### Comparison of clinical and bacteriological outcome at posttherapy/TOC

In the PPb population at posttherapy/TOC, all subjects who had a clinical outcome of cure also had a bacteriological outcome of satisfactory, i.e., a satisfactory therapeutic outcome; and all subjects who had a clinical outcome of failure had a bacteriological outcome of unsatisfactory.

A total of 18/22 (81.8%) of subjects at posttherapy/TOC had a satisfactory therapeutic outcome (HMR 3647 5-d: 6/7 [85.7%]; HMR 3647 10-d: 6/7 [85.7%]; AMC: 6/8 [75.0%]. Clinical outcome was failure and bacteriological outcome was unsatisfactory for 1 subject in the HMR 3647 5-d group (396/017), 1 subject in the HMR 3647 10-d group (174/049) and 2 subjects in the AMC group (175/020, 181/005).

### *Subsequent antimicrobial medication*

Antimicrobial medication was administered subsequent to study medication in 152/638 (23.8%) of the treated subjects in the mITT population (HMR 3647 5-d: 51/212 [24.1%]; HMR 3647 10-d: 54/215 [25.1%]; AMC: 47/211 [22.3%]). The most common subsequent antimicrobial medications were beta-lactam antibacterials (penicillin plus others) (HMR 3647 5-d: 27 [12.7%]; HMR 3647 10-d: 24 [11.2%]; AMC: 24 [11.4%]). The outcome of the subsequent antimicrobial medication was success for 35 (68.6%) of the 51 HMR 3647 5-d subjects, 32 (59.3%) of the 54 HMR 3647 10-d subjects and 26 (55.3%) of the 47 AMC subjects. A total of 7 subjects in the HMR 3647 5-d group, 11 subjects in the HMR 3647 10-d group and 12 subjects in the AMC had an outcome of failure. The outcome was unknown or missing for 9 subjects in the HMR 3647 5-d group, 11 subjects in the HMR 3647 10-d group and 9 subjects in the AMC group.

### *Efficacy analysis of special subject groups*

Analyses of clinical outcome were performed on subjects, who had demographic factors of special interest, general risk factors (underlying diseases) for morbidity, characteristics of the current infection and prognostic factors for AMS in the PPc population, as follows:

- Demographic characteristics: sex, age (<65 years, ≥65 years), race (white, black, Asian/Oriental, multiracial), smoking status (smoker, ex-smoker, and nonsmoker).
- General risk factors for morbidity: none, one, more than one.
- Characteristics of current infection and AMS-specific prognostic factors: number of AMS episodes that required antibiotic treatment in last 12

months (0, 1-3 or >3); history of asthma (yes/no); episodes of allergic rhinitis in the last 30 days (yes/no); nasal septal deviation (yes = mild/moderate/severe, no = absent); ENT-related surgical history; duration of current AMS episode (1 to 3 days, 4 to 6, 7 to 14, ≥15 days); investigator's assessment of intensity (mild/moderate/ severe); fever (yes/no); sinus X-ray findings.

Clinical outcome in subjects with special demographic factors of interest was as follows.

**Applicant's Clinical outcome in subjects with demographic factors of special interest – PPc population**

| | | Clinical outcome Number of subjects (%) | | | | |
|---|---|---|---|---|---|---|
| | | HMR 3647 10-d | | | AMC | |
| **Subgroup** | **N** | **Cure** | **Failure** | **N** | **Cure** | **Failure** |
| All Subjects: | 147 | 109 | 38 | 138 | 103 | 35 |
| Sex: | | | | | | |
| Male | 62 | 49 (79.0%) | 13 (21.0%) | 46 | 32 (69.6%) | 14 (30.4%) |
| Female | 85 | 60 (70.6%) | 25 (29.4%) | 92 | 71 (77.2%) | 21 (22.8%) |
| Age: | | | | | | |
| <65 years | 137 | 101 (73.7%) | 36 (26.3%) | 133 | 99 (74.4%) | 34 (25.6%) |
| ≥65 years | 10 | 8 (80.0%) | 2 (20.0%) | 5 | 4 (80.0%) | 1 (20.0%) |
| Race: | | | | | | |
| White | 131 | 94 (71.8%) | 37 (28.2%) | 126 | 94 (74.6%) | 32 (25.4%) |
| Black | 12 | 11 (91.7%) | 1 (8.3%) | 4 | 3 (75.0%) | 1 (25.0%) |
| Asian/Oriental | 2 | 2 (100%) | 0 (0%) | 7 | 6 (85.7%) | 1 (14.3%) |
| Multiracial | 2 | 2 (100%) | 0 (0%) | 1 | 0 (0%) | 1 (100%) |
| Smoking status: | | | | | | |
| Smoker | 37 | 23 (62.2%) | 14 (37.8%) | 33 | 25 (75.8%) | 8 (24.2%) |
| Ex-Smoker | 31 | 24 (77.4%) | 7 (22.6%) | 19 | 15 (78.9%) | 4 (21.1%) |
| Nonsmoker | 79 | 62 (78.5%) | 17 (21.5%) | 86 | 63 (73.3%) | 23 (26.7%) |

**FDA's Clinical outcome in subjects with demographic factors of special interest – PPc population**

| | | Clinical outcome Number of subjects (%) | | | | |
|---|---|---|---|---|---|---|
| | | HMR 3647 10-d | | | AMC | |
| **Subgroup** | **N** | **Cure** | **Failure** | **N** | **Cure** | **Failure** |
| All Subjects: | 141 | 103 | 38 | 137 | 102 | 35 |
| Sex: | | | | | | |
| Male | 59 | 46 (78.0%) | 13 (22.0%) | 45 | 31 (68.6%) | 14 (30.4%) |
| Female | 81 | 57 (69.5%) | 25 (30.5%) | 92 | 71 (69.6%) | 21 (22.8%) |
| Age: | | | | | | |
| <65 years | 131 | 95 (72.5%) | 36 (27.5%) | 132 | 98 (74.3%) | 34 (25.7%) |
| ≥65 years | 10 | 8 (80.0%) | 2 (20.0%) | 5 | 4 (80.0%) | 1 (20.0%) |
| Race: | | | | | | |
| White | 130 | 93 (71.5%) | 36 (28.5%) | 125 | 93 (74.4%) | 32 (25.6%) |
| Black | 7 | 6 (85.7%) | 1 (14.3%) | 4 | 3 (75.0%) | 1 (25.0%) |
| Asian/Oriental | 2 | 2 (100%) | 0 (0%) | 7 | 6 (85.7%) | 1 (14.3%) |
| Multiracial | 2 | 2 (100%) | 0 (0%) | 1 | 0 (0%) | 1 (100%) |
| Smoking status: | | | | | | |
| Smoker | 33 | 19 (57.8%) | 14 (42.2%) | 32 | 24 (75.0%) | 8 (25.0%) |
| Ex-Smoker | 31 | 24 (77.4%) | 7 (22.6%) | 19 | 15 (78.9%) | 4 (21.1%) |
| Nonsmoker | 77 | 60 (77.9%) | 17 (22.1%) | 86 | 63 (73.3%) | 23 (26.7%) |

**Applicant's Clinical outcome in subjects with**
**Demographic factors of special interest – PPc population**

| | | Clinical outcome Number of subjects (%) | | | | |
|---|---|---|---|---|---|---|
| | | HMR 3647 5-d | | | AMC | |
| **Subgroup** | **N** | **Cure** | **Failure** | **N** | **Cure** | **Failure** |
| All Subjects: | 149 | 113 | 36 | 138 | 103 | 35 |
| Sex: | | | | | | |
| Male | 68 | 54 (79.4%) | 14 (20.6%) | 46 | 32 (69.6%) | 14 (30.4%) |
| Female | 81 | 59 (72.8%) | 22 (27.2%) | 92 | 71 (77.2%) | 21 (22.8%) |
| Age: | | | | | | |
| <65 years | 143 | 108 (75.5%) | 35 (24.5%) | 133 | 99 (74.4%) | 34 (25.6%) |
| ≥65 years | 6 | 5 (83.3%) | 1 (16.7%) | 5 | 4 (80.0%) | 1 (20.0%) |
| Race: | | | | | | |
| White | 133 | 101 (75.9%) | 32 (24.1%) | 126 | 94 (74.6%) | 32 (25.4%) |
| Black | 5 | 5 (100%) | 0 (0%) | 4 | 3 (75.0%) | 1 (25.0%) |
| Asian/Oriental | 9 | 6 (66.7%) | 3 (33.3%) | 7 | 6 (85.7%) | 1 (14.3%) |
| Multiracial | 2 | 1 (50.0%) | 1 (50.0%) | 1 | 0 (0%) | 1 (100%) |
| Smoking status: | | | | | | |
| Smoker | 33 | 25 (75.8%) | 8 (24.2%) | 33 | 25 (75.8%) | 8 (24.2%) |
| Ex-Smoker | 34 | 27 (79.4%) | 7 (20.6%) | 19 | 15 (78.9%) | 4 (21.1%) |
| Nonsmoker | 82 | 61 (74.4%) | 21 (25.6%) | 86 | 63 (73.3%) | 23 (26.7%) |

**FDA's Clinical outcome in subjects with**
**Demographic factors of special interest – PPc population**

| | | Clinical outcome Number of subjects (%) | | | | |
|---|---|---|---|---|---|---|
| | | HMR 3647 5-d | | | AMC | |
| **Subgroup** | **N** | **Cure** | **Failure** | **N** | **Cure** | **Failure** |
| All Subjects: | 147 | 111 | 36 | 137 | 102 | 35 |
| Sex: | | | | | | |
| Male | 66 | 52 (78.8%) | 14 (21.5%) | 45 | 31 (68.6%) | 14 (30.4%) |
| Female | 81 | 59 (72.8%) | 22 (27.2%) | 92 | 71 (77.2%) | 21 (22.8%) |
| Age: | | | | | | |
| <65 years | 141 | 106 (75.5%) | 35 (24.5%) | 132 | 98 (74.4%) | 34 (25.6%) |
| ≥65 years | 6 | 5 (83.3%) | 1 (16.7%) | 5 | 4 (80.0%) | 1 (20.0%) |
| Race: | | | | | | |
| White | 133 | 101 (75.9%) | 32 (24.1%) | 125 | 93 (74.4%) | 32 (25.6%) |
| Black | 3 | 3 (100%) | 0 (0%) | 4 | 3 (75.0%) | 1 (25.0%) |
| Asian/Oriental | 9 | 8 (88.9%) | 1 (11.1%) | 7 | 6 (85.7%) | 1 (14.3%) |
| Multiracial | 2 | 1 (50.0%) | 1 (50.0%) | 1 | 0 (0%) | 1 (100%) |
| Smoking status: | | | | | | |
| Smoker | 33 | 25 (75.8%) | 8 (24.2%) | 33 | 25 (75.8%) | 8 (24.2%) |
| Ex-Smoker | 31 | 24 (77.4%) | 7 (22.6%) | 19 | 15 (78.9%) | 4 (21.1%) |
| Nonsmoker | 76 | 59 (76.6%) | 17 (22.4%) | 86 | 63 (73.3%) | 23 (26.7%) |

Clinical outcome in subjects according to risk factors specific for AMS was as follows.

**Applicant's Clinical outcome according to characteristics of current infection and AMS-specific prognostic factors – PPc population**

| | | Clinical outcome number of subjects (%) HMR 3647 10-d | | | AMC | |
|---|---|---|---|---|---|---|
| **Subgroup** | **N** | **Cure** | **Failure** | **N** | **Cure** | **Failure** |
| AMS episodes in the last year | 60 | 40 (66.7%) | 20 (33.3%) | 58 | 38 (65.5%) | 20 (34.5%) |
| AMS episodes requiring antimicrobial treatment | | | | | | |
| 0 | 0 | - | - | 2 | 1 (50.0%) | 1 (50.0%) |
| 1-3 | 60 | 40 (66.7%) | 20 (33.3%) | 56 | 37 (66.1%) | 19 (33.9%) |
| > 3 | 0 | - | - | 0 | - | - |
| History of asthma | 21 | 18 (85.7%) | 3 (14.3%) | 22 | 16 (72.7%) | 6 (27.3%) |
| Episodes of allergic rhinitis in last 30 days | 20 | 16 (80.0%) | 4 (20.0% | 20 | 13 (65.0%) | 7 (35.0%) |
| Nasal septal deviation | 32 | 25 (78.1%) | 7 (21.9%) | 19 | 14 (73.7%) | 5 (26.3%) |
| ENT related surgical history | 28 | 21 (75.0%) | 7 (25.0%) | 20 | 15 (75.0%) | 5 (25.0%) |
| Duration of current AMS episode: | | | | | | |
| 1-3 days | 19 | 15 (78.9%) | 4 (21.1%) | 18 | 13 (72.2%) | 5 (27.8%) |
| 4-6 days | 39 | 30 (76.9%) | 9 (23.1%) | 36 | 28 (77.8%) | 8 (22.2%) |
| 7-14 days | 64 | 48 (75.0%) | 16 (25.0%) | 66 | 46 (69.7%) | 20 (30.3%) |
| >15 days | 25 | 16 (64.0%) | 9 (36.0%) | 18 | 16 (88.9%) | 2 (11.1%) |
| Investigator's assessment of intensity: | | | | | | |
| Mild | 10 | 8 (80.0%) | 2 (20.0%) | 11 | 8 (72.7%) | 3 (27.3%) |
| Moderate | 116 | 84 (72.4%) | 32 (27.6%) | 106 | 80 (75.5%) | 26 (24.5%) |
| Severe | 21 | 17 (81.0%) | 4 (19.0%) | 21 | 15 (71.4%) | 6 (28.6%) |
| Fever | | | | | | |
| Yes | 1 | 0 (0.0%) | 1 (100.0%) | 1 | 1 (100.0%) | 0 (0.0%) |
| No | 146 | 109 (74.7%) | 37 (25.3%) | 137 | 102 (74.5%) | 35 (25.5%) |
| Sinus X-ray findings: | | | | | | |
| Air fluid level | 54 | 40 (74.1%) | 14 (25.9%) | 59 | 47 (79.7%) | 12 (20.3%) |
| Total opacity | 29 | 24 (82.8%) | 5 (17.2%) | 17 | 12 (70.6%) | 5 (29.4%) |
| Mucosal thickening ≥6 mm | 97 | 70 (72.2%) | 27 (27.8%) | 97 | 71 (73.2%) | 26 (26.8%) |
| Unilateral | 99 | 76 (76.8%) | 23 (23.2%) | 83 | 65 (78.3%) | 18 (21.7%) |
| Bilateral | 48 | 33 (68.8%) | 15 (31.3%) | 55 | 38 (69.1%) | 17 (30.9%) |
| X-ray severity | | | | | | |
| Air fluid level/total opacity with mucosal thickening ≥ 6 mm | 28 | 20 (71.4%) | 8 (28.6%) | 33 | 25 (75.8%) | 8 (24.2%) |
| Air fluid level/total opacity without mucosal thickening ≥ 6 mm | 49 | 39 (79.6%) | 10 (20.4%) | 41 | 32 (78.0%) | 9 (22.0%) |
| Mucosal thickening ≥ 6 mm only | 69 | 50 (72.5%) | 19 (27.5%) | 64 | 46 (71.9%) | 18 (28.1%) |
| Other | 1 | 0 (0.0%) | 1 (100%) | 0 | 0 (0.0%) | 0 (0.0%) |

