isolated was *C. pneumoniae* (n = 65). Susceptibility testing was not done on this pathogen.
- 2) The second most prevalent pathogen was *M. pneumoniae* (n = 60). Susceptibility testing was not done on this pathogen.
- 3) The third most prevalent pathogen isolated was *S. pneumoniae* (n = 56). Of these, 49 (88%) were susceptible to azithromycin, one was of intermediate susceptibility, and six (11%) were resistant (A0661075 Table 5.6). Forty-nine isolates (88%) had a MIC to azithromycin < 0.25 µg/ml (A0661075 Table 5.6.5). Fifty-four isolates (96%) had a MIC < 4 µg/ml. The two isolates with MIC values of 32 µg/ml and 128 µg/ml were from the US.

The genotyping results for the seven nonsusceptible isolates are summarized in A0661075 Table 5.6.6.

- a) Two isolates that had only the *mef* gene were from Canada.
- b) From the US, one isolate carried the *erm*(TR) gene, another had the *mef* + *erm*(TR) genes, and another had the *mef* + *erm*(B) genes.
- c) Two isolates, one from the US and another from Argentina, were negative for all three macrolide resistance genes.

Of the 56 isolates, 50 (89%) were susceptible to clarithromycin, and six were resistant (A0661075 Table 5.6). Of the 56 isolates, 38 (68%) were PSSP, 16 (29%) were PISP, and two (3.6%) were PRSP (A0661075 Table 2.7).

- 4) The fourth most prevalent pathogen was *S. aureus* (n = 50). Of the 50 isolates, 45 (90%) collected across both arms were susceptible to azithromycin and clarithromycin, and five were resistant (A0661075 Table 5.6). Forty-seven were oxacillin susceptible, and three were oxacillin resistant (A0661075 Table 2.7).
- 5) The fifth most prevalent pathogen was *H. influenzae* (n = 47). All 47 isolates were susceptible to azithromycin with MIC values < 4 µg/ml. Of the 47 isolates, 45 had MIC values < 2 µg/ml. Two isolates had MIC values of 4 µg/ml. Forty isolates were susceptible to clarithromycin, and seven were of intermediate susceptibility (A0661075 Table 5.6). Eight were β-lactamase positive, and 38 (83%) were β-lactamase negative; one isolate was not tested (A0661075 Table 2.7).
- 6) The sixth most prevalent pathogen was *M. catarrhalis* (n = 16). There are no agreed upon breakpoints for this pathogen. Eighty-one percent (n = 13) were β-lactamase positive, and 19% (n = 3) were β-lactamase negative (A0661075 Table 2.7).

***Correlation of microbiological and clinical response with in vitro susceptibility results from Study A0661075.*** For all pathogens assessed at TOC, 123/134 (92%) were eradicated in the Azithromycin SR arm, and 153/169 (91%) were eradicated in the clarithromycin arm of the BPP subjects (A0661075 Table 5.5). In the Azithromycin SR arm, the clinical cure rate in the CPP subjects, 187/202 (93%), is similar to the results from the BPP subjects (A0661075 Table 5.2). For the clarithromycin arm, 198/209 (95%) of the CPP subjects were cured, which is four percentage points higher than the cure rate in the BPP subjects.

For the atypical pathogens, *M. pneumoniae* and *C. pneumoniae*, there was no difference in the clinical cure rates and the bacteriologic eradication rates for BPP subjects in each arm of the study at TOC. For subjects infected with *M. pneumoniae*, the clinical cure rate and the bacteriologic eradication rate were 25/26 (96%) in the Azithromycin SR arm and 20/21 (95%) in the clarithromycin arm. For subjects infected with *C. pneumoniae*, the clinical cure rate and the bacteriologic cure rates were 19/21 (90%) in the Azithromycin SR arm and 29/31 (94%) in the clarithromycin arm (A0661075 Tables 5.3.3 and 5.5.1). No *in vitro* susceptibility data were collected for these isolates.

In BPP subjects infected with *S. pneumoniae* at baseline, 17/19 (90%) in the Azithromycin SR arm had clinical and microbiological cures at TOC (A0661075 Table 5.3.3 and A0661075 Table 5.5.1). Sixteen of the subjects with a clinical cure and bacterial eradication had a sensitive isolate and one had a resistant isolate (A0661075 Tables 5.6.3 and 5.6.4). The resistant isolate from the subject with a clinical cure and bacterial eradication carried the *mef* gene and had a MIC of 4 µg/ml to azithromycin and a MIC of 1 µg/ml to penicillin (PISP) [A0661075 Table 5.5.2 and Section 13, Table 2.4]. Of the two subjects with clinical and bacteriological failures in the Azithromycin SR arm, one had a sensitive isolate, and the other had a *mef* + *ermTR* containing strain with a MIC of 4 µg/ml to azithromycin and a MIC of 2 µg/ml to penicillin (PRSP) [A0661075 Table 5.6.3, A0661075 Table 5.5.2 and Section 13, Table 2.4].

In subjects infected with *S. pneumoniae* in the clarithromycin arm, 26/29 (90%) had a clinical cure and bacterial eradication (A0661075 Table 5.5.1 and A0661075 Table 5.6.3). One of the subjects with a clinical cure and presumed bacterial eradication had a resistant isolate carrying the *mef* gene (MIC = 2 µg/ml to clarithromycin and a MIC of 0.25 µg/ml to penicillin (PISP), [Subject 10381016, Section 13, Tables 2.3.1 and 2.4.1], and the other 25 subjects with a clinical cure and presumed bacterial eradication had baseline isolates that were susceptible to clarithromycin (A0661075 Table 5.6.3 and A0661075 Table 5.6.4). Of the three subjects who failed in their clinical and bacteriological responses in the clarithromycin arm, 2/3 of the subjects had baseline *S. pneumoniae* isolates that were sensitive to clarithromycin, and one was resistant [MIC = 1 µg/ml to clarithromycin, but no resistance gene was detected; it also had a MIC of 0.25 µg/ml to penicillin (PISP); Subject 10021002, A0661075 Table 5.6.3, A0661075 Table 5.6.4, and Section 13, Tables 2.3.1 and 2.4.1].

With respect to penicillin susceptibility of the *S. pneumoniae* isolates from the BPP subjects at TOC, in the Azithromycin SR arm, 11/12 (92%) subjects with PSSP, 6/6

subjects with PISP, and 0/1 subjects with PRSP were cured and had bacterial eradication (A0661075 Table 5.3.3 and A0661075 Table 5.5.1). In the clarithromycin arm, 18/20 (90%) subjects with PSSP, 7/8 (88%) subjects with PISP, and 1/1 subjects with PRSP had bacterial eradication (A0661075 Table 5.5.1) and similarly for clinical cures except that penicillin sensitivity was not captured for two subjects (A0661075 Table 5.3.3).

In the Azithromycin SR arm, 14/15 (93%) of the BPP subjects infected with *H. influenzae* had clinical cure and bacterial eradication at TOC (A0661075 Table 5.3.3 and A0661075 Table 5.5.1). The one failure was attributed to an isolate with a MIC of 2 µg/ml to azithromycin (A0661075 Table 5.5.3). All three isolates that were β-lactamase positive and 11/12 (92%) β-lactamase negative isolates were eradicated and were in subjects with clinical cures TOC (A0661075 Table 5.3.3 and A0661075 Table 5.5.1). In the clarithromycin arm, 23/26 (89%) subjects in the BPP group had a clinical cure and bacterial eradication at TOC (A0661075 Table 5.3.3 and A0661075 Table 5.5.1). Four of these subjects with clinical and bacteriological cures had *H. influenzae* isolates that were Intermediate susceptibility to clarithromycin (A0661075 Table 5.6.3 and A0661075 Table 5.6.4). Of the three clinical and bacteriological failures, two of the baseline isolates were Susceptible, and one was of Intermediate susceptibility (A0661075 Table 5.6.3 and A0661075 Table 5.6.4). In the clarithromycin arm, all four subjects infected with β-lactamase positive *H. influenzae* strains and 19/22 (86%) subjects infected with a β-lactamase negative strain had clinical cures and bacteriological eradication (A0661075 Table 5.3.3 and A0661075 Table 5.5.1).

For the eight BPP subjects infected with *M. catarrhalis* in the Azithromycin SR arm, all eight subjects had bacteriological eradication and clinical cures (A0661075 Table 5.3.3 and A0661075 Table 5.5.1). Six of the subjects had β-lactamase positive strains, and the two others had β-lactamase negative strains (A0661075 Table 5.3.3 and A0661075 Table 5.5.1). In the clarithromycin arm, 2/4 (50%) subjects infected with β-lactamase positive *M. catarrhalis* strains and the one subject infected with a β-lactamase negative strain had clinical cures and bacteriological eradication (A0661075 Table 5.3.3 and A0661075 Table 5.5.1).

For the *S. aureus*-infected subjects, 17/19 (89%) of the subjects with clinical cures at TOC had isolates that were sensitive to azithromycin, and two were resistant (A0661075 Table 5.6.3). One subject with a resistant isolate failed in their clinical response in the Azithromycin SR arm. In the clarithromycin arm, 15/16 (94%) of the subjects with clinical cures had isolates sensitive to clarithromycin, and one was resistant. The two subjects with clinical failures had isolates that were sensitive to clarithromycin. In the Azithromycin SR arm, 17/18 (94%) subjects with oxacillin susceptible *S. aureus* and both subjects with oxacillin resistant *S. aureus* strains had clinical cures and bacterial eradication (A0661075 Table 5.3.3 and Table 5.5.1). In the clarithromycin arm, 15/17 (88%) of the subjects with oxacillin susceptible *S. aureus* isolates had clinical cures and 14/17 (82%) had bacterial eradication, and the one subject with an oxacillin resistant strain had positive clinical and bacteriological responses (A0661075 Table 5.3.3 and Table 5.5.1).

In the CPP subjects at the LTFU visit, 99% (175/176) of the subjects in the Azithromycin SR arm had a clinical cure, and 97% (172/177) of the subjects in the clarithromycin arm had a clinical cure (A0661075 Table 5.2).

***Listing of pathogens associated with unfavorable outcomes and their susceptibility to test drug from Study A0661075.*** At the TOC for patients in the Azithromycin SR arm, there was a failure in the clinical response in 1/26 (4%) patients initially infected with *M. pneumoniae* and in 2/21 (10%) patients initially infected with *C. pneumoniae* (A0661075 Table 5.3.3). In the clarithromycin treated groups, there were failures in the clinical response for 1/21 (5%) subjects initially infected with *M. pneumoniae* and in 2/31 (6%) subjects initially infected with *C. pneumoniae*. Susceptibility to the test drugs was not collected for these two atypical pathogens.

In patients infected initially with *S. pneumoniae*, 2/19 (11%) subjects failed at TOC in the Azithromycin SR arm. In these two failures, one of the initial isolates had a MIC of 4 µg/ml and carried the *mef* and *erm*(TR) resistance determinants (A0661075 Section 13, Table 2.4). The other isolate was sensitive to azithromycin; MIC = 0.06 µg/ml (Subject 10681006; A0661075 Section 13, Table 2.3.1). However, there was a clinical cure in one patient who had an isolate with a MIC of 4 µg/ml and carried the *mef* gene. In the clarithromycin treated group, 3/29 (10%) subjects had a failure in their clinical response. Two of the isolates were sensitive to clarithromycin, and one was resistant, MIC = 1 µg/ml (A0661075 Section 13, Table 2.4.1).

In the Azithromycin SR arm at TOC, 1/15 (7%) subjects initially infected with *H. influenzae* failed in their clinical and bacteriological responses (A0661075 Table 5.5.3). A baseline isolate from the US with a MIC of 2 µg/ml was identified from this subject (A0661075 Table 5.5.3). In the clarithromycin arm, 3/26 (12%) subjects initially infected with *H. influenzae* failed in their clinical response (A0661075 Table 5.6.3). Two subjects were initially infected with sensitive strains and one subject was infected with a strain of intermediate susceptibility (A0661075 Table 5.6.3).

Of the 20 subjects initially infected with *S. aureus*, there was one failure (5%) in a resistant isolate in the Azithromycin SR arm (A0661075 Table 5.6.3); MIC ≥ 4 µg/ml (Subject 10081004; A0661075 Section 13, Table 2.3.1). There were 2/18 (11%) failures in clinical response in the clarithromycin arm. Both isolates were sensitive to clarithromycin (A0661075 Table 5.6.3).

For subjects initially infected with *M. catarrhalis*, there were no failures in clinical and bacteriological responses in eight subjects in the Azithromycin SR arm at TOC and LTFU (A0661075 Table 5.6.3). In the clarithromycin arm, 2/5 (40%) subjects were assigned as failures in their clinical response at TOC (A0661075 Table 5.6.3).

