Physical examination

At the pretherapy/entry, on-therapy, and posttherapy/TOC visits, the subject underwent a full physical examination. A physical examination was also to have been performed at the final visit if the subject withdrew from the study or subsequent antibiotic therapy was initiated for treatment of AMS or at the posttherapy visit, if a visit were necessary. If pathologic findings emerged or worsened from the pretherapy/entry assessment, and the finding met the criteria for a serious adverse event, the appropriate procedures for reporting such events was followed If the finding did not meet serious criteria, a nonserious adverse event page of the case report form was completed.

Vital signs

The following vital signs were recorded in the case report form at the pretherapy/entry, on-therapy, end of therapy and posttherapy/TOC visits: heart rate, temperature, respiratory rate, and blood pressure. Vital signs were measured at the late posttherapy visit if the subject experienced worsening of clinical signs and symptoms and a change in antibiotic therapy was necessary.

Twelve-lead ECG

A 12-lead ECG was to be performed for each subject at the pretherapy/entry, on-therapy, and end-of-therapy visits. If no ECG were performed at the end-of-therapy visit or if an ECG were considered to be clinically important, an additional ECG was to be performed at the posttherapy/TOC visit. If an ECG were indicated but not performed at the posttherapy/TOC visit, the ECG was to be done at the late posttherapy visit.

The study protocol specified that subjects were to be excluded from the study if the pretherapy/entry QTc interval were > 450 msec and were to be discontinued from the study if the QTc interval were found to be > 500 msec. The exclusion and discontinuation requirements were modified by amendment no. 5 on 22 February 1999 as follows: the exclusion criteria for QTc interval of > 450 msec was removed and the discontinuation requirement was amended to require study discontinuation if the QTc interval was found to be > 500 msec and had increased from pretherapy/entry by 60 msec.

The ECG collection process was changed by amendment no. 2 on 20 July 1998. ECGs were performed at each study site and were transmitted to a central laboratory, — , where the ECG was initially machine read and the

results were faxed to the study site within 30 minutes. In addition, the ECG was read by a cardiologist at — and these results were faxed to the study sites within approximately two hours. In many cases, the initial machine read ECG results from — were used by the investigator to make subject management decisions such as, study entry or exclusion and continued study participation. If a study site entered a subject into the study based on the machine read ECG results and then received a different ECG result interpretation from the — cardiologist that affected inclusion/exclusion study criteria, the study site called the sponsor and a decision was made as to whether or not a waiver would be granted on a case by case basis.

The following ECG parameters were recorded in the '— ' database: PR interval duration, QRS interval duration, the longest and shortest QT interval duration and heart rate. — used the longest QT interval in the Bazett method to calculate a corrected QT (QTc) interval as follows: Bazett's QTc = uncorrected QT long interval divided by the square root of the RR interval.

To provide uniform evaluation and interpretation of ECG data across study sites and across clinical protocols, an independent cardiologist experienced in ECG analysis, Dr. — was hired by the sponsor to over-read all ECG data from subjects enrolled in the study. Without detail regarding subject demographics or history and blinded to study treatment, Dr. — interpreted the ECG recording and made any necessary changes to interval length (PR, QRS, QT short, and QT long) on a one-page form provided by — . This form was returned to — and any changes from Dr. — ECG over-read were added to the HMR ECG study database.

If Dr. — over-read a different value for either the QT long interval or the heart rate, the QTc was recalculated at using Dr. — values. The re-calculated QTc based on Dr — over-read was added to the HMR ECG database. The HMR ECG database maintained by — was electronically transferred to HMR and loaded into the clinical trial database.

Based on the recommendation of Dr — the ECG QTc analyses were performed using two methods for calculating QTc, the Bazett and Fridericia methods. The Bazett and Fridericia QTc values used in the ECG analyses were calculated by using the original Bazett and Fridericia formulas to calculate two QTc values, once using the QT long interval in the original formulas and a second time using the QT short interval in the original formulas. The results from both of the Bazett calculations were added together and then divided by two to arrive at the Bazett's QTc used in the ECG analyses. The same method was used to arrive at the Fridericia QTc used in the ECG analyses.