**Applicant's Clinical outcome according to characteristics of current infection and AMS-specific prognostic factors – PPc population**

| | | Clinical outcome number of subjects (%) HMR 3647 5-d | | | AMC | |
|---|---|---|---|---|---|---|
| **Subgroup** | **N** | **Cure** | **Failure** | **N** | **Cure** | **Failure** |
| AMS episodes in the last year | 52 | 40 (76.9%) | 12 (23.1%) | 58 | 38 (65.5%) | 20 (34.5%) |
| AMS episodes requiring antimicrobial treatment | | | | | | |
| 0 | 4 | 3 (75.0%) | 1 (25.0%) | 2 | 1 (50.0%) | 1 (50.0%) |
| 1-3 | 48 | 37 (77.1%) | 11 (22.9%) | 56 | 37 (66.1%) | 19 (33.9%) |
| > 3 | 0 | 0 (0%) | 0 (0%) | 0 | 0 (0%) | 0 (0%) |
| History of asthma | 20 | 17 (85.0%) | 3 (15.0%) | 22 | 16 (72.7%) | 6 (27.3%) |
| Episodes of allergic rhinitis in last 30 days | 23 | 16 (69.6%) | 7 (30.4%) | 20 | 13 (65.0%) | 7 (35.0%) |
| Nasal septal deviation | 30 | 24 (80.0%) | 6 (20.0%) | 19 | 14 (73.7%) | 5 (26.3%) |
| ENT related surgical history | 25 | 16 (64.0%) | 9 (36.0%) | 20 | 15 (75.0%) | 5 (25.0%) |
| Duration of current AMS episode: | | | | | | |
| 1-3 days | 16 | 13 (81.3%) | 3 (18.8%) | 18 | 13 (72.2%) | 5 (27.8%) |
| 4-6 days | 41 | 32 (78.0%) | 9 (22.0%) | 36 | 28 (77.8%) | 8 (22.2%) |
| 7-14 days | 59 | 47 (79.7%) | 12 (20.3%) | 66 | 46 (69.7%) | 20 (30.3%) |
| >15 days | 33 | 21 (63.6%) | 12 (36.4%) | 18 | 16 (88.9%) | 2 (11.1%) |
| Investigator's assessment of intensity: | | | | | | |
| Mild | 8 | 7 (87.5%) | 1 (12.5%) | 11 | 8 (72.7%) | 3 (27.3%) |
| Moderate | 123 | 92 (74.8%) | 31 (25.2%) | 106 | 80 (75.5%) | 26 (24.5%) |
| Severe | 18 | 14 (77.8%) | 4 (22.2%) | 21 | 15 (71.4%) | 6 (28.6%) |
| Fever | | | | | | |
| Yes | 5 | 4 (80.0%) | 1 (20.0%) | 1 | 1 (100.0%) | 0 (0.0%) |
| No | 144 | 109 (75.7%) | 35 (24.3%) | 137 | 102 (74.5%) | 35 (25.5%) |
| Sinus X-ray findings: | | | | | | |
| Air fluid level | 45 | 36 (80.0%) | 9 (20.0%) | 59 | 47 (79.7%) | 12 (20.3%) |
| Total opacity | 34 | 27 (79.4%) | 7 (20.6%) | 17 | 12 (70.6%) | 5 (29.4%) |
| Mucosal thickening ≥6 mm | 107 | 82 (76.6%) | 25 (23.4%) | 97 | 71 (73.2%) | 26 (26.8%) |
| Unilateral | 85 | 66 (77.6%) | 19 (22.4%) | 83 | 65 (78.3%) | 18 (21.7%) |
| Bilateral | 64 | 47 (73.4%) | 17 (26.6%) | 55 | 38 (69.1%) | 17 (30.9%) |
| X-ray severity | | | | | | |
| Air fluid level/total opacity with mucosal thickening ≥ 6 mm | 36 | 32 (88.9%) | 4 (11.1%) | 33 | 25 (75.8%) | 8 (24.2%) |
| Air fluid level/total opacity without mucosal thickening ≥ 6 mm | 42 | 31 (73.8%) | 11 (26.2%) | 41 | 32 (78.0%) | 9 (22.0%) |
| Mucosal thickening ≥ 6 mm only | 71 | 50 (70.4%) | 21 (29.6%) | 64 | 46 (71.9%) | 18 (28.1%) |
| Other | 0 | 0 (0.0%) | 0 (0.0%) | 0 | 0 (0.0%) | 0 (0.0%) |

### *Applicant's Efficacy Conclusions*

The efficacy conclusions are as follows:

- The primary analysis demonstrated equivalence between HMR 3647 800 mg once daily (given for both 5 days and 10 days) with amoxicillin/clavulanic acid 500/125 mg given three times daily for 10 days in terms of clinical outcome at posttherapy/TOC for the PPc population, and also for the mITT population, which reinforces the results of the primary efficacy analysis.
- The results of the secondary analyses of clinical outcome at late posttherapy were comparable between treatment groups and support the results of the primary analysis. Although bacteriological data were limited in this study, bacteriological outcomes at posttherapy/TOC and at late posttherapy were comparable across the three treatment groups.
- Eradication rates for the primary endpoint were the following: S. *pneumoniae* (HMR 3647 10-d: 2/2; HMR 3647 5-d: 2/2; and AMC: 2/4), *H. influenzae* (HMR 3647 10-d: 3/3; HMR 3647 5-d: 2/2; and AMC: 1/1), *H. parainfluenzae* (HMR 3647 5-d: 1/1; HMR 3647 10-d: 0/0, and AMC: 0/0), and *M. catarrhalis* (HMR 3647 10-d: 0/0; HMR 3647 5-d: 0/0; and AMC: 1/1) .
- Of the 8 isolates of *S. pneumoniae,* 1 was resistant to Penicillin G and Erythomycin A and had a bacteriological outcome at posttherapy/TOC of presumed eradication. This subject was a relapse and presumed persistence at late posttherapy.
- The results of the primary efficacy analysis were reproduced using the logistic regression model, confirming the conclusion of equivalence between each of the two HMR 3647 treatment groups and AMC.

## RESULTS - SAFETY

### Extent of exposure

Seven hundred seventy-eight (778) out of 790 subjects (98%) received at least one dose of study medication (257 in the HMR 3647 5-d group; 266 in the HMR 3647 10-d group; and 255 in the AMC group) and had at least one post pretherapy/entry safety assessment and were therefore evaluable for safety. The reasons these 12 remaining subjects did not have post pretherapy/entry safety assessments were the following: lost to follow-up (1 in the HMR 3647 5-d group, 3 in the HMR 3647 10-d group, and 4 in the AMC group), subject did not wish to continue (3 in the AMC group) and other reason (1 in the HMR 3647 10-d group).

The mean treatment duration in the safety population was 9.7 days in the HMR 3647 5-d group, 10.0 days in the HMR 3647 10-d group, and 10 days in the AMC group. In the HMR 3647 5-d group, 22 subjects received active treatment for less than 5 days and 234 subjects received active treatment for 5 days. In the HMR 3647 10-d group, 29 subjects received active treatment for less than 10 days and 237 subjects received active treatment for 10 or more days. In the AMC group, 32 subjects received active treatment for less than 10 days and 221 subjects received active treatment for 10 or more days.

The cumulative number of days of active treatment derived from the median number of doses of active treatment was 4.7 days in the HMR 3647 5-d group, 9.3 days in the HMR 3647 10-d group, and 9.1 days in the AMC group in the safety population.

### Adverse events

Adverse events are presented by body system, both for all adverse events and all TEAEs irrespective of relationship to study medication and for possibly related adverse events. Serious adverse events are presented by seriousness criterion, according to whether the event occurred before, during or after treatment

### Safety analysis excluding selected sites for sinusitis study 3005

The following is an evaluation of the effect on safety conclusions resulting from the exclusion of two sites (3005/150, 3005/191) from sinusitis study 3005. A sensitivity analysis is carried out comparing findings with and without the selected sites. These sites contributed 13 patients on Telithromycin 5 days, 12 on Telithromycin 10 days and 10 patients on comparator in the safety dataset.

Results are extracted from the attached revised tables and compared to those presented in the original NDA submission for the following.

- most frequent TEAEs (>2%)
- hepatic TEAEs
- cardiovascular TEAEs
- serious TEAEs
- frequencies of clinically noteworthy abnormal laboratory values
- frequencies of significant prolongation of QTc intervals
- mean and mean changes in QT and corrected QT values

Numbers and frequencies are shown side-by-side for all investigators in the NDA submission and for the revised numbers excluding the selected investigators. These are presented for Telithromycin 5 and 10-day treatment durations and comparator (amoxicillin/clavulanic acid for 10 days).

The safety findings excluding the selected sites were consistent with the results reported in the NDA submission. The selected sites represented about 5% of the total population and their findings were consistent with the overall safety experience considering their relatively small patient counts.

**TEAE frequencies > 2%**

| **Possibly related** | **Telithromycin 5-day** | | | | **Telithromycin 10-day** | | | |
|---|---|---|---|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | | All investigators | | Revised counts | |
| Total | 257 | | 244 | | 266 | | 254 | |
| Diarrhea | 49 | 19.07% | 47 | 19.26% | 53 | 19.92% | 52 | 20.47% |
| Nausea | 30 | 11.67% | 29 | 11.89% | 24 | 9.02% | 24 | 9.45% |
| Headache | 2 | 0.78% | 2 | 0.82% | 10 | 3.76% | 10 | 3.94% |
| Dizziness | 13 | 5.06% | 13 | 5.33% | 13 | 4.89% | 13 | 5.12% |
| Flatulence | 10 | 3.89% | 10 | 4.10% | 5 | 1.88% | 5 | 1.97% |
| Vomiting | 5 | 1.95% | 5 | 2.05% | 11 | 4.14% | 11 | 4.33% |
| Abdominal pain | 8 | 3.11% | 8 | 3.28% | 14 | 5.26% | 13 | 5.12% |
| Asthenia | 5 | 1.95% | 5 | 2.05% | 2 | 0.75% | 2 | 0.79% |
| Dyspepsia | 7 | 2.72% | 6 | 2.46% | 9 | 3.38% | 8 | 3.15% |
| Liver function test abnormal | 5 | 1.95% | 5 | 2.05% | 2 | 0.75% | 2 | 0.79% |
| Dry mouth | 5 | 1.95% | 4 | 1.64% | 5 | 1.88% | 5 | 1.97% |
| Rhinitis | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Somnolence | 3 | 1.17% | 3 | 1.23% | 4 | 1.50% | 4 | 1.57% |
| Vaginal moniliasis | 4 | 1.56% | 4 | 1.64% | 8 | 3.01% | 8 | 3.15% |
| Gastrointestinal pain | 3 | 1.17% | 3 | 1.23% | 5 | 1.88% | 5 | 1.97% |
| Upper respiratory infection | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Abnormal stools | 2 | 0.78% | 2 | 0.82% | 5 | 1.88% | 5 | 1.97% |
| Rash* | 1 | 0.39% | 1 | 0.41% | 3 | 1.13% | 3 | 1.18% |
| Sore throat* | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Pharyngitis* | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Vaginitis* | 2 | 0.78% | 2 | 0.82% | 3 | 1.13% | 3 | 1.18% |

| **Possibly related** | **Comparator** | | | |
|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | |
| Total | 255 | | 245 | |
| Diarrhea | 61 | 23.92% | 58 | 23.67% |
| Nausea | 19 | 7.45% | 19 | 7.76% |
| Headache | 3 | 1.18% | 3 | 1.22% |
| Dizziness | 5 | 1.96% | 5 | 2.04% |
| Flatulence | 4 | 1.57% | 3 | 1.22% |
| Vomiting | 5 | 1.96% | 5 | 2.04% |
| Abdominal pain | 7 | 2.75% | 6 | 2.45% |
| Asthenia | 2 | 0.78% | 2 | 0.82% |
| Dyspepsia | 3 | 1.18% | 3 | 1.22% |
| Liver function test abnormal | 1 | 0.39% | 1 | 0.41% |
| Dry mouth | 6 | 2.35% | 4 | 1.63% |
| Rhinitis | 0 | 0.00% | 0 | 0.00% |
| Somnolence | 0 | 0.00% | 0 | 0.00% |
| Vaginal moniliasis | 13 | 5.10% | 13 | 5.31% |
| Gastrointestinal pain | 7 | 2.75% | 7 | 2.86% |
| Upper respiratory infection | 0 | 0.00% | 0 | 0.00% |
| Abnormal stools | 3 | 1.18% | 3 | 1.22% |
| Rash* | 5 | 1.96% | 5 | 2.04% |
| Sore throat* | 0 | 0.00% | 0 | 0.00% |
| Pharyngitis* | 0 | 0.00% | 0 | 0.00% |
| Vaginitis* | 6 | 2.35% | 6 | 2.45% |

| **All TEAEs** | **Telithromycin 5-day** | | | | **Telithromycin 10-day** | | | |
|---|---|---|---|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | | All investigators | | Revised counts | |
| Total | 257 | | 244 | | 266 | | 254 | |
| Diarrhea | 51 | 19.84% | 49 | 20.08% | 56 | 21.05% | 55 | 21.65% |
| Nausea | 33 | 12.84% | 31 | 12.70% | 28 | 10.53% | 28 | 11.02% |
| Headache | 16 | 6.23% | 16 | 6.56% | 23 | 8.65% | 21 | 8.27% |
| Dizziness | 15 | 5.84% | 15 | 6.15% | 15 | 5.64% | 14 | 5.51% |
| Flatulence | 11 | 4.28% | 11 | 4.51% | 5 | 1.88% | 5 | 1.97% |
| Vomiting | 8 | 3.11% | 8 | 3.28% | 11 | 4.14% | 11 | 4.33% |
| Abdominal pain | 9 | 3.50% | 9 | 3.69% | 14 | 5.26% | 13 | 5.12% |
| Asthenia | 8 | 3.11% | 8 | 3.28% | 6 | 2.26% | 6 | 2.36% |
| Dyspepsia | 9 | 3.50% | 8 | 3.28% | 10 | 3.76% | 9 | 3.54% |
| Liver function test abnormal | 6 | 2.33% | 6 | 2.46% | 2 | 0.75% | 2 | 0.79% |
| Dry mouth | 6 | 2.33% | 5 | 2.05% | 5 | 1.88% | 5 | 1.97% |
| Rhinitis | 6 | 2.33% | 6 | 2.46% | 4 | 1.50% | 4 | 1.57% |
| Somnolence | 5 | 1.95% | 5 | 2.05% | 5 | 1.88% | 5 | 1.97% |
| Vaginal moniliasis | 4 | 1.56% | 4 | 1.64% | 8 | 3.01% | 8 | 3.15% |
| Gastrointestinal pain | 4 | 1.56% | 4 | 1.64% | 6 | 2.26% | 6 | 2.36% |
| Upper respiratory infection | 2 | 0.78% | 2 | 0.82% | 7 | 2.63% | 7 | 2.76% |
| Abnormal stools | 2 | 0.78% | 2 | 0.82% | 5 | 1.88% | 5 | 1.97% |
| Rash* | 3 | 1.17% | 3 | 1.23% | 3 | 1.13% | 3 | 1.18% |
| Sore throat* | 3 | 1.17% | 3 | 1.23% | 4 | 1.50% | 4 | 1.57% |
| Pharyngitis* | 4 | 1.56% | 4 | 1.64% | 1 | 0.38% | 1 | 0.39% |
| Vaginitis* | 2 | 0.78% | 2 | 0.82% | 3 | 1.13% | 3 | 1.18% |

| **All TEAEs** | **Comparator** | | | |
|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | |
| Total | 255 | | 245 | |
| Diarrhea | 61 | 23.92% | 58 | 23.67% |
| Nausea | 21 | 8.24% | 21 | 8.57% |
| Headache | 19 | 7.45% | 19 | 7.76% |
| Dizziness | 9 | 3.53% | 9 | 3.67% |
| Flatulence | 4 | 1.57% | 3 | 1.22% |
| Vomiting | 7 | 2.75% | 7 | 2.86% |
| Abdominal pain | 8 | 3.14% | 7 | 2.86% |
| Asthenia | 5 | 1.96% | 5 | 2.04% |
| Dyspepsia | 7 | 2.75% | 8 | 3.27% |
| Liver function test abnormal | 1 | 0.39% | 1 | 0.41% |
| Dry mouth | 9 | 3.53% | 7 | 2.86% |
| Rhinitis | 6 | 2.35% | 6 | 2.45% |
| Somnolence | 1 | 0.39% | 1 | 0.41% |
| Vaginal moniliasis | 15 | 5.88% | 15 | 6.12% |
| Gastrointestinal pain | 9 | 3.53% | 9 | 3.67% |
| Upper respiratory infection | 3 | 1.18% | 3 | 1.22% |
| Abnormal stools | 4 | 1.57% | 4 | 1.63% |
| Rash* | 7 | 2.75% | 7 | 2.86% |
| Sore throat* | 6 | 2.35% | 6 | 2.45% |
| Pharyngitis* | 5 | 1.96% | 5 | 2.04% |
| Vaginitis* | 6 | 2.35% | 6 | 2.45% |