***In vitro susceptibility of baseline isolates from Study A0661103.*** Two hundred seventy-two isolates representing 23 species of bacteria (three groups were identified to the genus level only) were recovered at baseline from all treated patients in both arms (A0661103 Table 2.7). The pathogens and their susceptibility to azithromycin and levofloxacin for all

randomized subjects are listed in A0661103 Table 5.6 (n = 140 isolates with susceptibility data to azithromycin and 190 isolates for levofloxacin). The  $\beta$ -lactamase characteristics for *H. influenzae* and *M. catarrhalis* and susceptibility to oxacillin for *S. aureus* or to penicillin for *S. pneumoniae* isolated from all treated subjects are listed in A0661103 Table 2.7. Some characteristics of the eight most prevalent pathogens isolated from all treated subjects across both arms of the study are listed here.

1. The most prevalent pathogen isolated was *C. pneumoniae* (n = 44). Susceptibility testing was not done on this pathogen.
2. The second most prevalent pathogen was *S. aureus* (n = 43). Of the 43 isolates, 37 (86%) isolates collected across both arms were susceptible to azithromycin and six were resistant (A0661103 Table 5.6). Of the 43 isolates, 42 (98%) isolates collected across both arms were susceptible to levofloxacin and one was resistant (A0661103 Table 5.6). 41 were oxacillin susceptible, and two were oxacillin resistant (A0661103 Table 2.7).
3. The third most prevalent pathogen isolated was *H. parainfluenzae* (n = 35). All 35 isolates were susceptible to both azithromycin and levofloxacin (A0661103 Table 5.6).
4. Tied for fourth most prevalent pathogen was *S. pneumoniae* (n = 28). Twenty-one (75%) were susceptible to azithromycin and seven (25%) were resistant (A0661103 Table 5.6). Twenty-one (75%) had a MIC to azithromycin < 0.25  $\mu\text{g/ml}$  (A0661103 Table 5.6.5). Twenty-six (93%) had a MIC < 4  $\mu\text{g/ml}$ . The isolate with a MIC value of > 4  $\mu\text{g/ml}$  was from Lithuania, and the one with a MIC of > 256  $\mu\text{g/ml}$  was from the US. The genotyping results for 6/7 (86%) nonsusceptible isolates are summarized in A0661103 Table 5.6.6. (One isolate was not tested). Of the four isolates that had only the *mef* gene, two were from Canada, one from Chile, and one from the US. From the US, one isolate carried the *erm(B)* gene. One isolate from the US was negative for all three macrolide resistance genes. Twenty-eight (100%) were susceptible to levofloxacin (A0661103 Table 5.6). Nineteen (68%) were PSSP, eight (29%) were PISP, and one (3.6%) was PRSP (A0661103 Table 2.7).
5. Tied for fourth most prevalent pathogen was *M. pneumoniae* (n = 28). Susceptibility testing was not done on this pathogen.
6. The sixth most prevalent pathogen was *H. influenzae* (n = 26). All 26 isolates were susceptible to azithromycin with MIC values < 2  $\mu\text{g/ml}$  (A0661103 Table 5.6.5). Of these, 19/26 (73%) had MIC values < 1  $\mu\text{g/ml}$ . All 26 isolates were susceptible to levofloxacin (A0661103 Table 5.6). Four were  $\beta$ -lactamase positive, and 22 (85%) were  $\beta$ -lactamase negative (A0661103 Table 2.7).
7. The seventh most prevalent pathogen was *Klebsiella pneumoniae* (n = 14). There are no azithromycin breakpoints for *K. pneumoniae*. Of these, 13/14 (93%) were sensitive to levofloxacin (A0661103 Table 5.6).

8. The eighth most prevalent pathogen was *M. catarrhalis* (n = 10). There are no agreed upon breakpoints for this pathogen. Of these, 78% (n = 7) were  $\beta$ -lactamase positive, and 22% (n = 2) were  $\beta$ -lactamase negative (A0661103 Table 2.7). One was not tested.

***Correlation of microbiological and clinical response with in vitro susceptibility results.***

For all pathogens assessed at TOC, 97/107 (91%) were eradicated in the Azithromycin SR arm, and 120/130 (92%) were eradicated in the levofloxacin arm of the BPP subjects at TOC (A0661103 Table 5.5). The clinical cure rates in the CPP subjects at TOC were similar to the bacterial eradication rates in both arms of the study at TOC. In the Azithromycin SR arm at TOC, the clinical cure rate in the CPP subjects was 156/174 (90%), and for subjects in the levofloxacin arm, 177/189 (94%) of the CPP subjects were cured (A0661103 Table 5.2).

For the atypical pathogens, *M. pneumoniae* and *C. pneumoniae*, there was no difference in the clinical cure rates and the bacteriologic eradication rates for BPP subjects in each arm of the study at TOC. For subjects infected with *C. pneumoniae*, the clinical cure rate and the bacteriologic eradication rates were 18/19 (95%) in the Azithromycin SR arm and 21/22 (96%) in the levofloxacin arm (A0661103 Tables 5.3.3 and 5.5.1). For subjects infected with *M. pneumoniae*, the clinical cure rate and the bacteriologic eradication rate were 5/7 (71%) in the Azithromycin SR arm and 18/18 (100%) in the levofloxacin arm. No *in vitro* susceptibility data were collected for these isolates.

*H. influenzae*-infected subjects had high clinical cure rates. In the Azithromycin SR arm, 14/15 (93%) of the subjects had clinical cures and bacterial eradication (or presumed eradication) at TOC, and 12/13 had clinical cures at LTFU (A0661103 Tables 5.3.3, 5.5.1, and 5.6.3). The positive clinical and bacteriological response rates by baseline isolate azithromycin MIC values were 2/2 (100%) subjects with MIC values of 0.5  $\mu\text{g/ml}$ ; 8/9 (89%) with MICs of 1  $\mu\text{g/ml}$ , and 4/4 (100%) with MICs of 2  $\mu\text{g/ml}$  (A0661103 Table 5.5.3). In the Azithromycin SR arm, all three subjects infected with  $\beta$ -lactamase positive *H. influenzae* strains and 11/12 (92%) subjects infected with a  $\beta$ -lactamase negative strain had clinical cures and bacteriological eradication (A0661103 Table 5.3.3 and Table 5.5.1). In the levofloxacin arm, all eight subjects had clinical and bacteriological cures at TOC and at LTFU; all eight isolates were susceptible to levofloxacin and were  $\beta$ -lactamase negative (A0661103 Tables 5.6.3, 5.6.4, 5.3.3 and 5.5.1).

Subjects infected with *S. pneumoniae* had clinical cure rates of 79% (11/14) in the Azithromycin SR arm and 83% (10/12) in the levofloxacin arm at TOC. In the Azithromycin SR arm, of the 11 subjects who had a clinical cure and bacterial eradication, nine isolates were sensitive to azithromycin and two were resistant. One of the resistant isolates had a MIC of 2  $\mu\text{g/ml}$ , carried the *mef* gene, and had intermediate resistance to penicillin (A0661103 Tables 5.5.2.1 and Section 13, Table 2.4). The other resistant isolate had a MIC > 4  $\mu\text{g/ml}$  and intermediate resistance to penicillin; the genotype was not determined. For the three subjects who had a clinical failure, one isolate was sensitive and two were resistant. One had a MIC of 4  $\mu\text{g/ml}$ , carried the *mef*

gene, and was resistant to penicillin, and the other had a MIC > 256 µg/ml, carried the *erm(B)* gene, and had intermediate resistance to penicillin. Notably, the isolate from the latter subject (10111007) had a documented bacterial eradication (Section 13, Table 2.4). In the levofloxacin arm, all 12 of the baseline isolates were sensitive to levofloxacin. One of the clinical failures was attributed to an isolate that was sensitive to levofloxacin (MIC = 1 µg/ml), had intermediate susceptibility to penicillin (MIC = 0.12 µg/ml) and was resistant to erythromycin (MIC = 4 µg/ml) (A0661103 Section 13, Table 2.4.1).

With respect to penicillin susceptibility of the *S. pneumoniae* isolates from the BPP subjects at TOC, in the Azithromycin SR arm, 8/9 (89%) subjects with PSSP, 4/4 (100%) subjects with PISP, and 0/1 (0%) subjects with PRSP had bacterial eradication, and similarly for clinical cure except that 1/4 (25%) of the subjects with PISP failed (A0661103 Tables 5.3.3 and Table 5.5.1). In the levofloxacin arm, 7/8 (88%) of the subjects with PSSP and 3/4 (75%) subjects with PISP had bacterial eradication and clinical cure, and no subjects had PRSP (A0661103 Table 5.3.3 and A0661103 Table 5.5.1).

For the nine subjects infected with *M. catarrhalis* in the BPP population, all were cured and the bacteria were presumed to be eradicated (A0661103 Tables 5.3.3, 5.5.1, 5.3.4). There were seven in the Azithromycin SR arm and two in the levofloxacin arm. In the Azithromycin SR arm, five subjects were infected with β-lactamase positive *M. catarrhalis* strains, and two subjects were infected with β-lactamase negative strains. In the levofloxacin arm, one isolate was β-lactamase positive, and this characteristic was not recorded for the other isolate (A0661103 Tables 5.3.3 and 5.5.1).



For the *S. aureus*-infected subjects, all 11 patients in the Azithromycin SR arm and all 27 (100%) subjects in the levofloxacin arm had clinical cures and bacterial eradication at TOC in the BPP population (A0661103 Tables 5.3.3 and 5.5.1). In the Azithromycin SR arm, 10/11 (91%) of the subjects had isolates that were sensitive to azithromycin, and one was resistant. In the levofloxacin arm, 26/27 (96%) of the subjects had isolates sensitive to levofloxacin, and one was resistant (A0661103 Table 5.6.3). All 11 (100%) isolates in the Azithromycin SR arm and 25/27 isolates in the levofloxacin arm were oxacillin susceptible (A0661103 Tables 5.3.3 and 5.5.1).

In the Azithromycin SR arm, all four of the *K. pneumoniae* isolates (100%) were eradicated or presumed eradicated at TOC and LTFU and the subjects had clinical cures. (A0661103 Tables 5.3.3, 5.5.1 and 5.6.4). No breakpoints exist for azithromycin for this pathogen. In the levofloxacin arm, 7/8 (88%) of the isolates were sensitive to

levofloxacin and one was resistant, and all eight subjects had a clinical and bacteriological cure at TOC (A0661103 Tables 5.3.3, 5.5.1 and 5.6.3). At LTFU, six subjects with sensitive baseline isolates had clinical cures; the other two subjects were not evaluated (A0661103 Table 5.6.3).

In the CPP subjects at the LTFU visit, 100% (146/146) of the subjects in the Azithromycin SR arm had a clinical cure, and 99% (169/170) of the subjects in the levofloxacin arm had a clinical cure (A0661103 Table 5.2).

***Listing of pathogens associated with unfavorable outcomes and their susceptibility to test drug from Study A0661103.*** In subjects infected with *C. pneumoniae*, there was one clinical and bacteriological failure in each arm of the study – 1/19 (5%) in the Azithromycin SR arm and 1/22 (5%) in the levofloxacin arm (A0661103 Tables 5.3.3 and 5.5.1). No susceptibility data were collected for these isolates, though.

One patient out of 15 (7%) infected with *H. influenzae* at baseline in the Azithromycin SR arm failed in their bacteriological and clinical cure responses at TOC (A0661103 Tables 5.3.3 and 5.5.1). The isolate was susceptible to azithromycin with a MIC of 1 µg/ml (A0661103 Table 5.5.3). (The other 12 subjects who had baseline isolates with MIC values of 1 and 2 µg/ml were cured.) In the levofloxacin arm, all eight subjects (100%) were cured, both bacteriologically and clinically (A0661103 Tables 5.3.3 and 5.5.1).

For *S. pneumoniae* – infected subjects, 3/14 (21%) subjects in the Azithromycin SR arm failed in their clinical response and 2/14 (14%) failed in their bacteriological response (A0661103 Tables 5.3.3 and 5.5.1). Subject 10111007 who had an isolate with a baseline MIC of > 256 µg/ml to azithromycin, [attributed to *erm(B)*], and an intermediate MIC of 0.12 µg/ml to penicillin, had the bacteria eradicated, but failed in their clinical response (A0661103 Section 13, Table 2.4). Subject 10381002 failed in their clinical and bacteriological responses. The baseline isolate for this subject had a MIC of 4 µg/ml to azithromycin (*mef*) and was resistant to penicillin: MIC = 2 µg/ml. The third subject who had a clinical failure had an isolate sensitive to azithromycin. In the levofloxacin arm, 2/12 (17%) subjects failed in their bacteriological and clinical responses (A0661103 Tables 5.3.3 and 5.5.1). Both Subjects 10541012 and 10431020 had baseline *S. pneumoniae* isolates that were susceptible to levofloxacin (MIC values of 1 µg/ml) [A0661103 Table 5.6.3]. The isolate from Subject 10541012 was also resistant to erythromycin (MIC = 4 µg/ml) and had intermediate susceptibility to penicillin, MIC = 0.12 µg/ml (A0661103 Section 13, Table 2.4.1).