Pregnancy test

Urine pregnancy tests for females of childbearing potential were to be performed at pretherapy/entry at the study site. A serum pregnancy test was to be performed by the central laboratory (, at the pretherapy/entry and posttherapy/TOC visits or at late posttherapy if not done at posttherapy/ TOC. In addition, a serum pregnancy test was performed if the subject withdrew from the study or initiated subsequent antibiotic therapy for treatment of AMS. If the result of the pregnancy test was questionable or positive, the subject was to be discontinued from the study and every attempt was to be made to follow the subject to term.

Pharmacokinetic data

Blood samples (for plasma) were collected at the pretherapy/entry, on-therapy, and end of therapy visits. All subjects were to have blood samples taken, but only subjects randomized to HMR 3647 were to have their samples analyzed for HMR 3647 concentration.

Withdrawal and replacement procedures

As far as possible, all examinations scheduled for the posttherapy/TOC visit, including blood and urine samples for clinical laboratory testing and physical examination were to be performed on all subjects who received study medication but did not complete the study as scheduled according to the protocol. Additionally, a serum pregnancy test was to be done on females of childbearing potential.

Subjects could be withdrawn from study medication for the following reasons:

- At their own request, or at the request of their legally authorized representative.
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
- At the specific request of the sponsor.

Subjects were required to be withdrawn from study medication under the following circumstances:

- Pregnancy (every attempt was to be made to follow-up subjects who become pregnant to determine the outcome of the pregnancy).
- Deterioration of the clinical condition or delayed response—in the investigator's opinion—at least 48 hours after beginning study treatment (e.g., six doses of study medication and a new antibiotic therapy were considered necessary).

- Presence of a resistant pathogen that could be considered as causative (e.g., isolated from adequate sources), persistent pathogen, or superinfection. However, in the case of a clear clinical improvement, the originally assigned regimen could be continued at the discretion of the investigator.

The occurrence of alarming adverse event(s) that may have been related to study medication.

- QTc interval ≥500 msec and a 60 msec increase in the QTc value from the pretherapy/entry visit (added by protocol amendment no. 5, 22 February 1999).
- SGOT/AST or SGPT/ALT ≥3 x upper limit of reference range.
- Impaired renal function, as shown by creatinine clearance ≤50 mL/min.
- PT ratio of ≥1.3 times the control or INR of ≥1.3 times the control when ISI was 1.0, except for subjects receiving oral anticoagulants (added by protocol amendment no. 2, 20 July 1998).
- Addition of any oral or intravenous antibiotic during study medication administration.

In all cases, the reason for withdrawal was to be recorded in the case report form and in the subject's medical records. The subject was to be followed up to establish whether the reason was an adverse event and, if so, this was to be reported in accordance with the appropriate procedures.

The investigator was to make every effort to contact subjects lost to follow-up.

Subjects who withdrew or were lost to follow-up were not replaced, with the exception of 105 invalidated subjects who received study medication from the second packaging order (PK01732) and one subject who was randomized to expired study medication.

STATISTICAL PROCEDURES

Statistical analyses were performed by Biostatistics and Data Management at Hoechst Marion Roussel, Inc. in Romainville, France. All analyses were carried out using SAS Version 6.12 run under SAS HP-UX version C.

Analysis variables

Efficacy variables

The time windows for the posttherapy/TOC were changed from days 17 to 24 to days 17 to 21 and late posttherapy visits were changed from days 31 to 38 to days 31 to 36 by protocol amendment for the purposes of study conduct, to ensure that visits fell within a short time window for the majority of subjects.

However, the original time window of days 17 to 24 for posttherapy/TOC and an extended time window of days 31 to 45 for late posttherapy were used for the efficacy analyses. From this section onwards, the report will refer to the time windows used for the efficacy analyses.

The primary efficacy analysis variable was the clinical outcome at the posttherapy/TOC visit (days 17 to 24 inclusive), which was evaluated by the investigator according to the rules defined below.

Cure

- All AMS-related signs and symptoms had disappeared or had returned to the preinfection state and sinus X-ray findings showed no worsening

or

- AMS-related signs and symptoms had improved, sinus X-ray findings showed no worsening, and no subsequent antibiotic therapy was started for the treatment of the disease under investigation (postinfectious stigmata).