* >2% for comparator only

**Number of subjects (%) with hepatic TEAEs**

| **Possibly related** | **Telithromycin 5-day** | | | | **Telithromycin 10-day** | | | |
|---|---|---|---|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | | All investigators | | Revised counts | |
| Liver function test abnormal | 5 | 1.95% | 5 | 2.05% | 2 | 0.75% | 2 | 0.79% |
| SGPT/ALT increased | 1 | 0.39% | 1 | 0.41% | 0 | 0.00% | 0 | 0.00% |
| Alkaline phosphatase increased | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| SGOT/AST increased | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Lactic dehydrogenase increased | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Liver damage | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Cholestatic jaundice | 1 | 0.39% | 1 | 0.41% | 0 | 0.00% | 0 | 0.00% |
| Bilirubinemia | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Liver tenderness | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Hepatitis | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Jaundice | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |

| **Possibly related** | **Comparator** | | | |
|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | |
| Liver function test abnormal | 1 | 0.39% | 1 | 0.41% |
| SGPT/ALT increased | 0 | 0.00% | 0 | 0.00% |
| Alkaline phosphatase increased | 0 | 0.00% | 0 | 0.00% |
| SGOT/AST increased | 0 | 0.00% | 0 | 0.00% |
| Lactic dehydrogenase increased | 0 | 0.00% | 0 | 0.00% |
| Liver damage | 0 | 0.00% | 0 | 0.00% |
| Cholestatic jaundice | 0 | 0.00% | 0 | 0.00% |
| Bilirubinemia | 0 | 0.00% | 0 | 0.00% |
| Liver tenderness | 0 | 0.00% | 0 | 0.00% |
| Hepatitis | 0 | 0.00% | 0 | 0.00% |
| Jaundice | 0 | 0.00% | 0 | 0.00% |

| **All TEAEs** | **Telithromycin 5-day** | | | | **Telithromycin 10-day** | | | |
|---|---|---|---|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | | All investigators | | Revised counts | |
| Liver function test abnormal | 6 | 2.33% | 6 | 2.46% | 2 | 0.75% | 2 | 0.79% |
| SGPT/ALT increased | 1 | 0.39% | 1 | 0.41% | 0 | 0.00% | 0 | 0.00% |
| Alkaline phosphatase increased | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| SGOT/AST increased | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Lactic dehydrogenase increased | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Liver damage | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Cholestatic jaundice | 1 | 0.39% | 1 | 0.41% | 0 | 0.00% | 0 | 0.00% |
| Bilirubinemia | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Liver tenderness | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Hepatitis | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Jaundice | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |

| **All TEAEs** | **Comparator** | | | |
|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | |
| Liver function test abnormal | 1 | 0.39% | 1 | 0.41% |
| SGPT/ALT increased | 0 | 0.00% | 0 | 0.00% |
| Alkaline phosphatase increased | 0 | 0.00% | 0 | 0.00% |
| SGOT/AST increased | 0 | 0.00% | 0 | 0.00% |
| Lactic dehydrogenase increased | 0 | 0.00% | 0 | 0.00% |
| Liver damage | 0 | 0.00% | 0 | 0.00% |
| Cholestatic jaundice | 0 | 0.00% | 0 | 0.00% |
| Bilirubinemia | 0 | 0.00% | 0 | 0.00% |
| Liver tenderness | 0 | 0.00% | 0 | 0.00% |
| Hepatitis | 0 | 0.00% | 0 | 0.00% |
| Jaundice | 0 | 0.00% | 0 | 0.00% |

**Number of subjects (%) with TEAEs of the cardiovascular body system**

| **Possibly related** | **Telithromycin 5-day** | | | | **Telithromycin 10-day** | | | |
|---|---|---|---|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | | All investigators | | Revised counts | |
| Total No. (%) subjects with cardiovascular TEAEs | 0 | 0.00% | 0 | 0.00% | 2 | 0.75% | 2 | 0.79% |
| Palpitation | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Chest pain | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Vasodilatation | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Arrhythmia | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |

| **Possibly related** | **Comparator** | | | |
|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | |
| Total No. (%) subjects with cardiovascular TEAEs | 2 | 0.78% | 2 | 0.82% |
| Palpitation | 0 | 0.00% | 0 | 0.00% |
| Chest pain | 1 | 0.39% | 1 | 0.41% |
| Vasodilatation | 0 | 0.00% | 0 | 0.00% |
| Arrhythmia | 1 | 0.39% | 1 | 0.41% |

| **All TEAEs** | **Telithromycin** | | | | **Comparator** | | | |
|---|---|---|---|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | | All investigators | | Revised counts | |
| Total No. (%) subjects with cardiovascular TEAEs | 2 | 0.78% | 2 | 0.82% | 5 | 1.88% | 5 | 1.97% |
| Palpitation | 0 | 0.00% | 0 | 0.00% | 2 | 0.75% | 2 | 0.79% |
| Hypertension | 2 | 0.78% | 2 | 0.82% | 1 | 0.38% | 1 | 0.39% |
| Migraine | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Vasodilatation | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Arrhythmia | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Chest pain | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| Tachycardia | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |

| **All TEAEs** | **Comparator** | | | |
|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | |
| Total No. (%) subjects with cardiovascular TEAEs | 6 | 2.35% | 6 | 2.45% |
| Palpitation | 1 | 0.39% | 1 | 0.41% |
| Hypertension | 1 | 0.39% | 1 | 0.41% |
| Migraine | 0 | 0.00% | 0 | 0.00% |
| Vasodilatation | 1 | 0.39% | 1 | 0.41% |
| Arrhythmia | 1 | 0.39% | 1 | 0.41% |
| Chest pain | 1 | 0.39% | 1 | 0.41% |
| Tachycardia | 1 | 0.39% | 1 | 0.41% |

**All serious treatment-emergent cardiovascular events**

| **All serious TEAEs** | **Telithromycin** | | | | **Comparator** | | | |
|---|---|---|---|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | | All investigators | | Revised counts | |
| Cardiovascular System | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |

**Other serious TEAEs**

| | **Telithromycin 5-day** | | | | **Telithromycin 10-day** | | | |
|---|---|---|---|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | | All investigators | | Revised counts | |
| Total No. (%) subjects with serious TEAEs | 0 | 0.00% | 0 | 0.00% | 6 | 2.26% | 6 | 2.36% |
| Pseudomembranous colitis | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Gastroenteritis | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Allergic reaction | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Asthma | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Abnormality of accommodation | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |
| Kidney calculus | 0 | 0.00% | 0 | 0.00% | 1 | 0.38% | 1 | 0.39% |

| | Comparator | | | |
|---|---|---|---|---|
| Coded term | All investigators | | Revised counts | |
| Total | 255 | | 245 | |
| Total No. (%) subjects with serious TEAEs | 1 | 0.39% | 1 | 0.41% |
| Pseudomembranous colitis | 1 | 0.39% | 1 | 0.41% |
| Gastroenteritis | 0 | 0.00% | 0 | 0.00% |
| Allergic reaction | 0 | 0.00% | 0 | 0.00% |
| Asthma | 0 | 0.00% | 0 | 0.00% |
| Abnormality of accommodation | 0 | 0.00% | 0 | 0.00% |
| Kidney calculus | 0 | 0.00% | 0 | 0.00% |

**Number and percentage of subjects with clinically noteworthy abnormal laboratory values (CNALVs)**

| Lab parameter | Telithromycin (5 day) | | | | | | Telithromycin (10 day) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All investigators | | | Revised counts | | | All investigators | | | Revised counts | | |
| Hemoglobin | 0 / | 257 | 0.00% | 0 / | 244 | 0.00% | 0 / | 266 | 0.00% | 0 / | 254 | 0.00% |
| Platelets | 1 / | 257 | 0.39% | 0 / | 244 | 0.00% | 0 / | 266 | 0.00% | 0 / | 254 | 0.00% |
| PT INR | 6 / | 252 | 2.38% | 5 / | 239 | 2.09% | 12 / | 264 | 4.55% | 12 / | 252 | 4.76% |
| Leukocytes | 3 / | 257 | 1.17% | 3 / | 244 | 1.23% | 6 / | 266 | 2.26% | 5 / | 254 | 1.97% |
| Neutro (Abs.) | 9 / | 257 | 3.50% | 9 / | 244 | 3.69% | 8 / | 266 | 3.01% | 7 / | 254 | 2.76% |
| Eosino (Abs.) | 0 / | 257 | 0.00% | 0 / | 244 | 0.00% | 1 / | 266 | 0.38% | 1 / | 254 | 0.39% |
| SGOT/AST | 3 / | 257 | 1.17% | 3 / | 244 | 1.23% | 1 / | 266 | 0.38% | 1 / | 254 | 0.39% |
| SGPT/ALT | 5 / | 257 | 1.95% | 5 / | 244 | 2.05% | 4 / | 266 | 1.50% | 4 / | 254 | 1.57% |
| Alkaline phosphatase | 1 / | 256 | 0.39% | 1 / | 243 | 0.41% | 0 / | 266 | 0.00% | 0 / | 254 | 0.00% |
| Total Bilirubin | 1 / | 257 | 0.39% | 1 / | 244 | 0.41% | 0 / | 266 | 0.00% | 0 / | 254 | 0.00% |
| Creatinine clearance | 0 / | 257 | 0.00% | 0 / | 244 | 0.00% | 1 / | 266 | 0.38% | 1 / | 254 | 0.39% |
| Creatinine | 0 / | 257 | 0.00% | 0 / | 244 | 0.00% | 0 / | 266 | 0.00% | 0 / | 254 | 0.00% |
| Potassium | 0 / | 256 | 0.00% | 0 / | 243 | 0.00% | 2 / | 266 | 0.75% | 2 / | 254 | 0.79% |

| Lab parameter | Comparator | | | | | |
|---|---|---|---|---|---|---|
| | All investigators | | | Revised counts | | |
| Hemoglobin | 0 / | 255 | 0.00% | 0 / | 245 | 0.00% |
| Platelets | 0 / | 254 | 0.00% | 0 / | 244 | 0.00% |
| PT INR | 8 / | 250 | 3.20% | 8 / | 240 | 3.33% |
| Leukocytes | 1 / | 255 | 0.39% | 0 / | 245 | 0.00% |
| Neutro (Abs.) | 5 / | 255 | 1.96% | 5 / | 245 | 2.04% |
| Eosino (Abs.) | 2 / | 255 | 0.78% | 2 / | 245 | 0.82% |
| SGOT/AST | 2 / | 255 | 0.78% | 2 / | 245 | 0.82% |
| SGPT/ALT | 1 / | 255 | 0.39% | 1 / | 245 | 0.41% |
| Alkaline phosphatase | 0 / | 255 | 0.00% | 0 / | 245 | 0.00% |
| Total Bilirubin | 0 / | 255 | 0.00% | 0 / | 245 | 0.00% |
| Creatinine clearance | 0 / | 255 | 0.00% | 0 / | 245 | 0.00% |
| Creatinine | 0 / | 255 | 0.00% | 0 / | 245 | 0.00% |
| Potassium | 0 / | 255 | 0.00% | 0 / | 245 | 0.00% |

**Number and percentage of subjects with significant prolongation of QTc (Bazett formula)**

**HMR3647**

| Criteria | On therapy | | | | | | Post therapy | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All investigators | | | Revised counts | | | All investigators | | | Revised counts | | |
| QTc increase | | | | | | | | | | | | |
| >=30, <60 msec | 42 / | 468 | 8.97% | 38 / | 444 | 8.56% | 32 / | 440 | 7.27% | 30 / | 418 | 7.18% |
| >=60 msec | 0 / | 468 | 0.00% | 0 / | 444 | 0.00% | 0 / | 440 | 0.00% | 0 / | 418 | 0.00% |
| QTc value | | | | | | | | | | | | |
| >=450 msec men | 1 / | 212 | 0.47% | 0 / | 196 | 0.00% | 0 / | 200 | 0.00% | 0 / | 185 | 0.00% |
| >=470 msec women | 0 / | 261 | 0.00% | 0 / | 253 | 0.00% | 1 / | 246 | 0.41% | 1 / | 239 | 0.42% |
| >=500 msec | 0 / | 473 | 0.00% | 0 / | 449 | 0.00% | 0 / | 446 | 0.00% | 0 / | 424 | 0.00% |
| Both QTc >=60 and | | | | | | | | | | | | |
| >=450 msec men | 0 / | 211 | 0.00% | 0 / | 195 | 0.00% | 0 / | 199 | 0.00% | 0 / | 184 | 0.00% |
| >=470 msec women | 0 / | 257 | 0.00% | 0 / | 249 | 0.00% | 0 / | 241 | 0.00% | 0 / | 234 | 0.00% |
| >=500 msec | 0 / | 468 | 0.00% | 0 / | 444 | 0.00% | 0 / | 440 | 0.00% | 0 / | 418 | 0.00% |
| QT dispersion | | | | | | | | | | | | |
| >100 msec | 0 / | 473 | 0.00% | 0 / | 449 | 0.00% | 0 / | 446 | 0.00% | 0 / | 424 | 0.00% |

**Comparator**

| Criteria | On therapy | | | | | | Post therapy | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All investigators | | | Revised counts | | | All investigators | | | Revised counts | | |
| QTc increase | | | | | | | | | | | | |
| >=30, <60 msec | 20 / | 241 | 8.30% | 19 / | 231 | 8.23% | 10 / | 171 | 5.85% | 9 / | 164 | 5.49% |
| >=60 msec | 0 / | 241 | 0.00% | 0 / | 231 | 0.00% | 0 / | 171 | 0.00% | 0 / | 164 | 0.00% |
| QTc value | | | | | | | | | | | | |
| >=450 msec men | 0 / | 95 | 0.00% | 0 / | 86 | 0.00% | 0 / | 62 | 0.00% | 0 / | 56 | 0.00% |
| >=470 msec women | 0 / | 149 | 0.00% | 0 / | 148 | 0.00% | 0 / | 110 | 0.00% | 0 / | 109 | 0.00% |
| >=500 msec | 0 / | 244 | 0.00% | 0 / | 234 | 0.00% | 0 / | 172 | 0.00% | 0 / | 165 | 0.00% |
| Both QTc >=60 and | | | | | | | | | | | | |
| >=450 msec men | 0 / | 94 | 0.00% | 0 / | 85 | 0.00% | 0 / | 62 | 0.00% | 0 / | 56 | 0.00% |
| >=470 msec women | 0 / | 147 | 0.00% | 0 / | 146 | 0.00% | 0 / | 109 | 0.00% | 0 / | 108 | 0.00% |
| >=500 msec | 0 / | 241 | 0.00% | 0 / | 231 | 0.00% | 0 / | 171 | 0.00% | 0 / | 164 | 0.00% |
| QT dispersion | | | | | | | | | | | | |
| >100 msec | 0 / | 244 | 0.00% | 0 / | 234 | 0.00% | 0 / | 172 | 0.00% | 0 / | 165 | 0.00% |

***Medical Officer's Comments:***

*As it is evident from the safety data review, there was essentially very little difference between the outcome of the initial analysis and the revised analysis (excluding the two centers), thus the applicant's original safety numbers are used for the rest of the safety data review. Please note that the overall safety data review and the review of safety in specific populations are done in detail by Dr. David Ross and Dr. Edward Cox. Please refer to those two reviews.*

**Deaths**

There were no adverse events leading to death reported in this study.

***Other significant adverse events***

Adverse events were defined as "other significant" events if they met one or more of the following criteria: led to discontinuation of study medication, led to therapy interruption, required dose reduction, required treatment with a counteractive medication or was a laboratory abnormality reported as an adverse event.

Treatment with study medication had to be discontinued due to adverse events in 17 subjects (6.6%) in the HMR 3647 5-d group, 19 subjects (7.1%) in the HMR 3647 10-d group, and 14 (5.5%) in the AMC group. Although therapy interruption was not permitted by protocol design, 2 subjects interrupted therapy during the study: 1 subject (146/017) in the HMR 3647 5-day group interrupted therapy for gastroenteritis and 1 subject (171/005) in the HMR 3647 10-d group interrupted therapy for dyspepsia. In both of these subjects, the event did not recur when study medication was reintroduced and the subjects completed their full course of therapy. The investigator assessed these events as not related to study medication in both subjects. Dose reduction was not permitted by the protocol design so there were no adverse events reported which met this criterion. Treatment with a counteractive medication was required due to adverse events in 46 (17.9%) subjects in the HMR 3647 5-d group, 65 (24.4%) subjects in the HMR 3647 10-d group, and 70 (27.5%) subjects in the AMC group.

Laboratory abnormalities were reported as adverse events in a total of 10 (3.9%) subjects in the HMR 3647 5-d group, 7 (2.6%) subjects in the HMR 3647 10-d group and 4 (1.6 %) subjects in the AMC group.