Two of seven (29%) *M. pneumoniae* – infected subjects in the Azithromycin SR arm at TOC did not have a positive clinical or bacteriological response (A0661103 Tables 5.3.3 and 5.5.1). No azithromycin susceptibility data are available. However, all 18 *M. pneumoniae* – infected subjects in the levofloxacin arm were cured and had presumed bacterial eradication (A0661103 Tables 5.3.3 and 5.3.4).

**Community Acquired Pneumonia Combined Analyses (Studies A0661075 and A0661103; combined data collected in Appendix 2.7.3 of the main document)**

Across the two clinical studies at TOC, adults in the CPP population with mild to moderate community acquired pneumonia had a 91% (343/376) clinical cure rate in the Azithromycin SR arm and 94% (375/398) in the combined comparator arm (Appendix 2.7.3, Table CAP.INT.6.01). At LTFU in the CPP population, 99.7% (321/322) of the subjects in the Azithromycin SR arm had a clinical cure compared to 98.3% (341/347) in the combined comparators arms (Appendix 2.7.3, Table CAP.INT.6.01).

At baseline in the BPP populations, the most common infecting typical pathogens were *S. aureus* (n = 76), *S. pneumoniae* (n = 72), *H. influenzae* (n = 64), and *H. parainfluenzae* (n = 44). Prevalent atypical pathogens included *C. pneumoniae* (n = 93) and *M. pneumoniae* (n = 72) [Appendix 2.7.3, Table 10]. At TOC across both clinical studies, subjects in the BPP population had 91% bacteriologic eradication rates in both the Azithromycin SR arm (220/241) and in the combined comparator arm (273/299) [Appendix 2.7.3, Table 12]. The clinical cure rates and the bacteriologic cure rates were the same or nearly so for the major pathogens isolated in these studies within each treatment arm and are summarized in Table 13 below (data collated from Appendix 2.7.3, Tables 10 and 11). However, in a comparison of subjects treated with Azithromycin SR and the comparators, there was a 6% higher cure rate and eradication rate in the Azithromycin SR arms for *H. parainfluenzae*, but a 6% lower cure rate and eradication rate for subjects infected with *M. pneumoniae* in the Azithromycin SR arm.

**Table 13. Summary of Clinical Cure Rates and Bacteriologic Cure Rates by Pathogen in Both CAP Studies.**

Pathogen	No. Subjects Cured/No. Subjects with Pathogen (%)		No. Eradicated/No. Isolated (%)	
	Azithromycin SR	Comparators	Azithromycin SR	Comparators
<i>C. pneumoniae</i>	37/40 (93)	50/53 (94)	37/40 (93)	50/53 (94)
<i>S. pneumoniae</i>	28/33 (85)	35/39 (90)	29/33 (88)	36/41 (88)
<i>M. pneumoniae</i>	30/33 (91)	38/39 (97)	30/33 (91)	38/39 (97)
<i>H. influenzae</i>	28/30 (93)	31/34 (91)	28/30 (93)	31/34 (91)

In BPP subjects infected with *S. pneumoniae* in the Azithromycin SR arm, 25/27 (93%) subjects infected with Susceptible isolates (MIC < 0.5 µg/ml and > 18 mm by disk diffusion) had both bacterial eradication and clinical cure at TOC. No subjects in the Azithromycin SR arm were infected with *S. pneumoniae* isolates with Intermediate

susceptibility to azithromycin (A0661075 Tables 5.6.3 and 5.6.4; A0661103 Tables 5.6.3 and 5.6.4; Appendix 2.7.3, Table SUSC.7.1.adhoc5; data are also graphed, see pp 66-68 of this submission). Six subjects had azithromycin nonsusceptible (ANSSP) isolates, and two of these were also penicillin resistant (PRSP). Seventy-five percent (3/4) of the subjects with ANSSP only were cured, but neither of the two subjects with ANSSP and PRSP were cured in the Azithromycin SR arm (Appendix 2.7.3, Table SUSC.6.1). In both comparator arms, 3/5 (60%) of the subjects infected with ANSSP only were cured and the sole subject with PRSP was cured; no subjects in the comparator arms had isolates with both ANSSP and PRSP. None of the subjects in either arm had bacteremia associated with ANSSP, PRSP, or both (Appendix 2.7.3, Table SUSC. 6.2).

In the six *S. pneumoniae*-infected subjects with ANSSP in the Azithromycin SR arms, three of the isolates carried the *mef* gene (Appendix 2.7.3, Table SUSC. 5.1). One Canadian *mef*-carrying isolate with a MIC of 2 µg/ml was eradicated, and one Canadian *mef*-carrying isolate, but not the US isolate with a MIC of 4 µg/ml were eradicated. One US isolate that had a MIC of 4 µg/ml had both *mef* and *erm*(TR) and was not eradicated. Surprisingly, the US isolate with the highest MIC, > 256 µg/ml, was eradicated but the subject failed in the clinical response. (This may be due to the lower growth rate of *S. pneumoniae* isolates carrying methylated ribosomes, unpublished Pfizer laboratory observations.) One of the six isolates was not genotyped due to lack of viability of the isolate when shipped to the genotyping lab; its origin was Lithuania.

For the subjects infected with PSSP, 19/21 (91%) in the Azithromycin SR arm had positive clinical and bacteriological responses. In the comparator arms, 24/26 (92%) with PSSP had clinical cures and 25/28 (89%) had bacteriological eradication. In subjects identified with PISP, all 10 had bacterial eradication, 9/10 (90%) had clinical cures in the Azithromycin SR arms, and 10/12 (83%) in the comparator arms had clinical cure and bacteriological eradication. Both subjects carrying PRSP in the Azithromycin SR arms failed in their clinical and bacteriological responses, and the one subject with PRSP in the comparator arms had a positive clinical and bacteriological response (Section 2.7.3, Tables 10 and 11).

For the *H. influenzae*-infected subjects in both Azithromycin SR arms, 28/30 (93%) of the subjects had bacterial eradication and clinical cure (Appendix 2.7.3, Table SUSC. 7.1). All six subjects infected with isolates with MICs of 0.5 µg/ml were eradicated, and 15/16 (94%) with MICs of 1 µg/ml and 7/8 (88%) with MICs of 2 µg/ml were eradicated. All 30 isolates had disk diffusion zone diameters to azithromycin > 14 mm, within the susceptible range of > 12 mm (Appendix 2.7.3, Table SUSC.7.1.adhoc3). No isolates of *H. influenzae* with other MIC values or disk diffusion zone diameters were obtained in these two CAP trials. Graphs of the data are found on pp 66-68 of this submission.

In the Azithromycin SR arm, all six BPP subjects with β-lactamase positive strains and 22/24 (92%) of the BPP subjects with β-lactamase negative strains had positive clinical and bacteriological responses at TOC. In the comparator arms, 31/34 (91%) of the BPP subjects had clinical cures and bacteriological eradication at TOC. All four BPP subjects with β-lactamase positive strains and 27/30 (90%) of the BPP subjects with β-lactamase

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**Reviewer's comments:** According to the American Thoracic Society guidelines macrolides (azithromycin, clarithromycin) should be considered as first line agents in the treatment of CAP in patients < 60 years of age without comorbidities (223). Two recent reports suggest an important role for the macrolides in initial empirical therapy for patients with CAP.

In the first study, Stahl *et al.* studied the effect of macrolides on length of hospital stay in patients with CAP (224). A total of 76 patients hospitalized with CAP were prospectively studied according to the antibiotics they received. For 12 patients given a macrolide (alone or in combination) within the first 24 h of hospitalization, the length of stay was 50% shorter (2.75 vs. 5.3 days) than among patients receiving other antimicrobials ( $p = 0.01$ ). However, this association was only seen when the macrolides was given within the first 24 h. Interestingly, patients who received a macrolide were less likely to have a pathogen identified as compared to those receiving other antimicrobials within the first 24 h of admission ( $p \leq 0.06$ ). The authors concluded that the findings from this study reinforce guidelines recommending macrolide therapy for empirical therapy of CAP. Regardless of the use of these compounds either alone or in combination, their activity against atypical pathogens (*M. pneumoniae*, *C. pneumoniae*, *L. pneumophila*) was beneficial to patient care. As therapy for CAP is empirical, the presence of atypical pathogens is not likely to be determined in the majority of patients. Since  $\beta$ -lactam agents have no activity against the atypical agents, their coverage is restricted to bacterial pathogens only. Given that 11 of the 12 patients who received a macrolide within the first 24 h of admission also received a potent  $\beta$ -lactam agent, but that they play a useful adjunctive role in CAP.

In the second study, Gleason *et al.* investigated the initial antimicrobial therapy and outcome for elderly hospitalized patients with pneumonia (225). The authors sought to determine the association between 30 day mortality and initial antimicrobial therapy in elderly patients hospitalized for CAP. This retrospective study reviewed the hospital records of > 12,000 hospitalized patients what were > 65 years of age and suffering from pneumonia. The authors of this study concluded that decreased 30-day mortality is associated with initial antimicrobial regimens with activity against both the most common typical bacterial pathogens (i.e., *S. pneumoniae*, *H. influenzae*) and the atypical pathogens (*Legionella* spp., *M. pneumoniae*, *C. pneumoniae*, *C. burnetti*). The role of atypical pathogens in CAP amongst the hospitalized elderly may be a more significant problem than most appreciate. For example, the incidence of atypical pneumonia leading to hospitalization is as high as 44% (*M. pneumoniae* 33% and *C. pneumoniae* 9%) [226-229]. *C. pneumoniae* has also been associated with deadly outbreaks of pneumonia in nursing home residents (230). Recently, Blondeau and Tillotson reviewed the etiology of CAP and demonstrated that atypical pathogens were being found more often in CAP, a finding that may represent increasing prevalence, better or more aggressive diagnostic testing or study designs attempting to document atypical pathogen prevalence rates (231).

The authors finally conclude that future randomized studies are warranted to confirm these findings.

Past guidelines from the Infectious Diseases Society of America recommended either the macrolides, newer fluoroquinolones or doxycycline for the empirical treatment of CAP based on certain clinical settings (232). For hospitalized patients that were not admitted to the intensive care unit, azithromycin was considered acceptable, however, for severe pneumonia treated in the ICU, a  $\beta$ -lactam in combination with a macrolide or fluoroquinolone was recommended. These same recommendations were further reiterated in a more recent publication from Bartlett *et al.* (233).

Finally, in an open-label, multicenter, and randomized clinical trial, Frank *et al.* compared levofloxacin and azithromycin plus ceftriaxone in hospitalized adults with community-acquired pneumonia (234). The clinical success rate (cured and improved) in clinically evaluable patients was 94.1% and 92.3% in the levofloxacin and azithromycin groups, respectively. The microbiologic eradication rates were 89.5% and 92.3% in the levofloxacin and azithromycin groups, respectively. In this study levofloxacin monotherapy was as effective as a combination regimen of azithromycin and ceftriaxone in providing coverage against the current causative pathogens in CAP.

The studies performed by the Applicant demonstrate the increased importance of atypical pathogens e.g. *C. pneumoniae* and *M. pneumoniae*, in the etiology of CAP. A comparison of the rankings of the pathogens isolated from the study subjects across both arms of the CAP studies reveals some surprising results (see Tables 14 and 15 below). In both studies, *C. pneumoniae* was the most commonly identified pathogen. The second most commonly identified pathogen was *M. pneumoniae* in the A0661075 study (clarithromycin as comparator) but *S. aureus* in the A0661103 study (levofloxacin as comparator). The third most commonly isolated pathogen was *S. pneumoniae* in the A0661075 study and the A0661103 study, respectively. When the data from the two studies are combined, *C. pneumoniae*, *S. pneumoniae* and *M. pneumoniae* are the first, second, and third most common pathogens, respectively.