Failure

- All AMS-related signs and symptoms remained unchanged or had worsened and/or sinus X-ray findings had worsened

or

- the subject developed new clinical findings consistent with active infection/AMS

or

- the subject died due to a complication of AMS **or**
- a subsequent antibiotic was given for AMS or any other RTI up to the end of day 24, and if each of the following two conditions are met: (1) the subsequent antibiotic was not given because the study drug was stopped due to a laboratory exclusion criterion that was present at pretherapy/entry but was only identified after the start of study drug, and (2) the subsequent antibiotic was not given because the study drug was stopped due to an adverse event that was already present at or before pretherapy/entry (even if that adverse event worsened while the subject was taking study drug).

Indeterminate

- if circumstances precluded classification as cure or failure, such as missing posttreatment information or early discontinuation of treatment for reasons that were not drug related

or

- a subsequent antibiotic was given for any reason other than AMS or any other RTI.

or

- an adverse event was present at or before pretherapy/entry (regardless of whether it worsened or not during treatment) and led to discontinuation of study drug, and a subsequent antibiotic was started for treatment of AMS.*

or

- a laboratory measurement fulfilling an exclusion criterion at pretherapy/entry that was only identified after starting study drug and led to discontinuation of study drug, and a subsequent antibiotic was started for treatment of AMS.*

One of the secondary efficacy analysis variables was clinical outcome at the late posttherapy visit (days 31 to 45 inclusive), which was evaluated by the investigator according to the rules defined below.

Cure

- cure at posttherapy/TOC **and**
- no occurrence of a new infection as described below **and**
- no further antibiotic treatment for AMS or complications resulting from AMS.

Failure

- failure at posttherapy/TOC **or**
- relapse/reinfection: any occurrence of a new infection (AMS or other RTI) that led to the initiation of an antibiotic treatment between the posttherapy/TOC visit and the late posttherapy visit.

Indeterminate

- if circumstances precluded classification as cure or failure, such as missing follow-up visit or early discontinuation of treatment for reasons that are not drug related

or

- a subsequent antibiotic was given for any reason other than AMS or any other RTI between the posttherapy/TOC visit and the late posttherapy visit

Bacteriological outcome per subject was assessed in a blinded manner using an algorithm based on the definitions below. It was based on outcome per pathogen (considered as causative) isolated from the sinus puncture sample taken at the initial visit and on the isolation of any new pathogen from a sinus puncture taken during the course of treatment or the posttreatment period. Bacteriological outcome was also assessed per pathogen.

At posttherapy/TOC (days 17 to 24), bacteriological outcome by subject (categories in brackets and bold are the corresponding subcategories for the outcome by pathogen) was defined as follows:

Satisfactory if, at the posttreatment TOC culture:

- the causative pathogen was absent in a culture obtained during the posttherapy/TOC time window (days 17 to 24) and no subsequent antibiotic therapy was started prior to the culture being obtained **(eradication)**

or

- the subject had improved clinically to such an extent that a proper follow-up culture could not be obtained (no adequate sample for culture available because of clinical cure, no indication for an invasive procedure to obtain an appropriate sample) and no subsequent antibiotic therapy had been started up to the end of the posttherapy/TOC time window (day 24), and the maxillary sinus X-ray was not worsened **(presumed eradication*)**

or

- a bacterial strain other than the primary causative pathogen was isolated and subject had no signs or symptoms of active infection **(colonization)**.

Unsatisfactory if, at the posttherapy/TOC culture:

- the causative pathogen was still present, whether or not signs of infection were present, and was not confirmed absent in any previous culture, OR, the causative pathogen was present at a culture obtained before the posttherapy/TOC time window and a subsequent antibiotic for AMS or any other RTI was started within 48 hours **(persistence)**

or

- the causative pathogen was assumed to have persisted because a subsequent antibacterial therapy was started for AMS or any other RTI (e.g., due to clinical failure, presence of a resistant pathogen, discontinuation due to an adverse event, or noncompliance) before a posttherapy/TOC culture was obtained, OR the subject died due to AMS complications before a posttherapy/TOC culture was obtained, OR the causative pathogen was present at a culture obtained before the posttherapy/TOC time window and a subsequent antibiotic for AMS or any other RTI was started more than 48 hours later, OR there was no posttherapy/TOC culture available because of clinical resolution and the maxillary sinus X-ray at posttherapy/TOC was classified as worsened **(presumed persistence)**.