## Treatment emergent adverse events leading to discontinuation

Treatment with study medication had to be discontinued due to TEAEs in 50/778 (6.4%) subjects : 17 (6.6%) subjects in the HMR 3647 5-d group, 19 (7.1%) subjects in the HMR 10-d group, and 14 (5.5%) subjects in the AMC group. Of these 50 subjects, 41 (5.3%) subjects discontinued treatment with study medication due to possibly related TEAEs: 16 (6.2%) subjects in the HMR 3647 5-d group, 14 (5.3%) subjects in the HMR 10-d group, and 11 (4.3%) subjects in the AMC group. The TEAEs leading to discontinuation of study medication are presented below:

**TEAEs leading to discontinuation of study medication**

| | Number of subjects (%) | | | | | |
|---|---|---|---|---|---|---|
| **Adverse event** | **HMR 3647 5-d** | | **HMR 3647 10-d** | | | **AMC** |
| Total no. of subjects in safety population | 257 | (100%) | 266 | (100%) | 255 | (100%) |
| Total with TEAEs leading to discontinuation | 17 | (6.6%) | 19 | (7.1%) | 14 | (5.5%) |
| Diarrhea | 6 | (2.3%) | 6 | (2.3%) | 4 | (1.6%) |
| Nausea | 5 | (1.9%) | 1 | (0.4%) | 3 | (1.2%) |
| Vomiting | 3 | (1.2%) | 3 | (1.1%) | 1 | (0.4%) |
| Abdominal pain | 2 | (0.8%) | 2 | (0.8%) | 1 | (0.4%) |
| Liver function test Abnormal | 2 | (0.8%) | 1 | (0.4%) | 0 | (0.0%) |
| Gastrointestinal pain | 0 | (0.0%) | 1 | (0.4%) | 2 | (0.8%) |
| Pseudomembranous Colitis | 0 | (0.0%) | 1 | (0.4%) | 1 | (0.4%) |
| Allergic reaction | 1 | (0.4%) | 1 | (0.4%) | 0 | (0.0%) |
| Rash | 0 | (0.0%) | 0 | (0.0%) | 2 | (0.8%) |
| Anorexia | 1 | (0.4%) | 0 | (0.0%) | 0 | (0.0%) |
| Dyspepsia | 1 | (0.4%) | 0 | (0.0%) | 0 | (0.0%) |
| Gastrointestinal fullness | 1 | (0.4%) | 0 | (0.0%) | 0 | (0.0%) |
| Gastroenteritis | 0 | (0.0%) | 1 | (0.4%) | 0 | (0.0%) |
| Gastrointestinal disorder | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.4%) |
| Glossitis | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.4%) |
| Asthenia | 1 | (0.4%) | 0 | (0.0%) | 0 | (0.0%) |
| Cyst | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.4%) |
| Infection | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.4%) |
| Dizziness | 1 | (0.4%) | 0 | (0.0%) | 0 | (0.0%) |
| Vertigo | 1 | (0.4%) | 0 | (0.0%) | 0 | (0.0%) |
| Headache | 0 | (0.0%) | 1 | (0.4%) | 0 | (0.0%) |
| Neuralgia | 0 | (0.0%) | 1 | (0.4%) | 0 | (0.0%) |
| Platelet count decreased | 1 | (0.4%) | 0 | (0.0%) | 0 | (0.0%) |
| Migraine | 0 | (0.0%) | 1 | (0.4%) | 0 | (0.0%) |
| Asthma | 0 | (0.0%) | 1 | (0.4%) | 0 | (0.0%) |
| Bronchitis | 0 | (0.0%) | 1 | (0.4%) | 0 | (0.0%) |
| Urticaria | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.4%) |
| Abnormality of Accommodation | 0 | (0.0%) | 1 | (0.4%) | 0 | (0.0%) |
| Urinary retention | 0 | (0.0%) | 1 | (0.4%) | 0 | (0.0%) |

The most common adverse events leading to discontinuation were in the digestive system and included diarrhea , nausea, and vomiting. Six subjects (144/012, 194/009, 189/051, 197/006, 201/009, and 202/002) reported 2 of these events and 1 subject (188/058) reported all 3 of these events. All other 17 subjects reported just one of these events.

Out of the 24 subjects (11 subjects in the HMR 3647 5-d group, 7 subjects in the HMR 10-d group, and 6 subjects in the AMC group) who reported these 3 digestive adverse events that led to discontinuation, 10 subjects reported these adverse events on day 1, 7 subjects reported these adverse events on day 2 and 7 subjects reported these adverse events on day 3- 7. The investigator assessed all of these events as possibly related to study medication with the exception of 1 subject in the AMC group (201/009) who reported both nausea and vomiting that was assessed as not related to study medication. The next most frequent reasons for discontinuation of study medication were abdominal pain, liver function test abnormal, and gastrointestinal pain.

Abdominal pain or gastrointestinal pain which led to discontinuation of study medication was reported in 2 subjects (0.8%) in the HMR 3647 5-d group, 3 subjects (1.1%) in the HMR 3647 10-d group and 3 subjects (1.2%) in the AMC group. Four subjects (146/010, 146/027, 155/014, and 197/006) reported abdominal pain or gastrointestinal pain along with diarrhea or nausea which led to discontinuation of study medication. The other 4 subjects, 1 in the HMR 3647 5-d group (185/015) and 1 in the HMR 3647 10-d group (188/037) and 2 in the AMC group (164/003 and 188/22) reported the abdominal pain or gastrointestinal pain on day 1 and the investigator assessed all of these adverse events as possibly related to study medication.

Liver function test abnormal which led to discontinuation of study medication was reported in 2 subjects (157/020 and 168/012) in the HMR 3647 5-d group and 1 subject (173/023) in the HMR 3647 10-d group. The investigator assessed all of these events as possibly related to study medication.

Other adverse events which led to discontinuation of study medication occurred less frequently and included the following adverse events in the HMR 3647 5-d group: gastrointestinal fullness (subject 155/014), anorexia (subject 163/058), asthenia (subject 163/058), dizziness (subject 168/007), allergic reaction (subject 169/009), dyspepsia (subject 188/027), decreased platelet count (subject 196/017) and vertigo (subject 202/002).

In the HMR 3647 10-d group other reasons for discontinuation of study medication included: bronchitis (subject 144/008), headache (subject 147/004), asthma (subject 156/004), allergic reaction (subject 174/003), pseudomembranous colitis (subject 188/032), urinary retention (subject 188/048), neuralgia (subject 189/045), migraine (subject 189/063), gastroenteritis (subject 194/012), and abnormality of accommodation (subject 197/021).

In the AMC group other reasons for discontinuation of study medication included: gastrointestinal disorder (subject 163/054), urticaria (subject 188/064), glossitis (subject 189/001), rash (subjects 189/064 and 201/016), pseudomenbranous colitis (subject 194/008), cyst (subject 202/003), and infection (subject 408/010).

### *Applicant's Safety conclusions*

The safety conclusions are as follows:

- HMR 3647 800 mg once daily, taken for either 5-or 10-days was generally as safe and well tolerated as the active comparator, amoxicillin/clavulanic acid. The safety data in terms of adverse events, laboratory values, vital signs and ECG findings did not reveal any serious safety concerns for HMR 3647.
- Treatment emergent adverse events were most commonly reported in the digestive system in all 3 treatment groups: 100/257 (38.9%) subjects in the HMR 3647 5-d group, 98/266 (36.8%) subjects in the HMR 3647 10-d group, and 99/255 (38.8%) subjects in the AMC group. Within the digestive body system, diarrhea was the most commonly reported TEAE: HMR 3647 5-d group: 51 (19.8%) subjects; HMR 3647 10-d group: 56 (21.1%) subjects; and AMC group: 61 (23.9%) subjects.
- Most of the TEAEs experienced by subjects were mild or moderate in intensity. Severe TEAEs were reported in 11.7% of subjects in the HMR 3647 5-d group, 9.8% of subjects in the HMR 3647 10-d group, and 7.8% of subjects in the AMC group.
- At least one serious TEAE was reported in 7/778 (0.9%) subjects: 0 subjects in the HMR 3647 5-d group, 6 (2.3%) subjects in the HMR 3647 10-d group; and 1 (0.4%) subject in the AMC group. Three subjects (1.1%) in the HMR 3647 10-d group and 1 subject (0.4%) in the AMC group reported serious TEAEs that were assessed by the investigator as possibly related to study medication.
- Treatment with study medication had to be discontinued due to TEAEs in 50/778 (6.4%) subjects: 17 subjects (6.6%) in the HMR 3647 5-d group, 19 subjects (7.1%) in the HMR 10-d group, and 14 subjects (5.5%) in the AMC group. Sixteen subjects (6.2%) in the HMR 3647 5-d group, 14 subjects

(5.3%) in the HMR 10-d group, and 11 subjects (4.3%) in the AMC group discontinued study medication due to TEAEs that were assessed by the investigator as possibly related to study medication.

- The laboratory values, analyzed as PCAs and CNALVs, did not show any statistically significant differences between treatment groups, in particular for transaminases.
- There was no evidence of treatment-related changes in blood pressure or heart rate.
- There was no clear association between QTc interval increases and study treatment. Observed increases were all <60 msec, no subject had a QTc interval that exceeded 500 msec, and for HMR 3647 subjects, QTc interval changes were not associated with any adverse events.

**Medical Officer's Review of Study 3002:**

**Title**

Evaluation of the efficacy and safety of oral HMR 3647 800 mg once a day for 5 days versus HMR 3647 800 mg once a day for 10 days in the treatment of acute maxillary sinusitis in adults. A multicenter, randomized, double-blind, comparative study.

**Investigator(s), study site(s)**

Multinational, multicenter study, (37 centers): Austria (1), Croatia (3) (added by protocol amendment no. 2, 20 July 1998), Czech Republic (4), Denmark (6), Finland (4), France (6), Germany (5), Greece (3), Sweden (5).

**Phase 3**

**Indication**
Acute maxillary sinusitis (AMS)

**Objectives**

**Primary objective:**
To assess the clinical efficacy (equivalence testing) and to assess the safety of oral HMR 3647 800 mg once daily given for 5 days compared to HMR 3647 800 mg once daily given for 10 days in the treatment of AMS in adult subjects at the posttherapy/test of cure (TOC) visit.

**Secondary objective:**
To demonstrate the bacterial efficacy of HMR 3647 at a level of ≥70% in subjects in both treatment groups at posttherapy/TOC.

**Design**
This was an international, prospective, multicenter, double-blind, comparative, randomized, two-arm parallel-group (1:1) study that included an interim analysis.

There were five visits: a pretherapy/entry visit (day 1), an on-therapy visit (days 3 to 5), an end of therapy visit (days 11 to 13), a posttherapy/TOC visit (days 17 to 21, changed by protocol amendment no. 2, 20 July 1998 to days 17 - 24), and a late posttherapy visit (days 31 - 36, changed by protocol amendment no. 2, 20 July 1998, to days 31 - 38). Study medication was first administered on day 1.

## Population

Adult men and women aged 18 to 65 years old with clinical signs and symptoms and radiological signs of AMS. Approximately 340 subjects were to be enrolled in order to obtain at least 260 clinically evaluable subjects and 200 bacteriologically evaluable subjects.

## Number of subjects

A total of 340 subjects were to be enrolled and treated. A maximum of 48 subjects were to be enrolled per center. (The minimum of 12 subjects per center was deleted by protocol amendment no. 1, 02 February 1998).

### *Medical Officer's Comments:*

*The Inclusion and Exclusion criteria were identical to Study 3005.*

### *Dosage schedule*

All subjects in the study were randomized to receive either HMR 3647, 800 mg (400 mg tablets x 2) once daily for 5 days, followed by matched placebo tablets for 5 days, or HMR 3647, 800 mg (400 mg tablets x 2) once daily for 10 days.

The time of first and last dose of study medication administration was to be documented on the case report form.

## *INTERIM ANALYSIS*

An interim analysis was planned to investigate whether the shorter 5-day HMR 3647 regimen based on pharmacokinetic/pharmacodynamic data had a significantly lower cure rate than the classical treatment duration of 10 days used in the HMR 3647 10-d group. If the cure rate in subjects treated with HMR 3647 for 5 days was significantly lower than that in subjects who received HMR 3647 for 10 days, it could be considered unethical to continue randomizing subjects to an inferior treatment.

A data monitoring and safety committee was convened to assess the results of the interim analysis. This committee consisted of the clinical manager (Dr [redacted]), the head of clinical development (Dr [redacted], the drug safety manager (Dr [redacted]), a designated statistician other than the study statistician ([redacted], and two experts in infectious diseases (Prof. [redacted] Prof. [redacted]). If the cure rate in the HMR 3647 5-d group

was significantly lower than the cure rate in the HMR 3647 10-d group, and the cure rate in the HMR 3647 5-d group was less than 80%, the committee could recommend that the HMR 3647 5-d arm be stopped.

For the interim analysis, the significance test at the 5% level (one-sided test) for the difference in cure rate between the two treatment groups after the completion of 50% of total subjects (170 subjects) was performed in the PPc population, using a chi-squared test. The null hypothesis was that the HMR 3647 5-d group has a cure rate no lower than that in the HMR 3647 10-d group. The treatment groups were identified only as "A" and "B" for this test.

- If the chi-squared test statistic was less than or equal to the one-sided 5% critical value (less than 2.71), or both cure rates were at least 80%, the study was to be continued to the end. There would be no need to break the blind. The 95% confidence interval method was to be used to test equivalence at the end of study.
- If the chi-squared test statistic was greater than the one-sided 5% critical value (greater than 2.71), and at least one of the observed cure rates was less than 80%, it would be necessary to reveal the treatment decodes for A and B, to see if the HMR 3647 5-d group had the lower cure rate. Only the members of the data monitoring and safety committee were to have access to these codes. The chairman of the data monitoring and safety committee could request additional analyses of cure rates in the mITT population and comparison of baseline characteristics between treatment groups. If the cure rate in the HMR 3647 5-d group was significantly lower than the cure rate in the HMR 3647 10-d group, and the cure rate in the HMR 3647 5-d group was less than 80%, the committee could recommend that the HMR 3647 5-d arm be stopped.

The result of the interim analysis was a chi-squared statistic of less than 2.71. As this result satisfied the criterion for continuing the study, the chairman of the data monitoring and safety committee did not send any information to the study manager indicating that the trial should be stopped and the trial was therefore continued. There was no formal meeting of the committee and the treatment codes were not unblinded.

There was no adjustment of the type I error in the final analysis because this interim analysis was performed for safety reasons alone, that is, the only possibility was to stop the HMR 3647 5-d treatment group. In particular, there was no possibility to stop the trial at the interim analysis and declare equivalence between the two treatment groups.

## RESULTS - STUDY SUBJECTS AND CONDUCT

The first subject entered the study on 2 April 1998 and the last subject completed the study on 15 April 1999.

Subjects were enrolled at 37 centers in nine countries. Center 603 enrolled the most subjects (48 subjects) and centers 402, 611, 702, 1513, and 1515 enrolled the least (one subject per center). For the efficacy analysis, centers were pooled by geographic region to give 17 pooled centers.

### *MEDICAL OFFICER'S COMMENTS:*

*The Medical Officer has reviewed all the efficacy data in detail, and concurs with the Applicant's results.*

**Subject disposition**

| **Disposition of subjects** | **Total** |
|---|---|
| Number of subjects enrolled | 343 |
| Number of investigators (centers) | 37 |
| Number of investigators (centers) who enrolled: | |
| Less than 12 evaluable subjects in mITT population | 28 |
| 12 or more evaluable subjects in mITT population | 9 |
| Number of investigator pools | 17 |

The numbers of subjects who were enrolled, randomized and treated were as follows:

***Subject accounting***

| | **HMR 3647 5-d** | **HMR 3647 10-d** | **Total** | |
|---|---|---|---|---|
| Enrolled | - | - | **343** | |
| Randomized | 170 | 171 | **341** | **(100.0%)** |
| Treated | 168 | 168 | **336** | **(98.5%)** |

Of the 343 subjects enrolled, two were not randomized (after giving informed consent),
one subject (1513/001) did not wish to continue in the study and one subject (1505/003) was not randomized due to "other" reason (exclusion criteria fulfilled because of dental disease at pretherapy/entry).

In total, 336 subjects were exposed to study medication (i.e., received at least one dose of HMR 3647).

All subjects received study treatment according to the randomization sequence.

Two subjects were randomized to the HMR 3647 5-d group but did not receive any treatment: both subjects (603/017 and 603/029) did not wish to continue in the study. Three subjects were randomized to the HMR 3647 10-d group but did not receive any treatment: subjects 603/003 and 603/028 did not wish to continue in the study, and subject 708/008 was not treated due to "other" reason (pregnancy at pretherapy/entry).

The most common reason for non enrolment was negative X-ray findings.

## Completion of study

The numbers of subjects who actually completed study visits (as opposed to subjects whose missing outcome was completed by the investigator based on previous visit assessments) are given in the table below:

| | **Study completion status** | | | | | |
|---|---|---|---|---|---|---|
| **Subjects with:** | **HMR 3647 5-d** | | **HMR 3647 10-d** | | **Total** | |
| Actual pretherapy/entry visit [a] | 170 | (100.0%) | 171 | (100.0%) | **341** | **(100.0%)** |
| Actual on-therapy visit | 163 | (95.9%) | 167 | (97.7%) | **330** | **(96.8%)** |
| Actual posttherapy/TOC visit | 154 | (90.6%) | 162 | (94.7%) | **316** | **(92.7%)** |
| Actual late posttherapy visit [b] | 154 | (90.6%) | 160 | (93.6%) | **314** | **(92.1%)** |
| Actual posttherapy/TOC and late posttherapy visits | 151 | (88.8%) | 158 | (92.4%) | **309** | **(90.6%)** |

[a] All randomized subjects
[b] Including telephone contact

Subjects could discontinue from study medication but they were encouraged to continue with the remaining visits as scheduled in the protocol, even if they were clinical failures. Numbers of subjects who withdrew from the study completely are described below.