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**Table 14. Rankings of pathogens isolated from randomized subjects across each arm of the CAP studies.**

Study A0661075 Clarithromycin as comparator			Study A0661103 Levofloxacin as comparator		
Organism	N	%	Organism	N	%
<i>C. pneumoniae</i>	65	17%	<i>C. pneumoniae</i>	44	19%
<i>M. pneumoniae</i>	60	16%			
<i>S. pneumoniae</i>	56	15%			
			<i>S. pneumoniae</i>	28	12%
<i>H. influenzae</i>	47	13%	<i>M. pneumoniae</i>	28	12%
			<i>H. influenzae</i>	26	11%
other	79	21%			
total	373	100%			
			other	9	4%
			total	237	100%

**Table 15. Combination ranking of pathogens isolated from randomized subjects across both arms of the BPP in the CAP studies.**

Organism	N	%
<i>C. pneumoniae</i>	109	18%
<i>M. pneumoniae</i>	88	14%
<i>S. pneumoniae</i>	84	14%
<i>H. influenzae</i>	73	12%
others	83	14%
total	610	100%

These results are surprising in light of reports from the literature. According to Mandell et al., *S. pneumoniae*, *H. influenzae*, and *S. aureus* are the most common bacterial etiological agents for CAP (235). Guidelines for CAP from the Infectious Disease Society of America state that *S. pneumoniae* is indicated in two-thirds of the CAP cases (233). Mulazimoglu states that for hospitalized CAP patients, *S. pneumoniae* remains the most common pathogen identified with 19% of the cases (236). *H. influenzae* accounts for 13% of isolates followed by *L. pneumophila* (14%), *C. pneumoniae* (10%), and *M. pneumoniae* (9%).

The reason for the differences in the rankings of the pathogens seen in the two studies and the deviation of these rankings from the literature is unclear.

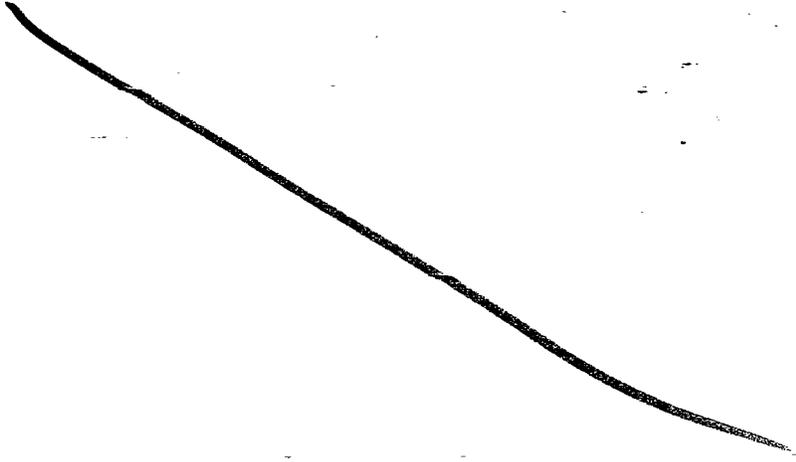
with *S. pneumoniae* would result in a lower percentage of *S. pneumoniae* of the total pathogens isolated.

The Applicant seeks approval of Zithromax SR for the treatment of community acquired pneumonia (CAP) due to *Chlamydophila pneumoniae*, *Haemophilus influenzae*,

~~\_\_\_\_\_~~ *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae*. The data provide evidence for the support of some of these organisms but not all of these organism. What follows is the rationale for the inclusion or exclusion of each of these organisms from the first list of the package insert.

***Chlamydophila pneumoniae***. Study results indicate that Zithromax SR is effective against most isolates of this atypical pathogen. Adequate numbers of isolates were identified (40 in the azithromycin arm, 53 in the comparator arms) and clinical cures and bacteriologic eradication rates were identical at 93% in the azithromycin arms and 94% in the comparator arms of the BPP. No *in vitro* susceptibility data were collected for these isolates.

***Haemophilus influenzae***. Study results indicate that Zithromax SR is effective against most isolates of this common bacterial pathogen. Adequate numbers of isolates were identified (30 in the azithromycin arm, 34 in the comparator arms). Clinical cures were similar between the two arms with 93% in the azithromycin arms and 91% in the comparator arms of the CPP. Bacteriologic eradication rates were also similar between the test and comparator arms at 93% and 91%, respectively, of the BPP. *In vitro* susceptibility results indicate all isolates had MICs between 0.5 and 4 µg/ml (Table 16 below). Of the 30 isolates, failures (clinical and bacteriologic) were seen in one isolate each with MICs = 1 µg/ml and 2 µg/ml, respectively. These failures are unexpected and worrisome since the susceptibility breakpoint for *Haemophilus* spp. is ≤ 4 µg/ml.



***Mycoplasma pneumoniae.*** Study results indicate that Zithromax SR is effective against most isolates of this atypical pathogen. Adequate numbers of isolates were identified (33 in the azithromycin arm, 39 in the comparator arms) and clinical cures and bacteriologic eradication rates were identical at 91% in the azithromycin arms and 97% in the comparator arms. No *in vitro* susceptibility data were collected for these isolates.

***Streptococcus pneumoniae.*** Study results indicate that Zithromax SR is effective against most isolates of this common bacterial pathogen. Adequate numbers of isolates were identified (33 in the azithromycin arm, 41 in the comparator arms). Clinical cures were similar between the two arms with 85% in the azithromycin arms and 90% in the comparator arms of the CPP. Bacteriologic eradication rates were identical between the test and comparator arms with 88% of the BPP. *In vitro* susceptibility results indicate all isolates had MICs between  $\leq 0.5$  and  $256 \mu\text{g/ml}$  (Table 16 below). Of the 33 total isolates, failures (clinical and bacteriologic) were seen in two isolates with MICs  $\leq 0.5 \mu\text{g/ml}$  and two isolates with MICs =  $4 \mu\text{g/ml}$ , respectively. One isolate was a bacteriologic success but a clinical failure had a MIC  $\geq 256 \mu\text{g/ml}$ . As the susceptibility breakpoint for *S. pneumoniae* is  $\leq 0.5 \mu\text{g/ml}$ , the failures at these MICs are expected. Of the four bacteriologic failures, two were susceptible to penicillin and two were resistant to penicillin. Both isolates that were penicillin resistant were also resistant to azithromycin, however, in this case, a definitive correlation between azithromycin and penicillin resistance cannot be drawn with such low numbers.

**Table 16. Correlation of *in vitro* susceptibility data with clinical and bacteriologic success rates by pathogen for the CAP studies.**

Organism	MIC	Clinical Success	Clinical Failure	Bacteriologic Success	Bacteriologic Failure
<i>S. pneumoniae</i>	< 0.5	25	2	25	2
	1	0	0	0	0
	2	1	0	1	0
	4	1	2	1	2
	>4	1	0	1	0
	>256	1	0	0	1
	<b>total</b>		<b>29</b>	<b>4</b>	<b>28</b>
<i>H. influenzae</i>	0.5	6	0	6	0
	1	15	1	15	1
	2	7	1	7	1
	4	0	0	0	0
	<b>total</b>		<b>28</b>	<b>2</b>	<b>28</b>

Source: Graphs, pp 66-71, Microbiology Section, this submission.

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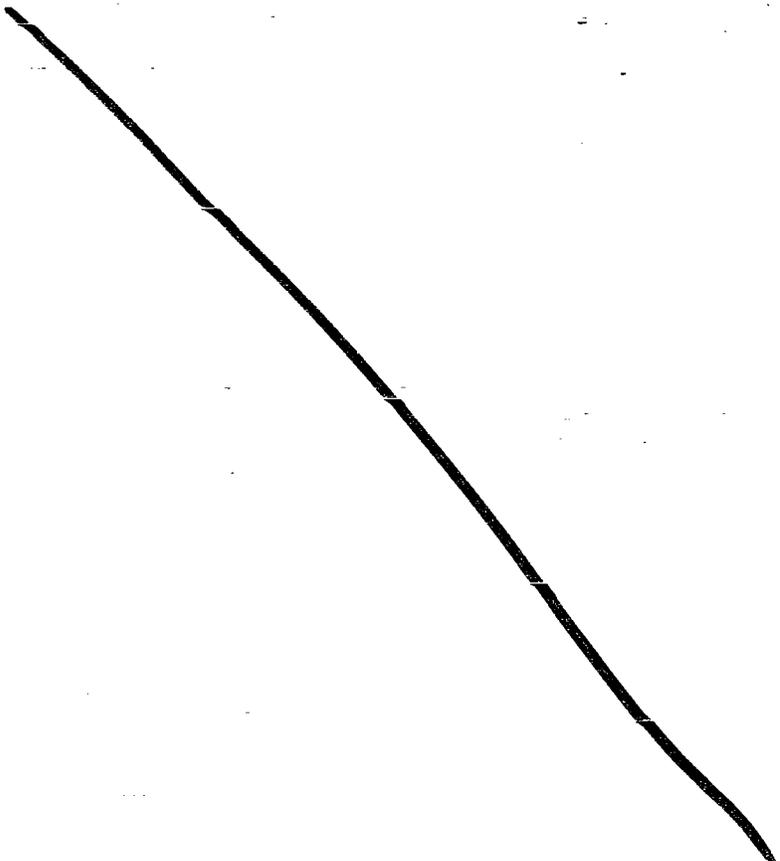
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**Acute Bacterial Sinusitis [ABS] (A0661078)**

**Brief overview of study design and results.** Efficacy and safety data using a single 2.0 gram dose of Azithromycin SR in ABS is contained in a single Phase 3, randomized, double-blind, double dummy, active-controlled, multicenter, comparative international study, **A0661078**. The *primary objective* of **Study A0661078** was to confirm the hypothesis that a single oral 2.0 g dose of Azithromycin SR is clinically non-inferior to levofloxacin, given at a dose of 500 mg once daily for 10 days. *Secondary objectives* were to assess bacteriologic efficacy and safety of the two treatment regimens.

Male or female subjects, aged 18 years and over, with a diagnosis of acute, uncomplicated maxillary sinusitis, and clinical evidence of the infection, as demonstrated by the presence of the following signs and symptoms for a minimum duration of seven days: facial pain, pressure and/or tightness over one or both maxillary sinuses, and/or

pain in one or both maxillary areas that worsens with movement or percussion; AND the presence of one or more of the following: purulent nasal discharge, purulent drainage in the posterior pharynx, or purulent discharge from the maxillary sinus orifice. In addition, presence of two or more of the following signs and symptoms was required: fever, leukocytosis, frequent cough, headache, nasal congestion, or postnasal drainage, and presence of either an air/fluid level or complete or partial opacification on a Water's view sinus X-ray. All subjects underwent a diagnostic transantral sinus puncture prior to the start of treatment for the purpose of determination of a causative pathogen.

The *primary efficacy endpoint* was the sponsor assessment of clinical response for the *Clinical Per Protocol* (CPP) population at the Test of Cure visit (TOC; study days 17-24). CPP subjects were all treated subjects with a clinical diagnosis of ABS, and meeting the protocol inclusion criteria, as stated above, and not otherwise excluded. In addition, subjects were required to take at least 80% of study medications and be assessed within the appropriate visit windows, except in cases of early discontinuation for treatment failures.

Prognostic factors collected for subset analyses of response included: smoking history, history of allergic rhinitis, number of episodes in the previous 12 months, number of maxillary sinuses involved, sinus x-ray results. In addition, the sponsor's assessment of clinical response was summarized by center, age, race, gender, and geographic area.

*Secondary endpoints* discussed in this summary for the CPP populations included sponsor's assessment of clinical response at end of therapy (EOT; days 11-13). Clinical and bacteriologic responses by baseline pathogen at TOC in the *Bacteriologic Per Protocol* (BPP) population were also assessed. Other efficacy assessments included sponsor's assessment of clinical response by baseline pathogen versus baseline susceptibility.

After study database closure, an error at site 1055 was found to have occurred wherein one subject (10551001) randomly assigned to receive active Azithromycin SR, actually received placebo only. This subject is reported in all analyses and data displays as being in the Azithromycin SR group, i.e., the group to which the subject had been randomly assigned. The subject's clinical and bacteriologic responses at the TOC visit were Cure and Presumed Eradication, respectively. There were no treatment related adverse events reported for this subject. From a statistical standpoint, study conclusions are not affected by this dosing error.

Five hundred seven subjects from 13 countries in North America, Latin America, Europe, and India (256 Azithromycin SR, 251 levofloxacin) were evaluated for efficacy in the primary analysis. The sponsor's assessments of clinical response rates in the CPP population at the TOC visit (17-24 days after the first dose) were 242/256 (95%) for Azithromycin SR and 233/251 (93%) for levofloxacin (A0661078 Table 5.2). The 95% confidence intervals for the difference in response rates (Azithromycin SR – levofloxacin) were [-2.5, 5.9], demonstrating that Azithromycin SR is non-inferior to levofloxacin in the treatment of acute, uncomplicated bacterial, maxillary sinusitis.

Clinical cure rates in the Bacteriologic Per Protocol population by baseline pathogen for the major respiratory organisms were: *S. pneumoniae* [36/37 (97%) Azithromycin SR; 36/39 (92%) levofloxacin], *H. influenzae* [(26/27 (96%) Azithromycin SR; 30/30 (100%) levofloxacin], and *M. catarrhalis* [8/8 (100%) Azithromycin SR, 10/11 (91%) levofloxacin] (A0661078 Table 5.3.3).

Bacteriologic response rates in the BPP populations were based primarily on clinical response at post-treatment assessment timepoints (presumed eradication or persistence for cures or failures, respectively), as sinus drainage in subjects with resolving infections is often markedly reduced and post-treatment sinus punctures were not required by protocol. However, if a post-baseline culture was obtained (e.g., in the event of clinical failure), then bacteriologic response could be documented. Overall bacteriologic eradication rates (combined sum of eradication plus presumed eradication) at TOC in the BPP population were similar between treatment groups [112/114 (98%) for Azithromycin SR and 120/129 (93%) for levofloxacin], exact 95% CI=[-2.1, 15.4] (A0661078 Table 5.5, Section 11, Item 11, Table 2). When compared for only the major typical respiratory pathogens: *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*, overall bacteriologic eradication rates were 71/72 (99%) for Azithromycin SR and 76/80 (95%) for levofloxacin, 95% CI=[-5.9, 17.8] (Appendix 2.7.3, Table ABS.1078.5.7).

Bacteriological eradication rates by baseline pathogen for the major respiratory organisms were: *S. pneumoniae* [37/37 (100%) Azithromycin SR; 36/39 (92%) levofloxacin], *H. influenzae* [26/27 (96%) Azithromycin SR; 30/30 (100%) levofloxacin], and *M. catarrhalis* [8/8 (100%) Azithromycin SR; 10/11 (90%) levofloxacin] (A0661078 Table 5.5.1).

In five subjects whose baseline pathogen was *S. pneumoniae* nonsusceptible to azithromycin, Azithromycin SR was effective with a clinical cure in 4/5 (80%) of the cases (80%, A0661078 Table 5.6.3). One clinical failure was noted (Subject 10251002). However, upon culture of the isolate at TOC from this subject, it was determined that the baseline *S. pneumoniae* pathogen, with a MIC > 256 µg/ml, was eradicated, and a positive culture for *E. coli* was obtained (A0661078 Table 5.6.4, Patient Profile).

The results demonstrate that a single dose of 2.0 g Azithromycin SR is safe and is clinically non-inferior to 10 days of levofloxacin 500 mg/day as an effective treatment for subjects with a diagnosis of ABS.

***In vitro susceptibility of baseline isolates.*** Two hundred forty-three isolates representing 29 species of bacteria (two groups were identified to the genus level only) were recovered at baseline from 228 patients in both arms in the bacterial per protocol population. The pathogens and their susceptibility to azithromycin and levofloxacin for all 228 treated subjects are listed in A0661078 Table 5.6 (n = 259 isolates). The β-lactamase characteristics and susceptibility to oxacillin or penicillin for selected pathogens are listed in A0661078 Table 2.7. Some characteristics of the four most prevalent pathogens isolated across both arms of the study are listed here.

1. The *most prevalent pathogen* isolated was *S. pneumoniae* (n = 81). Sixty-nine (85%) were susceptible to azithromycin, and 12 (15%) were resistant. Seventy-six (94%) had a MIC to azithromycin < 4 µg/ml. All 81 were susceptible to levofloxacin. Forty-six (57%) were PSSP, 22 (27%) were PISP, and 13 (16%) were PRSP.
2. The second most prevalent pathogen was *H. influenzae* (n = 61). All 60 isolates were susceptible to azithromycin with MIC values < 2 µg/ml, and all were susceptible to levofloxacin. Thirteen were β-lactamase positive, and 46 were β-lactamase negative; one isolate was not tested.

4. The fourth most prevalent pathogen was *M. catarrhalis* (n = 21). There are no agreed upon breakpoints for this pathogen. Eighty-six percent (n = 18) were β-lactamase positive, and 9.5% (n = 2) were β-lactamase negative; one isolate was not tested.

#### **Correlation of microbiological and clinical response with *in vitro* susceptibility results**

For all pathogens assessed at TOC, 112/114 (98%) were eradicated in the azithromycin arm, and 120/129 (93%) were eradicated in the levofloxacin arm (A0661078 Table 5.5). The results for the azithromycin arm are slightly higher for the BPP subjects, compared to the 242/256 (94.5%) clinical cure rate in the CPP subjects (A0661078 Table 5.2). For the levofloxacin arm, 233/251 (93%) of the CPP subjects were cured, which is identical to the cure rate in the BPP subjects.

All 37 *S. pneumoniae* isolates were eradicated or presumed eradicated in the Azithromycin SR arm, and 36/39 (92%) were presumed eradicated in the levofloxacin arm (A0661078 Table 5.6.4). The clinical response was nearly identical to the bacteriological response with the exception of one clinical failure in the Azithromycin SR arm (A0661078 Tables 5.6.3 and 5.5.4 adhoc3 and data are shown as graphs on pp 86-88 of this submission for subjects in the Azithromycin SR arm). Subject 10251002 in the BPP group in the Azithromycin SR arm was considered a failure in clinical response because *E. coli* was isolated at TOC, although the original *S. pneumoniae* isolate was not detected at TOC on day 24 (A0661078 Section 13, Table 2.3.1). Five of the 37 (14%) *S. pneumoniae* isolated in the azithromycin arm were resistant to azithromycin, but none of the 39 isolates in the levofloxacin arm were resistant to levofloxacin. Three of the azithromycin resistant isolates had MIC values ≥ 4 µg/ml. One of those carried the *mef* gene, and the other two were not genotyped due to loss of viability prior to arrival at the genotyping lab. One isolate contained the *ermB* gene (MIC = 8 µg/ml). The isolate containing both the *mef* and *ermTR* genes had a MIC of > 256 µg/ml (A0661078 Table 5.5.2). We obtained genotyping data to describe the resistance mechanism for the ten *S. pneumoniae* isolates that were not susceptible to azithromycin collected from all

randomized subjects (A0661078 Table 5.6.6). Four isolates had only the *mef* gene; one was from the US, and three were from Chile. Three isolates had only the *ermB* gene – one from Germany, Costa Rica, and Chile. One isolate from the US had *mef* and *ermTR*, and one isolate from Chile had both *ermB* and *ermTR*. We were not able to identify the resistance mechanism for one isolate from the US.

With respect to penicillin susceptibility of the *S. pneumoniae* isolates from the BPP subjects at TOC in the Azithromycin SR arm, all 18 subjects with PSSP, all 12 subjects with PISP, and all seven subjects with PRSP had bacterial eradication (A0661078 Table 5.5.1). Similarly for clinical cure, except one subject with a PRSP at baseline did not have a clinical cure (A0661078 Table 5.3.3). In the levofloxacin arm, 24/25 (96%) subjects with PSSP, 7/8 (88%) subjects with PISP, and 5/6 (83%) subjects with PRSP had bacterial eradication and clinical cures (A0661078 Tables 5.3.3 and 5.5.1). Graphs of the data are shown on pp 86-88 of this submission.

All subjects infected with *H. influenzae* were susceptible to azithromycin and to levofloxacin (A0661078 Table 5.6). In the Azithromycin SR arm, 26/27 (96%) of the subjects had positive clinical and bacteriological responses, and one patient was presumed to have a persistent pathogen and was noted as a failure in the clinical response (A0661078 Tables 5.5.3, 5.6.4 and 5.5.4 adhoc1 with data graphed on p 89 of this submission). On the basis of *in vitro* susceptibility, the patient with the failure in the Azithromycin SR arm had a baseline *H. influenzae* isolate with a MIC of 1 µg/ml to azithromycin. However, 11 other patients had successful clinical and bacteriological outcomes when their baseline pathogen also had a MIC of 1 µg/ml to azithromycin. Other positive clinical and bacteriological outcomes occurred with subjects infected with isolates that had MIC values of 2 µg/ml (6/6), 0.5 µg/ml (5/5), 0.25 µg/ml (3/3), and 0.12 µg/ml (1/1) (A0661078 Table 5.5.3 and Table 5.5.4 adhoc1 for disk diffusion data and subject responses). All 30 subjects with *H. influenzae* in the levofloxacin arm were cured and were presumed to have their pathogen eradicated (A0661078 Tables 5.6.3 and 5.6.4).

The majority of the *H. influenzae* baseline pathogens were β-lactamase negative; 22/27 (77%) isolates in the Azithromycin arm and 23/30 (81%) in the levofloxacin arm (A0661078 Tables 5.3.3 and 5.5.1). Of the 57 subjects carrying a strain of *H. influenzae*, the single bacteriological and clinical failure occurred in the Azithromycin SR arm in a subject that had a β-lactamase negative strain. All 12 subjects carrying β-lactamase positive isolates had positive clinical and bacteriological outcomes; five were in the Azithromycin SR arm and seven were in the levofloxacin arm (A0661078 Tables 5.3.3 and 5.5.1).

All eight BPP subjects infected with *M. catarrhalis* in the Azithromycin SR arm had a positive clinical response and presumed eradication of the pathogen. The azithromycin MIC values for the eight isolates from the BPP were 0.06 µg/ml (n = 5); 0.12 µg/ml (n = 2); and 0.5 µg/ml (n = 1) [A0661078 Tables 5.5.3 adhoc2 and 5.5.4 adhoc2 with data graphed on pp 90-91 of this submission].

One of the 11 patients in the levofloxacin arm did not respond clinically, and was presumed to have a persistent pathogen (A0661078 Table 5.6.4).

In the Azithromycin SR arm, eight patients with ██████████ (seven sensitive to azithromycin and one resistant) had a positive clinical response and the pathogen was eradicated or presumed eradicated (A0661078 Table 5.6.4). In the levofloxacin arm, 15/17 (88%) of the isolates were presumed eradicated; 11 were susceptible to levofloxacin, one was intermediate, and three were resistant (A0661078 Table 5.6.4). Of the two isolates that were presumed persistent in the levofloxacin arm, one was sensitive and the other was resistant.

**Listing of pathogens associated with unfavorable outcomes and their susceptibility to test drug:** One patient in the *S. pneumoniae* BPP group in the azithromycin arm was considered a failure in clinical response because *E. coli* was isolated at TOC, but not the baseline pathogen.

One patient with *H. influenzae* was presumed to have a persistent pathogen and was noted as a failure in the clinical response, but the isolate was sensitive to azithromycin (MIC = 1 µg/ml). However, 11 other patients in the same arm had isolates with MICs = 1 µg/ml, and they each had a positive clinical response.

Of the two *S. aureus* isolates that were presumed persistent in the levofloxacin arm, one was sensitive and the other was resistant to levofloxacin.

**Reviewer's comments:** Sinusitis is a common infectious disease affecting 13% or more of the US population (241). The most common pathogens associated with this infection include *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Comparative trials of acute maxillary sinusitis in adults has shown that agents such as phenoxymethylpenicillin, amoxicillin, erythromycin, clarithromycin, and azithromycin are effective. An open-label, non-comparative trial using azithromycin given over five days (1.5 g total), resulted in 86% clinical efficacy. Similar clinical efficacy was observed in short course therapy, three days with azithromycin vs. ten days with amoxicillin/clavulanate. In studies investigating clarithromycin, clinical response rates exceeded 91% compared to bacterial response rates of 87 – 89%.

According to Mandell, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* are the most common bacterial etiological agents for ABS (242). The Agency's guidance document for ABS states that isolation of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* from a maxillary sinus puncture aspirate is considered significant independent of colony count data (243).

Mandell states that *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* are responsible for 31%, 21%, and 8% of all cases of ABS. Results of this study show that *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* were responsible for 33%, 25%, and 9% of the cases reported, thus, the Applicant's study closely parallel the results reported from the literature (see Table 19 below).

**Table 19. Ranking of pathogens isolated from randomized subjects across both arms of the ABS studies.**

Organism	N	%
<i>S. pneumoniae</i>	81	33%
<i>H. influenzae</i>	61	25%
<i>M. catarrhalis</i>	21	9%
Others	52	21%
<b>total</b>	<b>243</b>	<b>100%</b>

The Applicant seeks approval of Zithromax SR for the treatment of acute bacterial sinusitis (ABS) due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*. The data provide evidence for the support of some of these organisms but not all of these organisms. What follows is the rationale for the inclusion or exclusion of each of these organisms from the first list of the package insert.

***Haemophilus influenzae***. Study results indicate that Zithromax SR is effective against most isolates of this common bacterial pathogen. Adequate numbers of isolates were identified (27 in the azithromycin arm, 30 in the comparator arm). Clinical cures and bacteriologic eradication rates were similar between the two arms with 96% in the azithromycin arms and 100% in the comparator arm. *In vitro* susceptibility results indicate all isolates had MICs between 0.12 and 2 µg/ml (Table 20 below). Of the 27 isolates, one failure (clinical and bacteriologic) was seen in an isolate with a MIC = 1 µg/ml. This failure is unexpected since the susceptibility breakpoint for *Haemophilus* spp. is ≤ 4 µg/ml.