A total of 21 subjects (HMR 3647 5-d, 13; HMR 3647 10-d, 8) withdrew from the study after starting study medication:

**Reasons for withdrawal from study**

| | Number of reasons | |
|---|---|---|
| **Reason for withdrawal from study** | **HMR 3647 5-d** | **HMR 3647 10-d** |
| Total subjects | 168 (100.0%) | 168 (100.0%) |
| Total subjects withdrawn from study [a] | 13 (7.7%) | 8 (4.8%) |
| New adverse event or worsening of an existing adverse event | 4 (2.4%) | 1 (0.6%) |
| Subject did not wish to continue in the study | 7 (4.2%) | 2 (1.2%) |
| Subject lost to follow-up | 1 (0.6%) | 2 (1.2%) |
| Other reason | 1 (0.6%) | 3 (1.8%) |

[a] A subject could discontinue study medication but complete the study.

Withdrawal due to "other" reason was as follows: low neutrophil count (one subject; HMR 3647 5-d), "did not heal" (one subject; HMR 3647 10-d), deterioration of sinusitis probably due to the bacteria Branhamella (one subject; HMR 3647 10-d), deterioration of clinical condition (one subject; HMR 3647 10-d).

## Discontinuation of study medication

A total of 17 (5.1%) subjects discontinued study medication before completion of the assigned treatment duration (HMR 3647 5-d: 13 [7.7%]; HMR 3647 10-d: 4[2.4%]). Reasons for discontinuation of study medication were as follows:

**Reasons for discontinuation of study medication**

| | Number of reasons | | | | |
|---|---|---|---|---|---|
| **Reason for discontinuation of study medication** | **HMR 3647 5-d** | | **HMR 3647 10-d** | | **Total** |
| Total subjects | 168 | (100.0%) | 168 | (100%) | **336 (100.0%)** |
| Total subjects discontinued study medication | 13 | (7.7%) | 4 | (2.4%) | **17(5.1%)** |
| Efficacy | 0 | (0.0%) | 0 | (0.0%) | **0 (0.0%)** |
| Other | 13 | (7.7%) | 4 | (2.4%) | **17 (5.1%)** |
| Transaminase ≥ 3 times ULN | 1 | (0.6%) | 1 | (0.6%) | **2 (0.6%)** [a] |
| New adverse event or worsening of an existing adverse event | 6 | (3.6%) | 1 | (0.6%) | **7 (2.1%)** |
| Subject did not wish to continue in the study | 5 | (3.0%) | 1 | (0.6%) | **6 (1.8%)** |
| Other | 1 | (0.6%) | 1 | (0.6%) | **2 (0.6%)** |

[a] Subject 404/004 in the HMR 3647 5-d group and subject 1105/009 in the HMR 3647 10-d group had ALT increased at pretherapy/entry that led to discontinuation of the study medication as it satisfied a laboratory exclusion criterion

ULN = Upper limit of normal range

Discontinuation of study medication due to "other" reason was as follows: low neutrophil count (one subject; HMR 3647 5-d), lost to follow-up (one subject; HMR 3647 10-d).

## Major protocol violations

A total of 87 major protocol violations, were identified in 79 subjects in the mITT population. These subjects were excluded from the PPc analyses. The major protocol violations were as follows:

**Summary of major protocol violations**

| Major protocol violations | HMR 3647 5-d | HMR 3647 10-d | TOTAL |
|---|---|---|---|
| Total in mITT analysis | 167 (100%) | 168 (100%) | 335 (100%) |
| Total excluded from PPc analysis | 44 (26.3%) | 35 (20.8%) | 79 (23.6%) |
| Previous antimicrobial treatment within 7 days prior to entry | 0 | 1 | 1 |
| Insufficient X-ray evidence of AMS at pretherapy/entry visit | 0 | 1 | 1 |
| Subject with laboratory exclusion criteria | 4 | 1 | 5 |
| Insufficient treatment duration | 7 | 5 | 12 |
| Wrong entry diagnosis | 1 | 1 | 2 |
| Missing appropriate posttreatment information | 18 | 20 | 38 |
| Concomitant antimicrobial therapy between pretherapy/entry and posttherapy/TOC visits (except failure) | 3 | 0 | 3 |
| Inability to determine treatment outcome at posttherapy/TOC | 6 | 4 | 10 |
| No X-ray within 2 days of first intake of study drug | 10 | 5 | 15 |

**Note:** One subject may have had more than one major protocol violation.

The numbers of subjects with major protocol violations were similar between treatment groups.

## Minor protocol violations

The following minor protocol violations were identified among the 256 subjects eligible for the PPc population at posttherapy/TOC:

- Neutropenia (neutrophils <1500/mm$^3$): HMR 3647 5-d: 4; HMR 3647 10-d: 2
- QTc with Bazett or Fridericia formula >450 msec at entry: HMR 3647 5-d: 4; HMR 3647 10-d: 0

- Maintenance corticosteroid therapy, oral or inhaled: HMR 3647 5-d: 2; HMR 3647 10-d: 0
- INR ≥1.3 or PT ratio ≥1.3 times upper limit of normal at entry: HMR 3647 5-d: 0; HMR 3647 10-d: 1
- Posttherapy/TOC visit between days 22 to 24 inclusive (except failures that occurred by the end of day 21, since failures are carried forward): HMR 3647 5-d: 29; HMR 3647 10-d: 33
- Patients hospitalized for administration reason: HMR 3647 5-d: 12; HMR 3647 10-d: 13.

The distribution of minor protocol violations was similar in both treatment groups.

## Administration of study medication

## Dosage and duration

There was no dosage adjustment in this study.

Treatment duration in the mITT population was as follows:

**Duration of treatment for the mITT population**

| Duration of Treatment | Total duration | Number of subjects (%) HMR 3647 5-d Duration with active HMR 3647 | HMR 3647 10-d |
|---|---|---|---|
| Total subjects | 167 (100.0%) | 167 (100.0%) | 168 (100.0%) |
| <2 days | 3 (1.8%) | 3 (1.8%) | 2 (1.2%) |
| 2 days | 3 (1.8%) | 3 (1.8%) | 0 (0.0%) |
| 3 days | 1 (0.6%) | 1 (0.6%) | 0 (0.0%) |
| 4 days | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 5 days | 2 (1.2%) | 160 (95.8%) | 0 (0.0%) |
| 6 days | 2 (1.2%) | - | 1 (0.6%) |
| 7 days | 0 (0.0%) | - | 0 (0.0%) |
| 8 days | 0 (0.0%) | - | 0 (0.0%) |
| 9 days | 2 (1.2%) | - | 1 (0.6%) |
| 10 days | 151 (90.4%) | - | 160 (95.2%) |
| 11 days | 3 (1.8%) | - | 1 (0.6%) |
| >11 days | 0 (0.0%) | - | 1 (0.6%) |
| Unknown | 0 (0.0%) | 0 (0.0%) | 2 (1.2%) |
| Median (days) | 10.0 | 5.0 | 10.0 |
| Mean (SD) (days) | 9.6 ± 1.8 | 4.9 ± 0.7 | 9.9 ± 1.1 |
| Range (days) | 1 to 11 | 1 to 5 | 1 to 15 |

The mean treatment duration was similar in both the 10- day treatment group and placebo group in the mITT population. Subject 603/031 in the

HMR 3647 10-d group had treatment duration of 15 days. Study medication was interrupted due to an adverse event, and restarted without recurrence of the event. In the HMR 3647 5-d group, the mean duration of active treatment was 4.9 days. In the PPc population, treatment duration was as follows:

| | Duration of treatment for the PPc population Number of subjects (%) | | |
|---|---|---|---|
| | HMR 3647 5-d | | |
| Duration of Treatment | Total duration | Duration with active HMR 3647 | HMR 3647 10-d |
| Total subjects | 123 (100.0%) | 123 (100.0%) | 133 (100.0%) |
| 2 days | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 3 days | 1 (0.8%) | 1 (0.8%) | 0 (0.0%) |
| 4 days | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 5 days | 0 (0.0%) | 122 (99.2%) | 0 (0.0%) |
| 6 days | 0 (0.0%) | - | 0 (0.0%) |
| 7 days | 0 (0.0%) | - | 0 (0.0%) |
| 8 days | 0 (0.0%) | - | 0 (0.0%) |
| 9 days | 1 (0.8%) | - | 1 (0.8%) |
| 10 days | 120 (97.6%) | - | 132 (99.2%) |
| 11 days | 1 (0.8%) | - | 0 (0.0%) |
| >11 days | 0 (0.0%) | - | 0 (0.0%) |
| Median (days) | 10.0 | 5.0 | 10.0 |
| Mean (SD) (days) | 9.9 ± 0.6 | 5.0 ± 0.2 | 10.0 ± 0.1 |
| Range (days) | 3 to 11 | 3 to 5 | 9 to 10 |

A treatment duration of 11 days occurred if the subject started treatment at midday or after on the first day and continued with the remaining medication on day 11.

The overall mean treatment duration was similar in both the 10-day treatment group and the placebo group in the PPc population; the mean active treatment duration in the HMR 3647 5-d group was 5.0 days. The median duration of treatment for clinically cured subjects was 10.0 days (includes patients on placebo) in the HMR 3647 5-d group and 10.0 days in the HMR 3647 10-d group in the PPc population. The only subject (705/006) who received less than 5 days of treatment in the HMR 3647 5-d group was a clinical failure.

In the HMR 3647 5-d group, subjects in the PPc population received a mean of 5.0 doses of active treatment. In the HMR 3647 10-d group, PPc subjects received a mean of 10.0 doses of active treatment. For clinically cured subjects, the mean number of active doses was 5.0 in the HMR 3647 5-d group and 10.0 in the HMR 3647 10-d group. The median cumulative number of days of active treatment derived from the median number of doses of active treatment was 5.0 days in the HMR 3647 5-d group and 10.0 days in the HMR 3647 10-d group in both mITT and PPc populations.

***Study populations analyzed***

All subjects who received at least one dose of study medication and who had a post pretherapy/entry safety assessment were included in the safety population. The efficacy analysis populations were the mITT, PPc, bmITT and PPb populations, as below. The total number of subjects evaluable for each analysis population was as follows:

**Number of subjects in each analysis population**

| Population | HMR 3647 5-d | HMR 3647 10-d | TOTAL |
|---|---|---|---|
| Total treated | 168 | 168 | 336 |
| mITT | 167 | 168 | 335 |
| PPc | 123 | 133 | 256 |
| bmITT | 97 | 104 | 201 |
| PPb | 70 | 69 | 139 |
| Safety | 166 | 167 | 333 |

Of the 336 subjects treated, one subject (709/003) in the HMR 3647 5-d group was excluded from the mITT population as the subject did not have X-ray findings consistent with the indication.
Of the total 335 subjects in the mITT population, 256 (76.4%) were included in the PPc analysis and 139 (41.5%) were included in the PPb analysis. Reasons for exclusion from the PPc and PPb analyses are summarized in the table below:

| | HMR 3647 5-d | HMR 3647 10-d | Total |
|---|---|---|---|
| **Total treated** | **168** | **168** | **336** |
| Total subjects excluded from mITT analysis [a] | 1 | 0 | 1 |
| Subject without signs and symptoms related to the study indication | 0 | 0 | 0 |
| Subject without X-ray findings consistent with the indication | 1 | 0 | 1 |
| **Total subjects in mITT analysis** | **167** | **168** | **335** |
| **Total subjects excluded from PPc analysis [a]** | **44** | **35** | **79** |
| Previous antimicrobial treatment | 0 | 1 | 1 |
| Insufficient signs and symptoms at entry | 0 | 0 | 0 |
| Insufficient X-ray evidence of AMS at V1 | 0 | 1 | 1 |
| Subject with lab. exclusion criteria | 4 | 1 | 5 |
| Insufficient treatment duration | 7 | 5 | 12 |
| Wrong entry diagnosis | 1 | 1 | 2 |
| Previously enrolled in the study | 0 | 0 | 0 |
| Missing appropriate post treatment information | 18 | 20 | 38 |
| Use of non study systemic antimicrobial between pretherapy/entry and posttherapy/TOC visits (except failure) | 3 | 0 | 3 |
| Inability to determine treatment outcome at posttherapy/TOC | 6 | 4 | 10 |
| Subject without X-ray within 2 days of first intake of study drug | 10 | 5 | 15 |
| Treatment unblinding before posttherapy/TOC visit | 0 | 0 | 0 |
| Treatment with sinus washing procedures | 0 | 0 | 0 |
| **Total subjects in PPc analysis** | **123** | **133** | **256** |
| **Total subjects excluded from PPb analysis [a]** | **53** | **64** | **117** |
| Subject without bacteriological sample at inclusion | 0 | 0 | 0 |
| Subject without valid causative pathogen at inclusion | 52 | 64 | 116 |
| Sample outside the time window at posttherapy/TOC | 1 | 0 | 1 |
| Inability to determine bacteriological outcome | 0 | 0 | 0 |
| **Total subjects in PPb analysis** | **70** | **69** | **139** |

a The same subject may have had more than one reason for exclusion

Exclusion of 117 PPc subjects from the PPb analysis was due to the following reasons: no causative pathogen at inclusion (HMR 3647 5-d: 52 subjects, HMR 3647 10-d: 64 subjects), sample outside time window at posttherapy/TOC (HMR 3647 5-d: 1 subject, HMR 3647 10-d: 0 subjects).

Three subjects (HMR 3647 5-d: 2; HMR 3647 10-d: 1) were excluded from the safety population; all three subjects had no post pretherapy/entry safety assessments.

### *Demographics and baseline characteristics*

The demographic details of subjects eligible for the mITT population are summarized by treatment group in the following table:

**Demographics and pretherapy/entry characteristics – mITT population**

| Characteristic | HMR 3647 5-d | HMR 3647 10-d |
|---|---|---|
| Total treated in mITT | 167 | 168 |
| **Sex** | | |
| Male N (%) | 83 (49.7%) | 81 (48.2%) |
| Female N (%) | 84 (50.3%) | 87 (51.8%) |
| **Age (years)** | | |
| Median (range) | 34.0 (18-65) | 39.0 (18-66) |
| <65 years N (%) | 165 (98.8%) | 167 (99.4%) |
| ≥65 years N (%) | 2 (1.2%) | 1 (0.6%) |
| BMI ($kg/m^2$) | | |
| Mean ± SD | 24.8 ± 3.8 | 24.7 ± 3.8 |
| Weight (kg) | | |
| Mean ± SD | 73.4 ± 13.6 | 72.4 ± 14.1 |
| **Smoking status** | | |
| Smoker N (%) | 56 (33.5%) | 53 (31.5%) |
| Ex-smoker N (%) | 25 (15.0%) | 20 (11.9%) |
| Non-smoker N (%) | 86 (51.5%) | 95 (56.5%) |
| **Race** | | |
| White N (%) | 160 (95.8%) | 162 (96.4%) |
| Black N (%) | 2 (1.2%) | 1 (0.6%) |
| Asian/Oriental N (%) | 4 (2.4%) | 4 (2.4%) |
| Multiracial N (%) | 1 (0.6%) | 1 (0.6%) |

The distribution of demographic and pretherapy/entry characteristics was similar in both treatment groups in the mITT population.

Demographic and pretherapy/entry characteristics of the PPc, bmITT, PPb and safety populations were also similar in both treatment groups.

## Primary disease

Characteristics at pretherapy/entry of the current infection and AMS-specific prognostic factors were as follows in the mITT population:

**Characteristics of current infection and AMS-specific prognostic factors**

| mITT population | Number of subjects HMR 3647 5-d | | HMR 3647 10-d | |
|---|---|---|---|---|
| Total number of subjects | 167 | (100.0%) | 168 | (100.0%) |
| Duration of current episode | | | | |
| 0 to 3 days | 54 | (32.3%) | 42 | (25.0%) |
| 4 to 6 days | 50 | (29.9%) | 53 | (31.5%) |
| 7 to 14 days | 45 | (26.9%) | 57 | (33.9%) |
| ≥15 days | 17 | (10.2%) | 16 | (9.5%) |
| Unknown | 1 | (0.6%) | 0 | (0.0%) |
| Sinus episode in the last year | 39 | (23.4%) | 32 | (19.0%) |
| Number of sinusitis episodes in last year requiring antibiotic treatment | | | | |
| 0 | 2 | (5.1%) | 1 | (3.1%) |
| 1 to 3 | 37 | (94.9%) | 31 | (96.9%) |
| >3 | 0 | (0.0%) | 0 | (0.0%) |
| Nasal septum deviation | 42 | (25.1%) | 42 [a] | (25.1%) |
| History of asthma | 4 | (2.4%) | 5 [a] | (3.0%) |
| Episodes of allergic rhinitis in last 30 days | 3 [a] | (1.8%) | 2 [a] | (1.2%) |
| Previous antimicrobial medications [b] | 0 | (0.0%) | 1 | (0.6%) |
| Investigator assessment of current episode | | | | |
| Mild | 8 | (4.8%) | 10 | (6.0%) |
| Moderate | 105 | (62.9%) | 111 | (66.1%) |
| Severe | 54 | (32.3%) | 47 | (28.0%) |
| Fever | 10 | (6.0%) | 9 | (5.4%) |
| ENT-related surgical history | 10 | (6.0%) | 11 | (6.5%) |
| X-ray/computerized tomography findings | | | | |
| Air fluid level | 84 | (50.3%) | 82 | (48.8%) |
| Total opacity | 104 | (62.3%) | 96 | (57.1%) |
| Mucosal thickening ≥6 mm | 74 | (44.3%) | 84 | (50.0%) |
| Unilateral | 86 | (51.5%) | 96 | (57.1%) |
| Bilateral | 81 | (48.5%) | 72 | (42.9%) |

[a] Unknown for one subject
[b] Received systemic antimicrobials in the 7 days prior to entry

Characteristics of current infection and AMS-specific prognostic factors were similar in both treatment groups in the mITT population.