***Moraxella catarrhalis***. Inadequate numbers of isolates were identified (8 in the azithromycin arm, 11 in the comparator arm). Both clinical cures and bacteriologic eradication rates were similar between the two arms with 100% in the azithromycin arm and 91% in the comparator arm. *In vitro* susceptibility results indicate all isolates had MICs between 0.06 and 0.5 µg/ml (Table 18 below). Of the eight isolates, there were no clinical or bacteriologic failures. An inadequate number of isolates were identified, **consequently, this organism may not be included in the first list of the Package Insert.**

***Streptococcus pneumoniae***. Study results indicate that Zithromax SR is effective against most isolates of this common bacterial pathogen. Adequate numbers of isolates were identified (37 in the azithromycin arm, 39 in the comparator arm). Clinical cures were similar between the two arms with 97% in the azithromycin arms and 92% in the comparator arms of the CPP. Bacteriologic eradication rates similar between the two arms with 100% in the azithromycin arms and 92% in the comparator arms of the BPP. *In vitro* susceptibility results indicate all isolates had MICs between ≤ 0.5 and > 256 µg/ml (Table 20 below). Of the 37 total isolates, one isolate was a clinical failure but a bacteriologic success and had a MIC ≥ 256 µg/ml. As the susceptibility breakpoint for *S. pneumoniae* is ≤ 0.5 µg/ml, the failure at this MIC is expected. The one clinical failure

was susceptible to penicillin. A definitive correlation between azithromycin and penicillin resistance cannot be drawn with such low numbers.

**Table 20. Correlation of *in vitro* susceptibility data with clinical and bacteriologic success rates by pathogen for the ABS study.**

Organism	MIC	Clinical Success	Clinical Failure	Bacteriologic Success	Bacteriologic Failure
<i>S. pneumoniae</i>	≤ 0.5	32	0	32	0
	1	0	0	0	0
	2	0	0	0	0
	4	2	0	2	0
	8	1	0	1	0
	≥ 256	0	1	1	0
<b>total</b>		<b>36</b>	<b>1</b>	<b>37</b>	<b>0</b>
<i>H. influenzae</i>	0.12	1	0	1	0
	0.25	3	0	3	0
	0.5	5	0	5	0
	1	11	1	11	1
	2	6	0	6	0
<b>total</b>		<b>26</b>	<b>1</b>	<b>26</b>	<b>1</b>
<i>H. parainfluenzae</i>	0.25	1	0	1	0
	0.5	4	1	4	1
	1	5	0	5	0
	2	1	0	1	0
	4	1	0	1	0
<b>total</b>		<b>12</b>	<b>1</b>	<b>12</b>	<b>1</b>
<i>M. catarrhalis</i>	0.06	5	0	5	0
	0.12	2	0	2	0
	0.25	0	0	0	0
	0.5	1	0	1	0
	<b>total</b>		<b>8</b>	<b>0</b>	<b>8</b>

Source: Graphs, pp 86-90, Microbiology Section, this submission.

### Combined Analysis of All Indications

***In vitro* susceptibility of all aerobic baseline isolates from adults.** Across the adult studies, typical respiratory pathogens were collected in 25 countries from North America, Latin America, Europe, and India from all randomized subjects without regard to treatment group. The most prevalent typical respiratory pathogen was *S. pneumoniae*; 83% (184/221) were susceptible to azithromycin and 97% (214/221) were susceptible to the comparator (Appendix 2.7.3, Table SUSC.1.1.1). Of the 179 *H. influenzae* isolates collected, all were susceptible to azithromycin, and 96% (172/179) were susceptible to the comparators. Of the 153 *S. aureus* isolates, 122 (80%) were susceptible to azithromycin and 135 (88%) were susceptible to the comparators. No breakpoints exist for *M. catarrhalis*, and therefore the susceptibility data for the 104 isolates were not collected. The 89 *H. parainfluenzae* isolates that were tested were 100% susceptible to azithromycin, and 89% (80/90) were susceptible to the comparators. Twenty of the 21 *S. pyogenes* isolates were susceptible to azithromycin. All 21 were susceptible to the comparators.

The MIC<sub>90</sub> for 221 *S. pneumoniae* isolates obtained from all adult randomized subjects without regard to treatment group was 4 µg/ml worldwide, and the MIC<sub>50</sub> was < 0.25 µg/ml for every country (Appendix 2.7.3, Table SUSC.3.1.1). The highest MIC<sub>90</sub> of 16 µg/ml occurred in the US, and 23% (18/79) of the US isolates were resistant, not > 30% as reported in the literature. The most prevalent resistant mechanisms employed by the 18 isolates tested from the US and the number of isolates in each category were *erm*(B), five; *mef*, four; *mef* + *erm*(B), two; *mef* + *erm*(TR), two (Appendix 2.7.3, Table SUSC.3.2.1). Three were negative for any of the genotypes, and their MICs were on the cusp of resistance. Of the six resistant isolates from Chile, four had *mef*, one had *erm*(B), and one had *erm*(B) + *erm*(TR). Four of the five resistant isolates from Canada contained *mef* and one had *erm*(B). Of the 37 resistant isolates obtained worldwide, only four other resistant *S. pneumoniae* isolates were characterized, one from each of four other countries of the world (Appendix 2.7.3, Table SUSC.3.2.1) [Four others were not viable upon arrival at the lab that performed the genotyping].

Worldwide, the MIC<sub>90</sub> for 179 *H. influenzae* isolates collected from all adult randomized subjects without regard to treatment group was 2 µg/ml, and the MIC<sub>50</sub> was 1 µg/ml (Appendix 2.7.3, Table SUSC.3.1.1). The highest MIC of 4 µg/ml occurred in three isolates worldwide; these were all from the US. For the five countries (Canada, US, Argentina, Chile, and Lithuania) that had at least 18 isolates, the MIC<sub>90</sub> was 2 µg/ml and the MIC<sub>50</sub> was 1 µg/ml.

Twenty-one *S. pyogenes* isolates were recovered from the [REDACTED] ABS, and both CAP studies. Twenty of the 21 *S. pyogenes* isolates were susceptible to azithromycin, and 19 had a MIC < 0.25 µg/ml. One isolate from India had a MIC of 0.5 µg/ml. The Russian isolate with a MIC of 4 µg/ml was unavailable for genotyping. All 21 were susceptible to the comparators.

Resistance rates and mechanisms of resistance for most of these pathogens from the various countries were either lower or consistent with that documented in the published literature as summarized earlier in this section.

The clinical cure and bacteriological eradication rates were 73/76 (96%) for the BPP subjects infected with Susceptible *S. pneumoniae* in the Azithromycin SR arms of the four clinical trials. For the 14 BPP subjects infected with Resistant *S. pneumoniae*, 10 (71%) had clinical cures and 11 (79%) had bacteriological eradication. Overall, 90 BPP subjects were infected with *S. pneumoniae*, and 83 (92%) had clinical cures and 84 (93%) had bacteriological eradication.

Due to the relatively small number of azithromycin-resistant *S. pneumoniae* isolates from BPP subjects from both arms of the four clinical trials, the isolates are listed on the following table (Table 21). The susceptibility of each isolate to azithromycin by liquid broth dilution and disk diffusion methods are listed along with the mechanism of resistance. The subject no., treatment group, and clinical and bacteriological responses are also listed. These isolates are also listed on the scattergrams in Appendix 5 (Microbiology section, this submission), but without this level of detail. Six of the 18

subjects (33%) with azithromycin-resistant *S. pneumoniae* in the Azithromycin SR arms across the four clinical trials failed in their clinical response. This occurred in subjects who had isolates with *mef*, *erm*, or a resistance mechanism that could not be determined due to loss of viability before arrival at the genotyping lab. It should be noted that MIC and disk diffusion results did not correlate well and may explain some of the lack of correlation between clinical response and bacteriological response.

**Table 21. Correlation of MIC and disk diffusion results for azithromycin resistant *S. pneumoniae* isolates from the BPP subjects.**

MIC (µg/ml)	Zone diam. (mm)	Genotype	Subject No. (day, if not baseline)	Treatment	Clinical Response*	Bacteriol. Response#
<b>Study A0661075</b>						
1	15	Negative	10491017	clarith	C	PE
2	11	Negative	10021002	clarith	F	PP
4	6	<i>mef</i> + <i>ermTR</i>	10061009	Azith SR	F	PP
4	6	<i>mef</i>	10391005	Azith SR	C	PE
4	7	<i>mef</i>	10391005 (D5)	Azith SR	C	PE
4	6	<i>mef</i>	10381016	clarith	C	PE
4	6	<i>ermB</i>	10481002 (D5 only)	Azith SR	C	PE
<b>Study A0661103</b>						
2	6	<i>mef</i>	10431008	Azith SR	C	PE
2	6	<i>mef</i>	10541012	levoflox	F	PP
4	6	<i>mef</i>	10381002	Azith SR	F	PP
4	6	<i>mef</i>	10591021	levoflox	C	PE
> 4	6	ND	10891013	Azith SR	C	PE
> 256	6	<i>ermB</i>	10111007	Azith SR	F	E
<b>Study A0661078</b>						
2	6	<i>mef</i>	10491009	levoflox	C	PE
2	6	Negative	10141009	levoflox	C	PE
2	7	ND	10251002 (D24; also <i>E. coli</i> )	Azith SR	F	E
4	6	<i>ermB</i> + <i>ermTR</i>	10491058	levoflox	C	PE
4	6	ND	10721002	Azith SR	C	PE
4	6	<i>mef</i>	10201018	levoflox	C	PE
4	9	<i>mef</i>	10491005	Azith SR	C	PE
4	9	<i>mef</i>	10491001	levoflox	C	PE
8	6	<i>ermB</i>	10491059	Azith SR	C	PE
> 4	6	ND	10711005	Azith SR	C	PE
> 256	6	<i>ermB</i>	10511023	levoflox	C	PE
> 256	6	<i>mef</i> + <i>ermTR</i>	10251002	Azith SR	F	E

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### **Discussion of *In Vitro* Susceptibility Testing Interpretative Criteria**

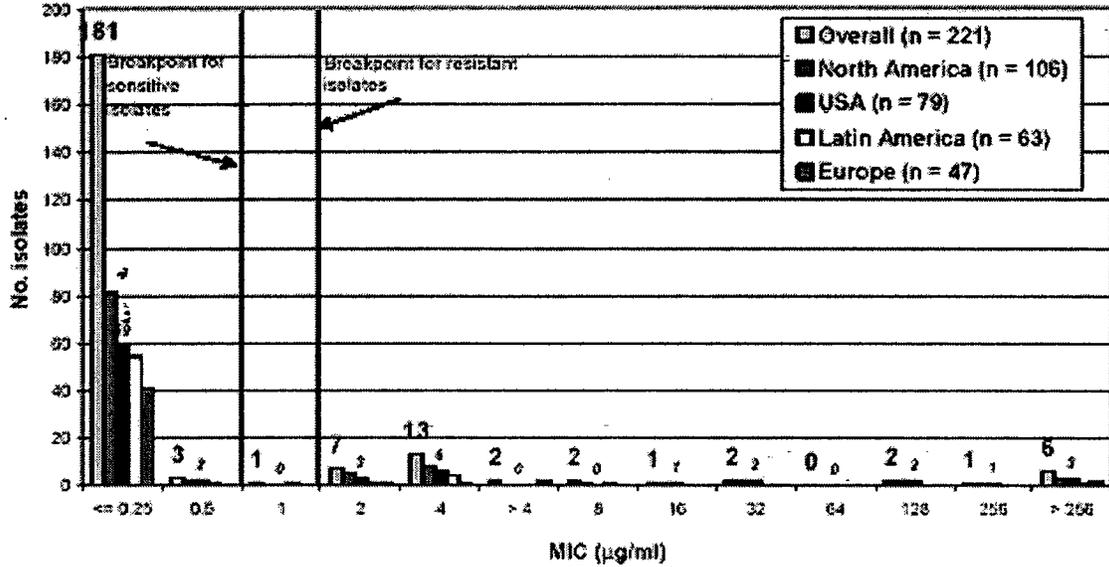
***Breakpoint Discussion for Streptococcus pneumoniae and other Streptococci.*** Overall, 181/221 (82%) of the *S. pneumoniae* isolates collected from the adults in these four studies had MIC values < 0.25 µg/ml, and in the US, 59/79 (75%) had the same MIC value (Appendix 2.7.3, Table SUSC.3.1.1.adhoc1). The current FDA and CLSI (NCCLS) breakpoints for streptococci isolates considered to be susceptible to azithromycin are < 0.5 µg/ml. In these four studies, 184/221 (83%) of the overall isolates fell within that category, while 77% (61/79) of the US isolates were included in the Susceptible category. From all the studies, only one isolate from Latin America fell into the Intermediate category (1.0 µg/ml). In the Resistant category (> 2.0 µg/ml), overall, there were 36/221 (16%) isolates, and 18/79 (23%) were from the US. These data are graphed immediately below, and data for the disk diffusion results are also graphed and presented in Appendix 2.7.3, Table SUSC.3.1.2.adhoc3. The interpretations are similar for the disk diffusion data. Overall, 36/216 (17%) of the isolates fell in the Resistant category (< 13 mm), and 18/79 (23%) of the US isolates were Resistant by disk diffusion. One of the isolates from the US was in the Intermediate category by disk diffusion (16 mm). Susceptible strains from the US accounted for 76% (60/79) of the isolates.

The clinical cure and bacteriological eradication rates were 73/76 (96%) for the patients infected with Susceptible *S. pneumoniae* in the Azithromycin SR arms of the four clinical trials. For the 14 patients infected with Resistant *S. pneumoniae*, 10 (71%) had clinical cures and 11 (79%) had bacteriological eradication. Overall, 90 patients were infected with *S. pneumoniae*, and 83 (92%) had clinical cures and 84 (93%) had bacteriological eradication.

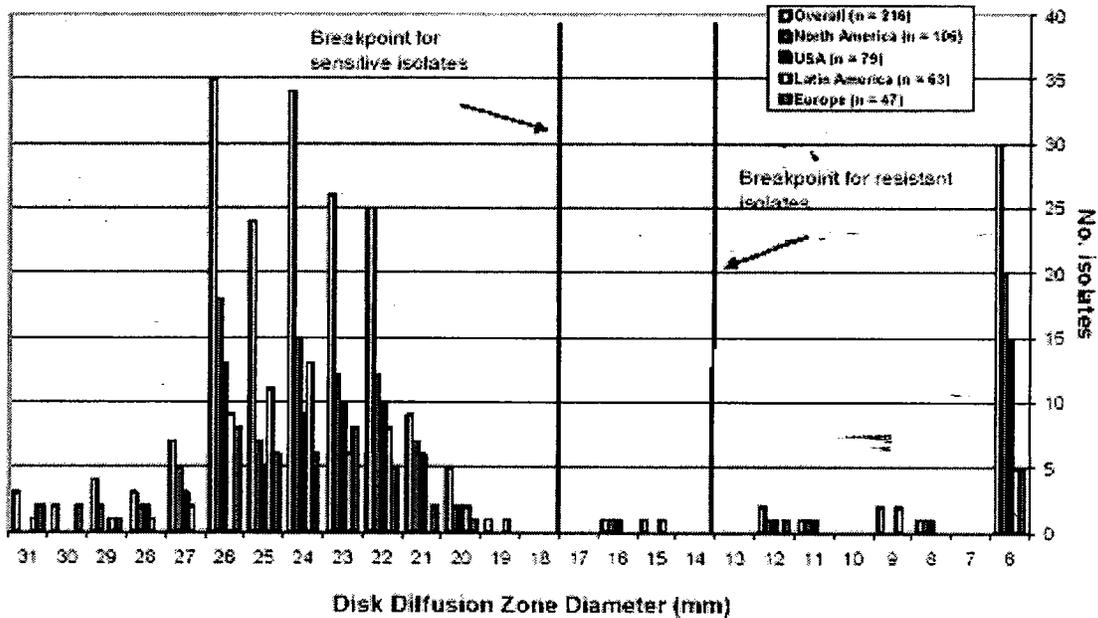
Twenty-one *S. pyogenes* isolates were collected from all randomized subjects without regard to treatment group in the four trials in adults. Nineteen had MIC values to azithromycin < 0.25 µg/ml; one had a MIC of 0.5 µg/ml (from India), and the other had a MIC of 4 µg/ml (from Russia) [Appendix 2.7.3, Table SUSC.3.1.1.adhoc1].

Of all of the streptococci that were in the BPP populations in the four clinical trials, there was only one discrepancy in the interpretation of the susceptibility to azithromycin between the two methods using the current CLSI (NCCLS) and FDA breakpoints. Patient 10681008 in study A0661078 had a *S. pyogenes* isolate with a MIC of 0.12 µg/ml, which indicates Susceptible to azithromycin, but a disk diffusion zone diameter of 14 mm, which indicates Intermediate susceptibility to azithromycin.

**Distribution of Azithromycin MIC values for *S. pneumoniae* from all Randomized Patients Across Four Clinical Trials in Adults**



**Distribution of Azithromycin Disk Diffusion values for *S. pneumoniae* from all Randomized Patients Across Four Clinical Trials in Adults**



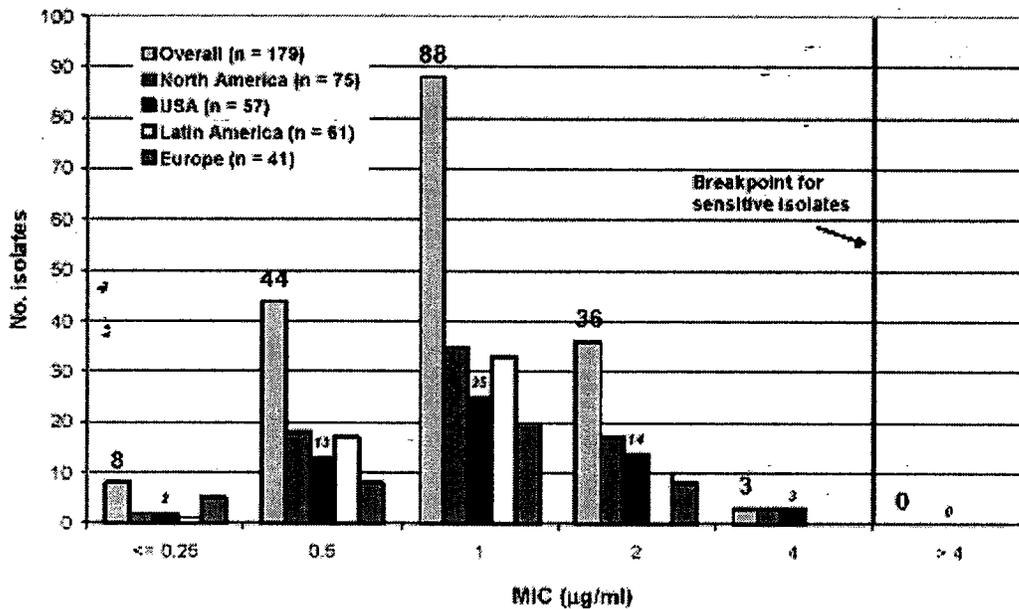
**Breakpoint Discussion for *Haemophilus* spp.** The current FDA and CLSI (NCCLS) breakpoints for *Haemophilus* spp. isolates sensitive to azithromycin are  $\leq 4$   $\mu\text{g/ml}$  or  $\geq 12$  mm. All 179 of the *H. influenzae* isolates collected from all randomized subjects without regard to treatment group in these four studies had MIC values  $< 4.0$   $\mu\text{g/ml}$ , including the 57 US isolates (Appendix 2.7.3, Table SUSC.3.1.1.adhoc1). Three isolates from the US had MIC values of  $4.0$   $\mu\text{g/ml}$ . Of the US isolates, 54/57 (95%) and 176/179 (98%) of all isolates had MIC values  $< 2.0$   $\mu\text{g/ml}$ . Seventy percent (40/57) of the US isolates and 78% of the overall isolates had MIC values  $< 1.0$   $\mu\text{g/ml}$ . Similar conclusions can be made about the same *H. influenzae* isolates using the results obtained from the disk diffusion analysis found in Appendix 2.7.3, Table SUSC.3.1.2.adhoc1. Data are graphed for both methods immediately below.

Ninety-five percent (72/76) of the BPP subjects infected with *H. influenzae* across the four clinical studies had bacteriological eradication and clinical cures in the Azithromycin SR arms. All 76 of these BPP subjects had a baseline *H. influenzae* that had a MIC  $< 4$   $\mu\text{g/ml}$  to azithromycin; all but one subject had a baseline strain with a MIC  $< 2$   $\mu\text{g/ml}$  (Data are graphed below).

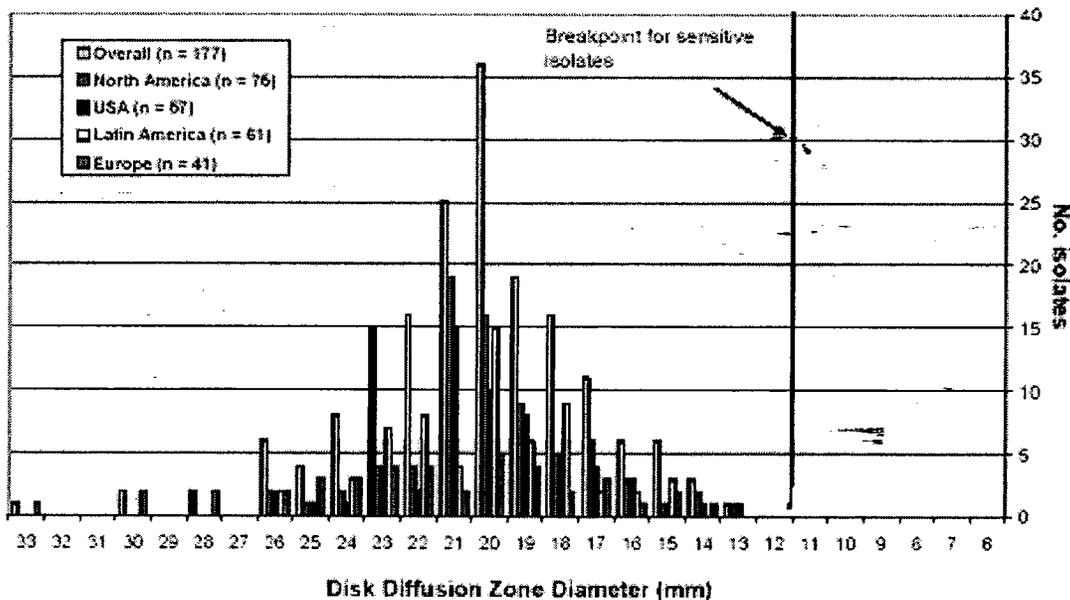
There were no discrepancies in the interpretation of susceptibility to azithromycin ~~\_\_\_\_\_~~ species of *Haemophilus*. (See the scatterplots in Appendix 5.)

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**Distribution of Azithromycin MIC Values for *H. influenzae* from all Randomized Patients Across Four Clinical Trials in Adults**



**Distribution of Azithromycin Disk Diffusion Values for *H. influenzae* from all Randomized Patients Across Four Clinical Trials in Adults**