For the majority of subjects, the investigator's assessment of disease severity was moderate although over one quarter of subjects in each group was considered to have severe disease. Except for one subject (609/006) in the HMR 3647 10-d group who only had a mucosal thickening of ≥6 mm in the sinus X-ray, all subjects in both treatment groups had air fluid level and/or total opacity as sinus X-ray findings. Forty-two subjects in each treatment group had nasal septum deviation, although none were severe enough to warrant exclusion.

Among the subjects in the mITT population, only one subject (2101/004) in the HMR 3647 10-d group had received an antimicrobial pretreatment in the 7 days before pretherapy/entry and was excluded from the PPc analysis. Subject 2101/004 had been treated with oral klavocin (beta-lactam antibacterial) for 10 days prior to randomization; the investigator was not aware of this until the subject had completed study medication.

### Concomitant illnesses

Thirteen (13 [3.9%]) subjects had at least one general risk factor for morbidity in the mITT population; two subjects (0.6%) had two or more risk factors. The most common general risk factors in the mITT population were diabetes mellitus (HMR 3647 5-d: 1 [0.6%]; HMR 3647 10-d: 4 [2.4%]) and unspecified disorder of liver (HMR 3647 5-d: 1 [0.6%]; HMR 3647 10-d: 3 [1.8%]). All other risk factors were reported in less than 2% of subjects.

Relevant concomitant illnesses are included within general risk factors for morbidity.

### Concomitant medication

Overall, 142 subjects (HMR 3647 5-d: 61 [36.5%]; HMR 3647 10-d: 81 [48.2%]) in the mITT population received concomitant medication.

#### *Concomitant nonantimicrobial medication*

One hundred forty-two (142) subjects (HMR 3647 5-d: 61 [36.5%]; HMR 3647 10-d: 81 [48.2%]) received concomitant non anti-infective medication during the treatment with study medication. The most commonly prescribed medications were nasal preparations (HMR 3647 5-d: 32 [19.2%]; HMR 3647 10-d: 29 [17.3%]), cough and cold preparations (HMR 3647 5-d: 25 [15.0%]; HMR 3647 10-d: 25 [14.9%]), analgesics (HMR 3647 5-d: 14 [8.4%]; HMR 3647 10-d: 9 [5.4%]) and sex hormones and other modulators of the genital system (HMR 3647 5-d: 7 [4.2%]; HMR 3647 10-d: 20 [11.9%]).

### Concomitant antimicrobial medication

No subjects in the mITT population received concomitant antimicrobial medication. There was no concomitant antimicrobial medication in the PPc, PPb and safety populations.

## *APPLICANT'S RESULTS - EFFICACY*

## Analyses of primary efficacy variable

### Number of subjects included in analyses

The primary efficacy variable was clinical outcome rate at posttherapy/TOC (days 17 to 24). The primary analysis population was the PPc population; the primary efficacy variable was also analyzed for the mITT population. The numbers of subjects included in each of these analyses were as follows:

**Number of subjects evaluable at posttherapy/TOC visit**

| | Number of subjects | |
|---|---|---|
| **Population** | **HMR 3647 5-d** | **HMR 3647 10-d** |
| mITT | 167 | 168 |
| PPc | 123 | 133 |

### Clinical outcome - assessment at posttherapy/TOC visit in the PPc population

The clinical outcome at posttherapy/TOC in the PPc population was the primary efficacy analysis in this study and is summarized in the table below.

**Clinical outcome at posttherapy/TOC – PPc population**

| | Number of subjects (%) | | | |
|---|---|---|---|---|
| **Assessment** | **HMR 3647 5-d** | **HMR 3647 10-d** | **Difference** | **95% CI [a]** |
| **N** | **123** | **133** | | |
| **Cure** | **112 (91.1%)** | **121 (91.0%)** | 0.1% | [-7.7, 7.9] |
| Returned to preinfection state | 35 | 51 | | |
| Improved or postinfectious stigmata [b] | 77 | 70 | | |
| **Failure** | **11 (8.9%)** | **12 (9.0%)** | | |

[a] Two-sided 95% confidence interval

[b] No nonstudy antimicrobial therapy started

The response rates were 91.1% in the HMR 3647 5-d group and 91.0% in the HMR 3647 10-d group, a difference between the groups of 0.1%. The 95%

confidence interval of the difference was (-7.7%, 7.9%) – that is, the lower bound was greater than –15% and the upper bound was greater than zero, thereby demonstrating that the two treatment regimens were equivalent. Among the 233 subjects assessed as cure, 35 subjects in the HMR 3647 5-d group and 51 subjects in the HMR 3647 10-d group were classified as "returned to pre-infection state", and 77 in the HMR 3647 5-d group and 70 in the HMR 3647 10-d group were classified as "improved with postinfectious stigmata".

## Clinical outcome – assessment at posttherapy/TOC visit in the mITT population

The clinical outcome at posttherapy/TOC in the mITT population is summarized in the table shown below.

**Clinical outcome at posttherapy/TOC – mITT population**

| | Number of subjects (%) | | | | | |
|---|---|---|---|---|---|---|
| **Assessment** | **HMR 3647 5-d** | | **HMR 3647 10-d** | | **Difference** | **95% CI [a]** |
| N | 167 | | 168 | | | |
| **Cure** | **138** | **(82.6%)** | **147** | **(87.5%)** | **-4.9%** | **[-13.1, 3.3]** |
| Returned to preinfection state | 49 | | 60 | | | |
| Improved or postinfectious stigmata [b] | 89 | | 87 | | | |
| **Failure** | **29** | **(17.4%)** | **21** | **(12.5%)** | | |
| Failure | 12 | | 13 | | | |
| Indeterminate | 17 | | 8 | | | |

[a] Two-sided 95% confidence interval
[b] No additional antimicrobial therapy started

The response rates were 82.6% in the HMR 3647 5-d group and 87.5% in the HMR 3647 10-d group, a difference between the groups of –4.9%. The 95% confidence interval of the difference was (-13.1%, 3.3%) – that is, the lower bound was greater than –15% and the upper bound was greater than zero, thereby providing further evidence that the two treatment regimens were equivalent. This result supports and reinforces the primary efficacy outcome in the PPc analysis.

The clinical cure rate at posttherapy/TOC was lower in the mITT population compared with the PPc population because indeterminate cases were classed as failure in the mITT analysis. The reasons for indeterminate outcome in the 25 subjects at posttherapy/TOC were: subject did not wish to continue in

the study (HMR 3647 5-d: 7; HMR 3647 10-d: 2), missing posttherapy/TOC visit (HMR 3647 5-d: 4; HMR 3647 10-d: 2), discontinued for laboratory exclusion criteria at pretherapy/entry (HMR 3647 5-d: 4; HMR 3647 10-d: 1), new antimicrobial given for reason other than AMS (HMR 3647 5-d: 1; HMR 3647 10-d: 0), lost to follow-up (HMR 3647 5-d: 0; HMR 3647 10-d: 2), discontinued for recurrence of preexisting adverse event (HMR 3647 5-d: 1; HMR 3647 10-d: 0), antimicrobial therapy in the 7 days prior to entry (HMR 3647 5-d: 0; HMR 3647 10-d: 1).

**Clinical outcome – other assessments at posttherapy/TOC visit**

Clinical outcome in the PPb population at posttherapy/TOC was cure for 65/70 subjects (92.9%) in the HMR 3647 5-d group and 63/69 subjects (91.3%) in the HMR 3647 10-d group.

Of the five subjects in the HMR 3647 5-d group with an outcome of failure at posttherapy/TOC, two subjects (708/018 and 1506/003) had *S. pneumoniae* isolated at pretherapy/entry.

Of the six subjects in the HMR 3647 10-d group with an outcome of failure at posttherapy/TOC, three subjects (504/002, 708/019 and 1903/014) had *S. pneumoniae* isolated at pretherapy/entry and one subject (708/003) had *H. influenzae* isolated at pretherapy/entry.

Clinical outcome in the ITT population was similar to that in the mITT population. Clinical outcome of cure at posttherapy/TOC was as follows: 139/168 subjects (82.7%) in the HMR 3647 5-d group and 147/168 subjects (87.5%) in the HMR 3647 10-d group.

**Analyses of secondary efficacy variables**

**Clinical outcome – assessment at late posttherapy visit**

The clinical outcome at late posttherapy was as follows:

**Clinical outcome at late posttherapy visit**

| Assessment | Number of subjects (%) HMR 3647 5-d | | HMR 3647 10-d | | Difference | 95% CI [a] |
|---|---|---|---|---|---|---|
| **PPc population** | | | | | | |
| N | 108 | | 120 | | | |
| **Cure** | **96** | **(88.9%)** | **107** | **(89.2%)** | **-0.3%** | **[-9.3, 8.7]** |
| **Failure** | **12** | **(11.1%)** | **13** | **(10.8%)** | | |
| **Failure at posttherapy/TOC** | **11** | | **12** | | | |
| Relapse/reinfection | 1 | | 1 | | | |
| **mITT population** | | | | | | |
| N | 167 | | 168 | | | |
| **Cure** | **135** | **(80.8%)** | **145** | **(86.3%)** | **-5.5%** | **[-14.0, 3.0]** |
| **Failure** | **32** | **(19.2%)** | **23** | **(13.7%)** | | |
| **Failure at posttherapy/TOC** | **12** | | **13** | | | |
| Relapse/reinfection | 1 | | 1 | | | |
| Indeterminate | 19 | | 9 | | | |

[a] Two-sided 95% confidence interval

The results at the late posttherapy visit were similar to those observed at posttherapy/TOC. In particular, the 95% confidence interval of the difference in cure rates provided further evidence of equivalence between HMR 3647 5-d and HMR 3647 10-d in both the PPc and mITT populations, with in each case, the lower bound being greater than -15% and the upper bound being greater than zero.

Brief narrative summaries for each of the cases considered as clinical cure at posttherapy/TOC but clinical failures at late posttherapy (two subjects) are presented here.

- Subject 502/002 in the HMR 3647 5-d group had *H. influenzae* (MIC 2 mg/L, susceptible to HMR 3647) isolated at pretherapy/entry. At posttherapy/TOC, the subject had a clinical outcome of cure and bacteriological outcome of presumed eradication. At late posttherapy, clinical signs and symptoms reappeared and subsequent antibiotic treatment was started. The clinical response was assessed as failure at late posttherapy and bacteriological response as recurrence (not documented).
- Subject 405/006 in the HMR 3647 10-d group had *H. influenzae* isolated at pretherapy/entry and was assessed as cured at posttherapy/TOC. At late posttherapy, clinical signs and symptoms reappeared, sinus X-ray had worsened and the clinical outcome was assessed as failure.

Bacteriological outcome was assessed as presumed eradication at posttherapy/TOC and late posttherapy.

Clinical outcome in the PPb population at late posttherapy was cure for 54/60 subjects (90.0%) in the HMR 3647 5-d group and 54/61 subjects (88.5%) in the HMR 3647 10-d group.

Clinical outcome in the ITT population was similar to that in the mITT population. Clinical outcome of cure at late posttherapy was as follows: 136/168 subjects (81.0%) in the HMR 3647 5-d group and 145/168 subjects (86.3%) in the HMR 3647 10-d group.

## Causative pathogens at pretherapy/entry

At pretherapy/entry, 250 pathogens considered by the investigator to be causative for AMS were isolated from 201 subjects in the bmITT population (HMR 3647 5-d: 119 pathogens from 97 subjects; HMR 3647 10-d: 131 pathogens from 104 subjects). All pathogens were isolated from the sinus puncture at pretherapy/entry.
The following table summarizes all the causative pathogens isolated at pretherapy/entry in the bmITT population.

**Causative pathogens isolated at pretherapy/entry – bmITT population**

| Pathogen | HMR 3647 5-d | HMR 3647 10-d | Total |
|---|---|---|---|
| **TOTAL** | **119** | **131** | **250** |
| *S. pneumoniae* | 37 | 33 | 70 (28.0%) |
| *H. influenzae* | 16 | 18 | 34 (13.6%) |
| *M. catarrhalis* | 8 | 8 | 16 (6.4%) |
| *Group A streptococcus (S.pyogenes)* | 1 | 1 | 2 (0.8%) |
| *H. parainfluenzae* | 3 | 1 | 4 (1.6%) |
| *K. pneumoniae* | 2 | 1 | 3 (1.2%) |
| *S. aureus* | 16 | 14 | 30 (12.0%) |
| Other | 36 | 55 | 91 (36.4%) |

The distribution of causative pathogens isolated at pretherapy/entry was similar for the two treatment groups in the PPb population as shown in the following table.

**Causative pathogens isolated at pretherapy/entry – PPb population**

| Pathogen | HMR 3647 5-d | HMR 3647 10-d | Total |
|---|---|---|---|
| **TOTAL** | **86** | **92** | **178** |
| *S. pneumoniae* | 30 | 28 | 58 (32.6%) |
| *H. influenzae* | 14 | 13 | 27 (15.2%) |
| *M. catarrhalis* | 7 | 4 | 11 (6.2%) |
| *Group A streptococcus (S.pyogenes)* | 1 | 1 | 2 (1.1%) |
| *H. parainfluenzae* | 2 | 0 | 2 (1.1%) |
| *K. pneumoniae* | 2 | 0 | 2 (1.1%) |
| *S. aureus* | 7 | 4 | 11 (6.2%) |
| Other | 23 | 42 | 65 (36.5%) |

## In vitro susceptibility of causative pathogens

### *Disk diffusion methodology at local laboratory*

Susceptibility test results by disk diffusion methodology of local laboratory were made available in this NDA and are reviewed by Dr. Fred Marsik, the microbiology reviewer for this submission. Please refer to his review for details.

## Bacteriological outcome by subject – assessment at posttherapy/TOC visit

The bacteriological outcome at posttherapy/TOC in the PPb population is shown in the table below.

**Bacteriological outcome by subject at posttherapy/TOC visit – PPb population**

| Assessment | Number of subjects (%) HMR 3647 5-d | HMR 3647 10-d | | Difference |
|---|---|---|---|---|
| N | 70 | 69 | | |
| Satisfactory [a] | 65 (92.9%) | 62 | (89.9%) | 3.0% |
| Unsatisfactory [b] | 5 (7.1%) | 7 | (10.1%) | |

*a* Includes eradication, presumed eradication.
*b* Includes persistence, presumed persistence, recurrence, eradication and reinfection, superinfection.

The bacteriological outcome rates at posttherapy/TOC are comparable between the treatment groups and satisfied the secondary objective of the study of demonstrating bacterial efficacy ≥70% at posttherapy/TOC in both treatment groups.

Bacteriological outcome was satisfactory for 80/97 subjects (82.5%) in the HMR 3647 5-d group and 93/104 subjects (89.4%) in the HMR 3647 10-d

group in the bmITT population. Indeterminate outcome was categorized as unsatisfactory in the bmITT analysis: of the subjects with unsatisfactory outcome, 12 of the 17 HMR 3647 5-d subjects and 3 of the 11 HMR 3647 10-d subjects had indeterminate outcome.

## Bacteriological outcome by pathogen – assessment at posttherapy/TOC visit

### Eradication rates

The bacteriological eradication rates by pathogen at posttherapy/TOC for all causative pathogens isolated at pretherapy/entry in the PPb population are summarized in the following table.