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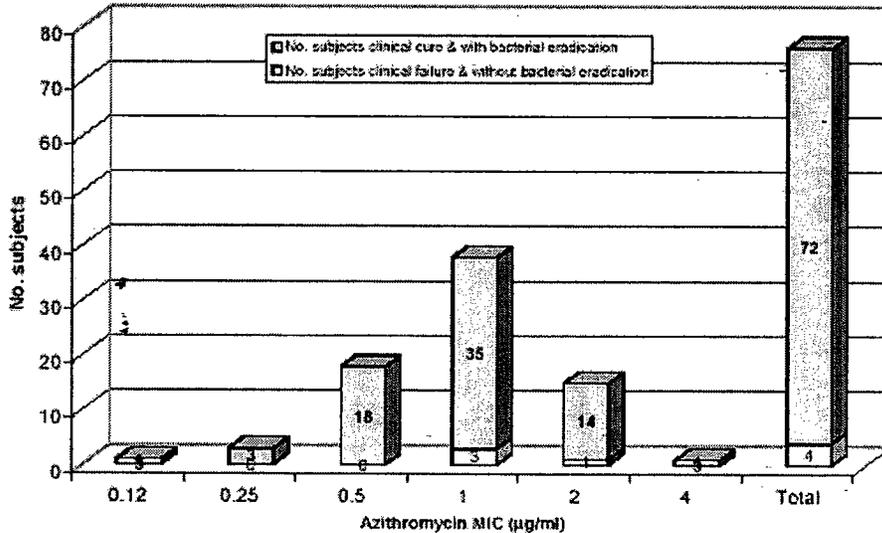
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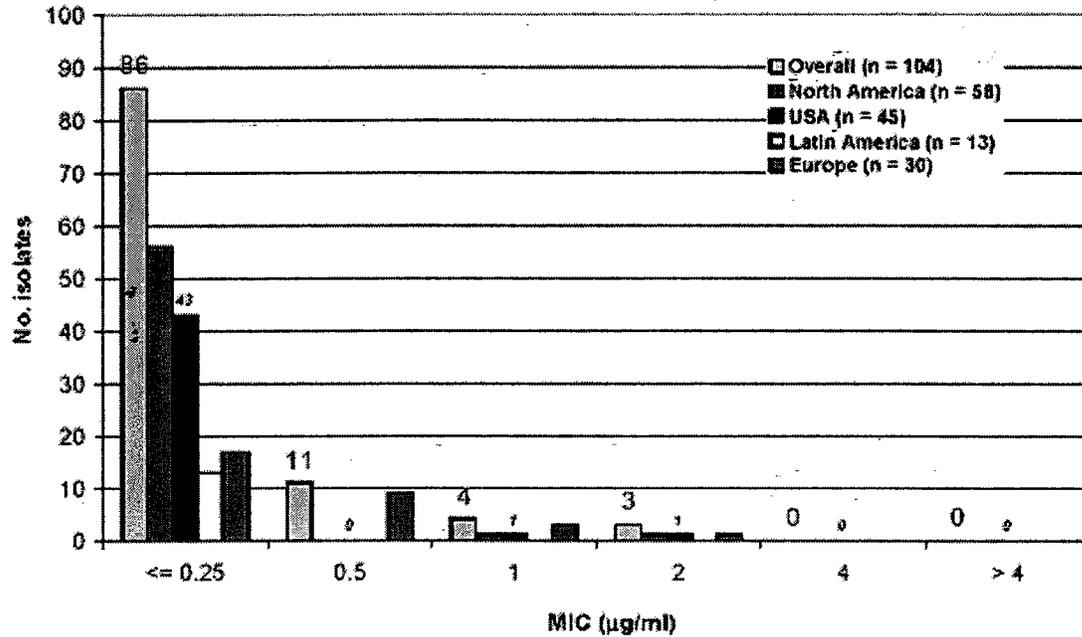
**Clinical Cure and Bacterial Eradication Rates for Azithromycin SR-treated Subjects at TOC for Four Adult Studies. BPP Subjects with *H. influenzae* Isolated at Baseline.**



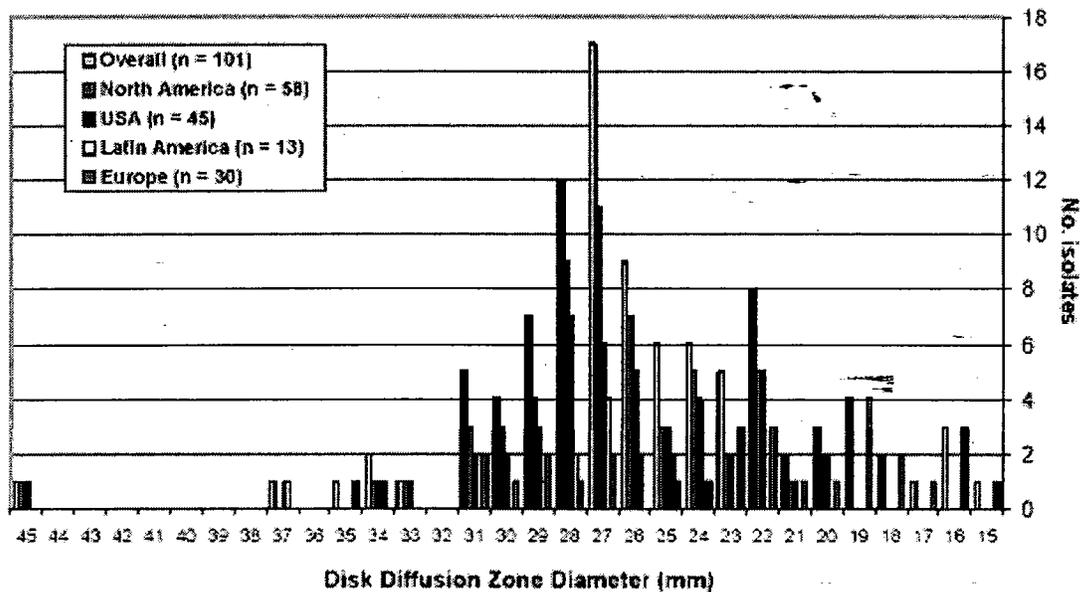
**Breakpoint Discussion for other pathogens.** Susceptibility data is not routinely collected for *Chlamydomphila pneumoniae* or *Mycoplasma pneumoniae*. No breakpoints have been defined for *M. catarrhalis* for this class of molecules. However, all 104 *M. catarrhalis* isolates obtained from all randomized subjects without regard to treatment group from the four clinical trials had MIC values  $< 2.0$  µg/ml (Appendix 2.7.3, Table SUSC.3.1.1.adhoc1) or  $< 15$  mm by the disk diffusion measurements (Appendix 2.7.3, Table SUSC.3.1.2.adhoc2). Ninety-three percent (97/104) had MIC values  $< 0.5$  µg/ml and disk diffusion zone diameters  $> 19$  mm. For the 45 isolates obtained in the US, 43 (96%) had MIC values  $< 0.25$  µg/ml and disk diffusion zone diameters  $> 21$  mm. The data for both susceptibility determination methods are graphed immediately below.

Across the four adult trials, of the 48 BPP subjects infected with *M. catarrhalis* in the Azithromycin SR arms, 46 (96%) had both bacteriological eradication and clinical cures. All but two of the isolates had MIC values  $< 0.5$  µg/ml to azithromycin; one at 1 µg/ml and the other at 2 µg/ml, but both were associated with clinical cures and bacteriological eradication.

**Distribution of Azithromycin MIC Values for *M. catarrhalis* from all Randomized Patients Across Four Clinical Trials in Adults**



**Distribution of Azithromycin Disk Diffusion Values for *M. catarrhalis* from all Randomized Patients Across Four Clinical Trials in Adults**



**Reviewer's comments:** The Applicant combined *in vitro* susceptibility data from all studies for *S. pneumoniae*, *H. influenzae*, [REDACTED] and *M. catarrhalis*. The combined data is presented in Table 22, below. *In vitro* susceptibility data was not collected for *C. pneumoniae* or *M. pneumoniae*.

**Table 22. *In vitro* susceptibility data for pertinent respiratory pathogens.**

Organism	N	MIC <sub>90</sub>	%S
<i>S. pneumoniae</i>	221	4	83%
<i>H. influenzae</i>	179	2	100%
<i>M. catarrhalis</i>	104	0.5	ND

%S=percent susceptible

In some instances, the *in vitro* susceptibility data obtained by the Applicant were consistent with data from the recent literature (see Table 23 below). However, some deviation in the MIC<sub>90</sub>s between the Applicant and the literature occurred. The Applicant found that 83% of their *S. pneumoniae* isolates were susceptible to azithromycin compared to isolates from the literature that exhibited a range of susceptibility to azithromycin from 34.4% to 94.4%. These data from the literature include penicillin resistant isolates which explains the low susceptibility data (34.4%). Most *S. pneumoniae* isolates from the literature demonstrated ~75% susceptibility to azithromycin which is lower than the 83% susceptibility seen with the Applicant's *S. pneumoniae* isolates. However, the MIC<sub>90</sub>s from the literature varied widely from 0.12 to 64 µg/ml while the MIC<sub>90</sub>s obtained by the Applicant was 4 µg/ml. Interestingly, the interpretive criterion for resistance of *S. pneumoniae* to azithromycin is 2 µg/ml. The cause for the deviation in the MIC<sub>90</sub>s data is unknown although one explanation could be the presence of isolates with high MICs presumably due to the *ermB* gene.

*H. influenzae* isolates identified by the Applicant demonstrated MIC<sub>90</sub>s of 2 µg/ml, identical to the MIC<sub>90</sub>s observed in the recent literature. While the Applicant's isolates demonstrated 100% susceptibility, the isolates shared similar values ranging from 95.5% to 100%. [REDACTED]

However, MIC<sub>90</sub>s for the Applicant's *M. catarrhalis* isolates (0.5 µg/ml) were significantly higher than MIC<sub>90</sub>s reported from the literature, ranging from 0.03 to 0.12 µg/ml. It should be noted that interpretative criteria for *M. catarrhalis* have not been defined at this time. Therefore, susceptibility could not be compared between isolates from the Applicant and the literature.

The Applicant lists the *S. pneumoniae* isolates that demonstrated high MIC values in Table 23. It is noteworthy that the isolates with MICs in excess of 256 µg/ml harbor the *ermB* determinant for altered target site while resistant isolates with MICs ≥ 4 µg/ml harbor the *mef* gene. The data from the clinical studies mirror the data obtained from the literature.

**Table 23. Compilation of *in vitro* susceptibility data for pertinent respiratory pathogens.**

organism	N	MIC <sub>50</sub>	MIC <sub>90</sub>	range	% S	ref #	
<i>S. pyogenes</i>	119	0.06	0.06	<0.06-->32	91.6	195	
	223	0.25	0.5	ND	90.6	244	
	66	0.12	4	<0.03--8	86	245	
	210	0.125	2	0.015--4	80	246	
<i>S. pneumoniae</i>	417	0.06	16	<0.06-->32	74.3	195	
	3042	0.06	8	<0.015-->32	74.3	70	
	3297	0.06	16	<0.015-->32	74.6	70	
	542	0.01	1	ND	90.2	244	
	100	0.12	16	0.008--16	ND	247	
	299	ND	>8	<0.015-->8	ND	246	
	729	9	>32	<0.03-->32	41	245	
<i>S. pneumoniae</i> (Pen-S)	249	0.06	0.12	<0.06-->32	94.4	195	
	112	ND	0.25	<0.015-->9	ND	246	
<i>S. pneumoniae</i> (Pen-I)	70	0.06	>64	<0.06-->64	58.6	195	
	91	ND	8	<0.015-->8	ND	246	
<i>S. pneumoniae</i> (Pen-R)	98	2	>64	<0.06-->64	34.7	195	
	96	ND	>8	<0.015-->8	ND	246	
<i>S. pneumoniae</i> (macrolide-R)b	90	8	>64	2-->64	NA	195	
<i>H. influenzae</i>	300	1	2	<0.06-->32	99	195	
	2000	1198	1	2	ND	99.7	248
	2001	1077	1	2	ND	99.4	248
	2002	1163	1	2	ND	99.4	248
	2001	729	1	2	<0.15-->32	98.9	70
	2002	566	1	2	0.12--8	99.6	70
		67	2	4	ND	95.5	244
		100	1	2	0.06--8	ND	247
		368	0.125	0.25	0.03--1	100	246
	beta-lactamase +	489	1	2	<0.06--16	99.6	175
beta-lactamase -	2459	1	2	<0.06-->16	99.8	175	
	2948	1	2	<0.06-->16	99	175	
	736	1	2	<0.06-->32	99	245	

<i>M. catarrhalis</i>	231	0.06	0.06	<0.06--0.25	ND	195	
	2000	525	<0.12	<0.12	ND	100	248
	2001	589	<0.12	<0.12	ND	100	248
	2002	574	<0.12	<0.12	ND	100	248
	2001	331	0.03	0.06	<0.015--0.06	100	70
	2002	312	0.03	0.03	<0.015--0.06	100	70
		100	0.06	0.12	0.03--0.25	ND	247
		107	0.03	0.06	0.03--0.125	ND	246
beta-lactamase +	1071	<0.06	<0.06	<0.06--0.25	100	175	
beta-lactamase -	60	<0.06	<0.06	<0.06	100	175	
	1131	<0.06	<0.06	<0.06--0.25	100	175	
	256	0.03	0.03	<0.03--2	ND	245	

ND=not determined

b=macrolide R defined as azithro resistant >2µg/ml

Breakpoints for *S. pneumoniae*, *H. influenzae*, and *H. influenzae* were consistent with the established CLIS (NCCLS) breakpoints. Susceptibility data for *C. pneumoniae* and *M. pneumoniae* were not collected. Interpretative criteria for *M. catarrhalis* have not been defined at this time. The Applicant does not request any changes to the breakpoints for any of the organisms sought in the proposed indications.

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Clinical Microbiology Review  
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**Conclusion/Recommendation:**

This application is **approvable** contingent upon changes to the Microbiology Section of the Package Insert as follows:

Peter Coderre, PhD, MBA  
Microbiology Reviewer

FMarsik, PhD Micro  
TL/HFD-520  
Finalized 5/26/05 FJM

LGavrilovich, MD  
/DepDir/HFD-520

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HFD-520/DepDir/LGavrilovich  
HFD-520/Smicro/FMarsik  
HFD-520/Micro/PCoderre  
HFD-520/MO/NMoledina  
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HFD-520/MO/MImoisili  
HFD-520/BioPharm/CBonapace  
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