**Eradication rates at posttherapy/TOC – PPb population**

| | Eradication rate (%) | | | |
|---|---|---|---|---|
| **Pathogen [a]** | **HMR 3647 5-d** | | **HMR 3647 10-d** | |
| **TOTAL** | **78/86** | **(90.7%)** | **84/92** | **(91.3%)** |
| *S. pneumoniae* | 28/30 | (93.3%) | 25/28 | (89.3%) |
| *H. influenzae* | 14/14 | (100.0%) | 11/13 | (84.6%) |
| *M. catarrhalis* | 6/7 | (85.7%) | 3/4 | (75.0%) |
| *Group A streptococcus (S.pyogenes)* | 1/1 | (100.0%) | 1/1 | (100.0%) |
| *H. parainfluenzae* | 2/2 | (100.0%) | - | - |
| *K. pneumoniae* | 2/2 | (100.0%) | - | - |
| *S. aureus* | 7/7 | (100.0%) | 4/4 | (100.0%) |
| Other | 18/23 | (78.3%) | 40/42 | (95.2%) |

[a] Single and multiple pathogen infections

Eradication includes both documented and presumed eradication.

Eradication rates at posttherapy/TOC for the principal RTI pathogens are comparable for the two treatment groups.

In the HMR 3647 5-d group, there were no recurrent or documented persistent pathogens, and eight pathogens with presumed persistence (*S. pneumoniae*, 2; *M. catarrhalis*, 1;

1). In the HMR 3647 10-d group, there were no recurrent pathogens, 2 pathogens with documented persistence (*H. influenzae*, 2) and 6 with presumed persistence (*S. pneumoniae*, 3; *M. catarrhalis*, 1;

In the bmITT population, these results were confirmed and the eradication rates (documented or presumed eradication) were 95/103 (92.2%) for HMR 3647 5-d group and 119/128 (93.0%) for the HMR 3647 10-d group. The

distribution of eradicated pathogens was similar to that seen in the PPb population.

**In vitro susceptibility of superinfection, reinfection and recurrence pathogens by disk diffusion methodology at local laboratory**

There were no superinfection pathogens isolated during the study in the bmITT population.

There was one reinfection pathogen isolated during the study in the bmITT population in a sample obtained by middle meatus aspiration from subject 501/005 in the HMR 3647 5-d group. This was one *H. influenzae* reinfection that was susceptible to HMR 3647.

- Subject 501/005 in the HMR 3647 5-d group had *Moraxella catarrhalis* isolated at pretherapy/entry (MIC 0.06 mg/L, susceptible to HMR 3647). At the on-therapy visit, clinical signs and symptoms were improved. At posttherapy/TOC, clinical signs and symptoms and sinus X-ray had worsened and sinus aspirate sample showed *H. influenzae* (MIC 1 mg/L, susceptible to HMR 3647). The clinical outcome was assessed as failure at posttherapy/TOC and late posttherapy and bacteriological outcome was assessed as re-infection for *H. influenzae* and presumed persistence for *Moraxella catarrhalis*.

There was one reinfection pathogen in the HMR 3647 5-d group in the PPb population (subject 501/005). There were no reinfection pathogens in the HMR 3647 10-d group in the PPb population.

There were no documented recurrent pathogens isolated during the study in the bmITT population. There were 3 pathogens classed as recurrence (not documented) at late posttherapy (subjects 502/002 and 504/009 in the HMR 3647 5-d group and subject 708/003 in the HMR 3647 10-d group) because the pathogen was eradicated at posttherapy/TOC but the subject started a new antibiotic for a lower respiratory tract infection between posttherapy/TOC and late posttherapy. Thus, there are no susceptibility data available for these pathogens at the time of classification as recurrence.

## Bacteriological outcome by subject – assessment at late posttherapy visit

The bacteriological outcome at late posttherapy in the PPb population is shown in the table below.

**Bacteriological outcome at late posttherapy – PPb population**

| Assessment | Number of subjects (%) HMR 3647 5-d | | HMR 3647 10-d | | Difference |
|---|---|---|---|---|---|
| N | 60 | | 61 | | |
| Satisfactory | 54 | (90.0%) | 53 | (86.9%) | 3.1% |
| Unsatisfactory | 6 | (10.0%) | 8 | (13.1%) | |
| Unsatisfactory at posttherapy/TOC | 5 | | 7 | | |
| Satisfactory at posttherapy/TOC | 1 | | 1 | | |
| Recurrence at late posttherapy [a] | 1 | | 1 | | |

[a] Recurrence not documented

In the PPb population, 10 subjects in the HMR 3647 5-d group and 8 subjects in the HMR 3647 10-d group became indeterminate for bacteriological response between posttherapy/TOC and late posttherapy, thus there were 60 subjects and 61 subjects evaluable for bacteriological response at late posttherapy in each group, respectively.

The bacteriological outcome rates at late posttherapy are comparable between the treatment groups. Bacteriological outcome rates at late posttherapy were slightly lower than those seen at posttherapy/TOC.

Bacteriological outcome was satisfactory for 77/97 subjects (79.4%) in the HMR 3647 5-d group and 91/104 subjects (87.5%) in the HMR 3647 10-d group in the bmITT population.

There were two subjects in the PPb population (HMR 3647 5-d: 1; HMR 3647 10-d: 1) who had a satisfactory bacteriological response at posttherapy/TOC but were unsatisfactory at late posttherapy, for the following reasons:

- Subject 502/002 (HMR 3647 5-d): *H. influenzae* was isolated from a sinus puncture at pretherapy/entry. At posttherapy/TOC (day 22), all signs and symptoms were absent, a sinus puncture was performed and no pathogen was isolated (eradication). On day 35 (1 day before late posttherapy), the subject experienced a new episode of sinusitis and a new antibiotic was prescribed (from day 35 to day 44). The clinical response was assessed as cure at posttherapy/TOC and failure at late posttherapy. Bacteriological response was assessed as satisfactory (eradication) at posttherapy/TOC and unsatisfactory (recurrence not documented) at late posttherapy.

- Subject 708/003 (HMR 3647 10-d): Streptococcus Group C and *H. influenzae* were isolated from a sinus puncture at pretherapy/entry. At posttherapy/TOC visit (day 21), clinical signs and symptoms were improved but the sinus X-ray had worsened from pretherapy/entry. A sinus puncture was performed and showed eradication, but a new antibiotic was started (from day 21 to day 30) because of the worsening X-ray. Clinical response was assessed as failure at posttherapy/TOC and late posttherapy. Bacteriological response was assessed as satisfactory at posttherapy/TOC and unsatisfactory (recurrence not documented) at late posttherapy.

The reason for unsatisfactory response in the one subject only in the bmITT population is as follows:

- Subject 504/009 (HMR 3647 5-d): *S. aureus* considered as not responsible ($10^2$ CFU/mL) was isolated at pretherapy/entry. At posttherapy/TOC (day 19), clinical signs and symptoms and sinus X-ray had worsened from pretherapy/entry and a new antibiotic was started (from day 19 to day 28). A sinus puncture was performed at posttherapy/TOC and showed eradication. The investigator assessed the clinical response as failure at posttherapy/TOC and late posttherapy. Bacteriological response was assessed as satisfactory at posttherapy/TOC and unsatisfactory (recurrence not documented) at late posttherapy.

## Bacteriological outcome by pathogen – assessment at late posttherapy visit

The bacteriological eradication rate by pathogen at late posttherapy for all causative pretherapy/entry pathogens is summarized in the following table:

**Eradication rates at late posttherapy – PPb population**

| | Eradication rate (%) | | | |
|---|---|---|---|---|
| **Pathogen *** | **HMR 3647 5-d** | | **HMR 3647 10-d** | |
| **TOTAL** | **63/72** | **(87.5%)** | **74/82** | **(90.2%)** |
| *S. pneumoniae* | 22/24 | (91.7%) | 22/25 | (88.0%) |
| *H. influenzae* | 11/12 | (91.7%) | 11/12 | (91.7%) |
| *M. catarrhalis* | 5/6 | (83.3%) | 3/4 | (75.0%) |
| *Group A streptococcus (S.pyogenes)* | 1/1 | (100.0%) | 1/1 | (100.0%) |
| *H. parainfluenzae* | 2/2 | (100.0%) | - | - |
| *K. pneumoniae* | 2/2 | (100.0%) | - | - |
| *S. aureus* | 7/7 | (100.0%) | 4/4 | (100.0%) |
| Other | 13/18 | (72.2%) | 33/36 | (91.7%) |

* Single and multiple pathogen infections

Eradication includes both documented and presumed eradication.

Twenty-four pathogens in 18 subjects in the PPc population were not evaluable at late posttherapy because the subjects had their late posttherapy visit outside the designated time window. Thus, the subjects were also excluded from the PPb population.

Eradication rates at late posttherapy for the principal RTI pathogens are comparable for the two treatment groups.

In the HMR 3647 5-d group, there was one recurrent (not documented) pathogen (*H. influenzae*, 1), no documented persistent pathogens, and eight pathogens with presumed persistence carried forward from posttherapy/TOC (*S. pneumoniae*, 2; *M. catarrhalis*, 1;

1). In the HMR 3647 10-d group, there were two recurrent (not documented) pathogens (*H. influenzae*, 1; Streptococcus [Group C], 1), no pathogens with documented persistence and six with presumed persistence carried forward from posttherapy/TOC (*S. pneumoniae*. 3: *M. catarrhalis*, 1;

Eradication rates (documented or presumed eradication) were 91/101 (90.1%) for HMR 3647 5-d group and 118/127 (92.9%) for the HMR 3647 10-d group in the bmITT population. The distribution of eradicated pathogens was similar to that seen in the PPb population.

### *Clinical outcome for pathogens of importance in AMS*

#### Clinical outcome by isolated pretherapy/entry causative pathogen

Clinical outcome at posttherapy/TOC for subjects in the PPb population with *S. pneumoniae*, *Group A streptococcus* (*S. pyogenes*), *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis* or *S. aureus* isolated at pretherapy/entry is shown in the following table.

**Clinical outcome in subjects with pathogens of importance in AMS – PPb population at posttherapy/TOC**

| | | Clinical outcome Number of subjects (%) | | | | |
|---|---|---|---|---|---|---|
| | | HMR 3647 5-d | | | HMR 3647 10-d | |
| Subgroup | N | Cure | Failure | N | Cure | Failure |
| Any pathogen | 57 | 54 (94.7%) | 3 (5.3%) | 56 | 52 (92.9%) | 4 (7.1%) |
| *Streptococcus pneumoniae* | 24 | 22 (91.7%) | 2 (8.3%) | 24 | 22 (91.7%) | 2 (8.3%) |
| *Haemophilus influenzae* | 8 | 8 (100.0%) | 0 (0.0%) | 9 | 9 (100.0%) | 0 (0.0%) |
| *Moraxella catarrhalis* | 6 | 5 (83.3%) | 1 (16.7%) | 4 | 3 (75.0%) | 1 (25.0%) |
| *Group A streptococcus (S.pyogenes)* | 0 | - | - | 1 | 1 (100.0%) | 0 (0.0%) |
| *Haemophilus parainfluenzae* | 2 | 2 (100.0%) | 0 (0.0%) | 0 | - | - |
| *Staphylococcus aureus* | 6 | 6 (100.0%) | 0 (0.0%) | 1 | 1 (100.0%) | 0 (0.0%) |

## Comparison of clinical and bacteriological outcome at posttherapy/TOC visit

In the PPb population, 126/139 (90.7%) of subjects at posttherapy/TOC had a therapeutic outcome, i.e., clinical outcome of cure and bacteriological outcome of satisfactory (HMR 3647 5-d: 65/70 [92.9%]; HMR 3647 10-d: 61/69 [88.4%]). Two subjects (402/001 and 504/007), both in the HMR 3647 10-d group, had a clinical outcome of cure but bacteriological response was unsatisfactory. One subject (708/003) in the HMR 3647 10-d group had satisfactory bacteriological outcome and clinical outcome of failure. Clinical outcome was failure and bacteriological outcome was unsatisfactory for 5 subjects in the HMR 3647 5-d group (404/003, 501/005, 603/001, 708/018 and 1506/003) and 5 subjects in the HMR 3647 10-d group (504/002, 708/019, 708/026, 1502/005 and 1903/014).

Many subjects did not have a bacteriological sample because of clinical resolution and thus the numbers are small. The results were similar in the bmITT population and for subjects with single or multiple pathogen infections due to pathogens of importance.

### *Efficacy analysis of special subject groups*

Analyses of clinical outcome were performed on subjects who had demographic factors of special interest, general risk factors (underlying diseases) for morbidity, and characteristics of the current infection and prognostic factors for AMS (PPc population), as follows:

- Demographic characteristics: sex, age (<65 years, ≥65 years), race (white, black, Asian/oriental, multiracial, other), smoking status (smoker, ex-smoker, nonsmoker)
- General risk factors for morbidity: none, 1, >1
- Characteristics of current infection and AMS-specific prognostic factors: sinusitis episodes in the last year, number of AMS episodes requiring antibiotic treatment in last 12 months, history of asthma, episodes of allergic rhinitis in last 30 days, nasal septum deviation, duration of current AMS episode, investigator assessment of current episode, fever, ENT related surgical history, sinus X-ray findings.

Clinical outcome in subjects with special demographic factors of interest was as follows:

**Clinical outcome in subjects with demographic factors of special interest – PPc population at posttherapy/TOC**

| | | | Clinical outcome Number of subjects (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | HMR 3647 5-d | | | | | HMR 3647 10-d | | |
| Subgroup | N | | Cure | | Failure | N | | Cure | Failure | |
| All subjects | 123 | 112 | (91.1%) | 11 | (8.9%) | 133 | 121 | (91.0%) | 12 | (9.0%) |
| Sex | | | | | | | | | | |
| Male | 65 | 58 | (89.2%) | 7 | (10.8%) | 60 | 56 | (93.3%) | 4 | (6.7%) |
| Female | 58 | 54 | (93.1%) | 4 | (6.9%) | 73 | 65 | (89.0%) | 8 | (11.0%) |
| Age | | | | | | | | | | |
| <65 years | 122 | 111 | (91.0%) | 11 | (9.0%) | 132 | 120 | (90.9%) | 12 | (9.1%) |
| ≥65 years | 1 | 1 | (100.0%) | 0 | (0.0%) | 1 | 1 | (100.0%) | 0 | (0.0%) |
| Race | | | | | | | | | | |
| White | 117 | 107 | (91.5%) | 10 | (8.5%) | 128 | 116 | (90.6%) | 12 | (9.4%) |
| Black | 2 | 2 | (100.0%) | 0 | (0.0%) | 0 | - | - | - | - |
| Asian/Oriental | 3 | 3 | (100.0%) | 0 | (0.0%) | 4 | 4 | (100.0%) | 0 | (0.0%) |
| Multiracial | 1 | 0 | (0.0%) | 1 | (100.0%) | 1 | 1 | (100.0%) | 0 | (0.0%) |
| Smoking status | | | | | | | | | | |
| Smoker | 39 | 37 | (94.9%) | 2 | (5.1%) | 39 | 37 | (94.9%) | 2 | (5.1%) |
| Ex-smoker | 22 | 18 | (81.8%) | 4 | (18.2%) | 18 | 16 | (88.9%) | 2 | (11.1%) |
| Nonsmoker | 62 | 57 | (91.9%) | 5 | (8.1%) | 76 | 68 | (89.5%) | 8 | (10.5%) |

Clinical outcome in subjects according to prognostic factors specific for AMS was as follows:

**Clinical outcome according to characteristics of current infection and AMS-specific prognostic factors – PPc population at posttherapy/TOC**

| | | | Clinical outcome Number of subjects (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | HMR 3647 5-d | | | | | HMR 3647 10-d | | |
| **Subgroup** | **N** | | **Cure** | **Failure** | | **N** | | **Cure** | **Failure** | |
| All subjects | 123 | 112 | (91.1%) | 11 | (8.9%) | 133 | 121 | (91.0%) | 12 | (9.0%) |
| No. of AMS episodes requiring antibiotic treatment in last 12 months | | | | | | | | | | |
| 0 | 2 | 2 | (100.0%) | 0 | (0.0%) | 1 | 1 | (100.0%) | 0 | (0.0%) |
| 1 to 3 | 28 | 24 | (85.7%) | 4 | (14.3%) | 26 | 22 | (84.6%) | 4 | (15.4%) |
| >3 | 0 | - | - | - | - | 0 | - | - | - | - |
| History of asthma | 2 | 2 | (100.0%) | 0 | (0.0%) | 3 | 3 | (100.0%) | 0 | (0.0%) |
| Episodes of allergic rhinitis in last 30 days | 2 | 2 | (100.0%) | 0 | (0.0%) | 2 | 2 | (100.0%) | 0 | (0.0%) |
| Nasal septum deviation | 33 | 30 | (86.7%) | 3 | (9.1%) | 32 | 30 | (85.2%) | 2 | (6.3%) |
| Duration of current AMS episode | | | | | | | | | | |
| 0 to 3 days | 41 | 39 | (95.1%) | 2 | (4.9%) | 33 | 32 | (97.0%) | 1 | (3.0%) |
| 4 to 6 days | 37 | 35 | (94.6%) | 2 | (5.4%) | 41 | 37 | (90.2%) | 4 | (9.8%) |
| >7 to 14 days | 34 | 27 | (79.4%) | 7 | (20.6%) | 46 | 40 | (87.0%) | 6 | (13.0%) |
| ≥15 days | 10 | 10 | (100.0%) | 0 | (0.0%) | 12 | 11 | (91.7%) | 1 | (8.3%) |
| Unknown | 1 | 1 | (100.0%) | 0 | (0.0%) | 0 | - | - | - | - |
| Investigator assessment of current episode | | | | | | | | | | |
| Mild | 5 | 5 | (100.0%) | 0 | (0.0%) | 9 | 8 | (88.9%) | 1 | (11.1%) |
| Moderate | 78 | 70 | (89.7%) | 8 | (10.3%) | 81 | 76 | (93.8%) | 5 | (6.2%) |
| Severe | 40 | 37 | (92.5%) | 3 | (7.5%) | 43 | 37 | (86.0%) | 6 | (14.0%) |
| Fever | 8 | 8 | (100.0%) | 0 | (0.0%) | 7 | 7 | (100.0%) | 0 | (0.0%) |
| ENT related surgical history | 6 | 5 | (83.3%) | 1 | (16.7%) | 9 | 7 | (77.8%) | 2 | (22.2%) |
| Sinus X-ray findings | | | | | | | | | | |
| Air fluid level | 66 | 59 | (89.4%) | 7 | (10.6%) | 65 | 59 | (90.8%) | 6 | (9.2%) |
| Total opacity | 75 | 69 | (92.0%) | 6 | (8.0%) | 76 | 69 | (90.8%) | 7 | (9.2%) |
| Mucosal thickening ≥6 mm | 60 | 54 | (90.0%) | 6 | (10.0%) | 62 | 55 | (88.7%) | 7 | (11.3%) |
| Unilateral | 62 | 55 | (88.7%) | 7 | (11.3%) | 77 | 73 | (94.8%) | 4 | (5.2%) |
| Bilateral | 61 | 57 | (93.4%) | 4 | (6.6%) | 56 | 48 | (85.7%) | 8 | (14.3%) |

Excluding sub-groups with too small a sample size, the clinical outcome for HMR 3647 in all subgroups analyzed was similar to the clinical outcome seen for HMR 3647 in the overall PPc population. The clinical outcome was similar between treatment groups in all subgroups analyzed.

### *Applicant's Efficacy conclusions*

The efficacy conclusions are as follows:

- The primary analysis demonstrated equivalence between HMR 3647 800 mg once daily for 5 days and HMR 3647 800 mg once daily for 10 days in terms of clinical outcome at posttherapy/TOC for the PPc population, and also for the mITT population, which reinforces the results of the primary efficacy analysis.
- The results of the secondary analyses of clinical outcome at late posttherapy, and of bacteriological outcome at posttherapy/TOC and at late posttherapy, were comparable between treatment groups and support the results of the primary analysis. The secondary objective of demonstrating bacterial efficacy ≥70% at posttherapy/TOC in both groups was also achieved: bacteriological outcome of satisfactory in the PPb population; HMR 3647 5-d (65/70 [92.9%]), HMR 3647 10-d (62/69 [89.9%]).
- Clinical efficacy in subjects with infection due to *S. pneumoniae* or *H. influenzae* was good. In the PPb population at posttherapy/TOC, clinical outcome was cure for 91.7% of subjects in both groups with *S. pneumoniae*, and 100.0% for subjects in both groups with *H. influenzae*.
- Eradication rates at posttherapy/TOC in the PPb population were as follows: Overall eradication rate: HMR 3647 5-d (78/86 [90.7%]), HMR 3647 10-d (84/92 [91.3%]), *S. pneumoniae*: HMR 3647 5-d (28/30 [93.3%]), HMR 3647 10-d (25/28 [89.3%]); *H. influenzae*: HMR 3647 5-d (14/14 [100.0%]), HMR 3647 10-d (11/13 [84.6%]); *M. catarrhalis*: HMR 3647 5-d (6/7), HMR 3647 10-d (3/4); *S. aureus*: HMR 3647 5-d (7/7), HMR 3647 10-d (4/4); Group A streptococcus (*S. pyogenes*): HMR 3647 5-d(1/1), HMR 3647 10-d (1/1).
- For single pathogen infections, no subjects in the HMR 3647 5-d group had *S. pneumoniae* resistant to penicillin G or erythromycin A. In the HMR 3647 10-d group, the 2/2 subjects with *S. pneumoniae* resistant to penicillin G and 4/5 subjects with *S. pneumoniae* resistant to erythromycin A had a clinical outcome of cure and the pathogen was eradicated. In two subjects in the HMR 3647 10-d group, *S. pneumoniae* (single pathogen infection) resistant to penicillin G was also resistant to erythromycin A.
- The logistic regression analysis supports the primary efficacy analysis and confirms the conclusion of equivalence between the two treatment groups.

## RESULTS – SAFETY

### *Medical Officer's Comments:*

*The overall safety data are reviewed by Dr. David Ross and Dr. Edward Cox. Please refer to their reviews.*

### Extent of exposure

Three hundred and thirty-six (336) out of 341 randomized subjects (98.5%) received at least one dose of study medication (168 in HMR 3647 5-d group; 168 in HMR 3647 10-d group). Two subjects (603/017 and 603/029) in the HMR 3647 5-d group and three subjects (603/003, 603/028 and 708/008) in the HMR 3647 10-d group were withdrawn from the study after treatment allocation but before receiving any treatment. Of those treated, 333 subjects had at least one post pretherapy/entry safety assessment and were therefore evaluable for safety. Subjects 2101/005 and 2103/003 in the HMR 3647 5-d group and subject 1901/019 in the HMR 3647 10-d group had no post pretherapy/entry clinical or laboratory safety assessments and were excluded from the safety population.

The mean treatment duration in the safety population was 9.7 days in the HMR 3647 5-d group and 10.0 days in the HMR 3647 10-d group. In the HMR 3647 5-d group, 5 subjects received active treatment for less than 5 days and 161 subjects received active treatment for 5 days. In the HMR 3647 10-d group, 3 subjects received active treatment for less than 10 days and 160 subjects received active treatment for 10 days. The following table depicts the duration of treatment for each group.

## Treatment Duration – Safety Population

| | HMR 3647 5-d | | | | HMR 3647 10-d | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Duration of study medication [a] | | Duration of active medication [b] | | Duration study medication [b] | | Duration study Medication | |
| Total treated | 166 | (100.0 %) | 166 | (100.0%) | 167 | (100.0 %) | 333 | (100.0 %) |
| Unknown | 0 | (0.0 %) | 0 | (0.0%) | 2 | (1.2 %) | 2 | (0.6 %) |
| < 2 days | 1 | (0.6 %) | 1 | (0.6%) | 1 | (0.6 %) | 2 | (0.6 %) |
| 2 days | 3 | (1.8 %) | 3 | (1.8%) | 0 | (0.0 %) | 3 | (0.9 %) |
| 3 days | 1 | (0.6 %) | 1 | (0.6%) | 0 | (0.0 %) | 1 | (0.3 %) |
| 4 days | 0 | (0.0 %) | 0 | (0.0%) | 0 | (0.0 %) | 0 | (0.0 %) |
| 5 days | 2 | (1.2 %) | 161 | (97.0%) | 0 | (0.0 %) | 2 | (0.6 %) |
| 6 days | 2 | (1.2 %) | | | 1 | (0.6 %) | 3 | (0.9 %) |
| 7 days | 0 | (0.0 %) | | | 0 | (0.0 %) | 0 | (0.0 %) |
| 8 days | 0 | (0.0 %) | | | 0 | (0.0 %) | 0 | (0.0 %) |
| 9 days | 2 | (1.2 %) | | | 1 | (0.6 %) | 3 | (0.9 %) |
| 10 days | 152 | (91.6 %) | | | 160 | (95.8 %) | 312 | (93.7 %) |
| 11 days | 3 | (1.8 %) | | | 1 | (0.6 %) | 4 | (1.2 %) |
| > 11 days | 0 | (0.0 %) | | | 1 | (0.6 %) | 1 | (0.3 %) |
| N | 166 | | 166 | | 165 | | 331 | |
| Mean | 9.7 | | 4.9 | | 10.0 | | | 9.8 |
| SD | 1.5 | | 0.5 | | 0.9 | | | 1.3 |
| Median | 10.0 | | 5.0 | | 10.0 | | 10.0 | |
| Range | 1 - 11 | | 1 - 5 | | 1 - 15 | | 1 - 15 | |

a Number of days between first dose and last dose of study medication (HMR 3647 5 days + placebo 5 days)
b Number of days between first dose and last dose of active medication

The cumulative number of days of active treatment derived from the median number of doses of active treatment was 4.9 days in the HMR 3647 5-d group and 9.9 days in the HMR 3647 10-d group in the safety population.

### Adverse events

Adverse events are presented by body system, both for all adverse events and all TEAEs irrespective of relationship to study medication and for possibly related adverse events. Serious adverse events are presented by seriousness criterion, according to whether the event occurred before, during or after treatment.

TEAEs are presented by body system, both for all TEAEs irrespective of relationship to study medication and for possibly related TEAEs (possibly related TEAEs includes all possibly related adverse events reported during the study). TEAEs are displayed by body system and intensity, for all TEAEs

and possibly related TEAEs. Body system tables are also included for all serious TEAEs, TEAEs by "other significant" adverse event criterion, TEAEs resulting in discontinuation of study medication and TEAEs that were medically important laboratory abnormalities.

### All adverse events

In all, 123 subjects had at least one adverse event (56 [33.7%] in the HMR 3647 5-d group; 67 [40.1%] in the HMR 3647 10-d group). The spectrum of all adverse events reported during the study was comparable to that for all TEAEs.

### All treatment-emergent adverse events

At least one treatment-emergent adverse event (TEAE), irrespective of relationship to study medication, was reported in 114 out of 333 subjects (34.2%). TEAEs by body system were as follows.

**TEAEs by body system**

| | Number of subjects (%) | | | |
|---|---|---|---|---|
| **Body system** | **HMR 3647 5-d** | | **HMR 3647 10-d** | |
| Total in safety population | 166 | (100.0%) | 167 | (100.0%) |
| Total with TEAEs | 50 | (30.1%) | 64 | (38.3%) |
| | | | | |
| Digestive system | 30 | (18.1%) | 37 | (22.2%) |
| Body as a whole | 8 | (4.8%) | 9 | (5.4%) |
| Urogenital system | 8 | (4.8%) | 5 | (3.0%) |
| Nervous system | 7 | (4.2%) | 8 | (4.8%) |
| Metabolic and nutritional Disorders | 5 | (3.0%) | 6 | (3.6%) |
| Special senses | 5 | (3.0%) | 3 | (1.8%) |
| Cardiovascular system | 2 | (1.2%) | 3 | (1.8%) |
| Skin and appendages | 2 | (1.2%) | 2 | (1.2%) |
| Respiratory system | 1 | (0.6%) | 3 | (1.8%) |
| Hemic and lymphatic system | 0 | (0.0%) | 2 | (1.2%) |
| Musculoskeletal system | 0 | (0.0%) | 1 | (0.6%) |

The Fisher's exact test indicated that there was no statistically significant difference between treatment groups in frequencies of TEAEs by body system.

TEAEs reported in at least 2% of subjects, irrespective of relationship to study medication, are summarized by treatment group in the table given below:

**TEAEs in ≥2% of subjects**

| | Number of subjects (%) | | | |
|---|---|---|---|---|
| **Adverse event** | **HMR 3647 5-d** | | **HMR 3647 10-d** | |
| Total in safety population | 166 | (100.0%) | 167 | (100.0%) |
| Total with TEAEs | 50 | (30.1%) | 64 | (38.3%) |
| | | | | |
| Diarrhea | 16 | (9.6%) | 22 | (13.2%) |
| Nausea | 8 | (4.8%) | 4 | (2.4%) |
| Vaginal moniliasis | 5 | (3.0%) | 3 | (1.8%) |
| ALT (SGPT) increased | 4 | (2.4%) | 1 | (0.6%) |
| Gastrointestinal pain | 3 | (1.8%) | 8 | (4.8%) |
| Vertigo | 1 | (0.6%) | 4 | (2.4%) |

Most of the TEAEs experienced by subjects were mild (HMR 3647 5-d, 54 events; HMR 3647 10-d, 59 events) or moderate (HMR 3647 5-d, 24 events; HMR 3647 10-d, 25 events) in intensity. One TEAE (vomiting) reported by one subject in the HMR 3647 5-d group and 5 TEAEs (diarrhea, nausea, gastrointestinal pain, liver function test abnormal and rhinitis) reported by four subjects in the HMR 3647 10-d group were considered severe in intensity.

Study medication was discontinued due to adverse events in seven (2.1%) subjects (6 [3.6%]subjects in the HMR 3647 5-d group; 1 [0.6%] subject in the HMR 3647 10-d group).

The body system in which TEAEs were most commonly reported was the digestive system.

Within the digestive system, diarrhea was the most common TEAE reported: (HMR 3647 5-d: 16 [9.6%]; HMR 3647 10-d: 22 [13.2%] (p=0.389, not statistically significant between treatment groups)), followed by nausea (HMR 3647 5-d: 8 [4.8%]; HMR 3647 10-d: 4 [2.4%]) and gastrointestinal pain (HMR 3647 5-d: 3 [1.8%]; HMR 3647 10-d: 8 [4.8%]).

Of the 16 (9.6%) subjects in the HMR 3647 5-d group with diarrhea, the event was of mild intensity for 12 subjects. Of the 22 (13.2%) subjects in the HMR 3647 10-d group with diarrhea, the event was of mild intensity for 14 subjects and severe intensity for one subject. None of the diarrhea events in either treatment group were reported as serious. Diarrhea led to discontinuation of study medication in one subject (1903/009) in the HMR 3647 5-d group.

Of the 8 (4.8%) subjects in the HMR 3647 5-d group with nausea, the event was of mild intensity for 4 subjects. Of the 4 (2.4%) subjects in the HMR 3647 10-d group with nausea, the event was of mild intensity for 3 subjects and severe intensity for one subject. None of the nausea events in either treatment group were reported as serious. Nausea led to

discontinuation of study medication in one subject (1903/009 who also discontinued study medication due to a diarrhea event) in the HMR 3647 5-d group.

Of the 3 (1.8%) subjects in the HMR 3647 5-d group with gastrointestinal pain, the event was of mild intensity for 2 subjects. Of the 8 (4.8%) subjects in the HMR 3647 10-d group with gastrointestinal pain, the event was of mild intensity for 4 subjects and severe intensity for one subject. None of the gastrointestinal pain events in either treatment group were reported as serious. Gastrointestinal pain led to discontinuation of study medication in one subject in the HMR 3647 10-d group.

After the digestive system, the body system in which TEAEs were most commonly reported was the "body as a whole" system, of which abdominal pain was the most common TEAE: (HMR 3647 5-d: 1 [0.6%]; HMR 3647 10-d: 3 [1.8%]). All abdominal pain events were of mild or moderate intensity, and none led to discontinuation of study medication.

Other frequent events included vaginal moniliasis, ALT/SGPT increased, and vertigo.

Of the 5 (3.0%) subjects in the HMR 3647 5-d group with vaginal moniliasis, the event was of mild intensity for all subjects. Of the 3 (1.8%) subjects in the HMR 3647 10-d group with vaginal moniliasis, the event was of mild intensity for one subject. None of the vaginal moniliasis events in either treatment group were reported as serious and none led to discontinuation of study medication.

Four (2.4%) subjects in the in the HMR 3647 5-d group and 1 (0.6%) subject in the HMR 3647 10-d group had an adverse event of ALT/SGPT increased. All of the events were of mild intensity, none led to discontinuation of study medication and none were reported as clinically noteworthy. Overall, the incidence of TEAEs related to the hepatic system was low in both treatment groups. Three (1.8%) subjects in the HMR 3647 10-d group had an adverse event of AST/SGOT increased (all of mild intensity) and one subject in each group had an event of alkaline phosphatase increased (moderate intensity in the HMR 3647 5-d group and mild intensity in the HMR 3647 10-d group). Two (1.2%) subjects in the HMR 3647 5-d group had an adverse event of liver function test abnormal (both moderate severity) compared with one (0.6%) subject in the HMR 3647 10-d group (severe intensity), and one (0.6%) subject in the in the HMR 3647 10-d group had an adverse event of liver damage (moderate intensity).

In the HMR 3647 5-d group, one (0.6%) subject (705/005) had an adverse event of vertigo, which was of moderate intensity and was reported as a