Or

- a new pathogen emerged during therapy (from the second day of treatment) or within 3 days after treatment had been completed, either at the sinuses or at a distant site with the emergence or worsening of associated clinical and laboratory evidence of infection, and a subsequent systemic antibacterial was prescribed for AMS or any other RTI **(superinfection)**

or

- elimination of the initial infecting organism was followed by replacement with a new species or with a new serotype or biotype of the same organism at the same site in the presence of signs and symptoms of AMS more than 3 days after the completion of therapy **(reinfection)**

or

- reappearance of the causative pretherapy/entry pathogen after eradication from the maxillary sinus i.e. the causative pathogen was

confirmed absent at a culture obtained before the posttherapy/TOC culture, and then present in the posttherapy/TOC culture **(recurrence*)**.

Indeterminate if it was not possible to categorize the microbiological outcome because of:

- withdrawal of the subject from the study before follow-up cultures could be obtained

or

- a subsequent antibiotic was given before the posttherapy/TOC sample was collected for any reason other than AMS or any other RTI, or the subject died due to a reason other than AMS or any other RTI before the posttherapy/TOC sample was collected, and at the previous visit the pathogen was absent or no bacteriological sample was collected because of clinical resolution

or

- a subsequent antibiotic was given during the posttherapy/TOC time window for any reason other than AMS or any other RTI, or the subject died during the posttherapy/TOC window due to a reason other than AMS or any other RTI, and no bacteriological sample was available at posttherapy/TOC because of clinical resolution

or

- an adverse event (other than AMS or any other RTI) occurred on therapy and led to discontinuation of study drug, and a subsequent antibiotic was started for treatment of AMS

or

- an adverse event (including possible complications of AMS) occurred on therapy, but it was already present at or before pretherapy/entry (regardless of whether it worsened or not during treatment) and led to discontinuation of study drug, and a subsequent antibiotic was started for treatment of AMS

or

- a laboratory measurement fulfilling an exclusion criterion at pretherapy/entry that was only identified after starting study drug and led to discontinuation of study drug, and a subsequent antibiotic was started for treatment of AMS.

At **late posttherapy** (days 31 to 45), bacteriological outcome by pathogen was assessed using similar categories to those at posttherapy/TOC, except that superinfection and colonization were not defined at late posttherapy. Bacteriological outcome by subject was defined based on the by-pathogen bacteriological outcome at late posttherapy and the by-subject bacteriological outcome at posttherapy/TOC, as follows:

Satisfactory

- Bacteriological outcome by subject at posttherapy/TOC was satisfactory (eradication, presumed eradication, or colonization)

and

- no recurrence or reinfection as described below **and**
- no subsequent antibiotic treatment for AMS.

Unsatisfactory

- Bacteriological outcome was **unsatisfactory** at posttherapy/TOC

or

- **Recurrence at LPT**: the by pathogen outcome at posttherapy/TOC was eradication, presumed eradication or recurrence and EITHER the causative pathogen was present in the late posttherapy culture (documented recurrence), OR a subsequent antibiotic was started for AMS or any other RTI between posttherapy/TOC and late posttherapy (recurrence – not documented)

or

- **Reinfection at LPT**: appearance of a new bacterial strain (or new serotype/biotype of the same organism isolated at inclusion) in presence of signs and symptoms of AMS from a culture obtained at late posttherapy

or

- **New antimicrobial during follow-up**: prescription of a subsequent antimicrobial during the follow-up period for an infection in the same maxillary sinus but without adequate cultures.

Indeterminate

If it was not possible to categorize the microbiological outcome because:

- a subsequent antibiotic was given between posttherapy/TOC and late posttherapy for any reason other than AMS or any other RTI, or the subject died between posttherapy/TOC and late posttherapy due to a

reason other than AMS or any other RTI, and the outcome at posttherapy/TOC was eradication, presumed eradication or colonization*

or

- of withdrawal of the subject from the study before follow-up cultures could be obtained

If more than one causative pathogen were isolated from the pretreatment culture(s) and the bacteriological outcome was not the same for all the pathogens, the subject was classified as unsatisfactory (multiple pathogens with partial eradication) if the outcome of at least one pathogen fell into this category.

Safety variables

Adverse events

All adverse events occurring during this study were separated into those occurring pretreatment, on-treatment, and posttreatment. For information regarding collection of adverse events.

- Pretreatment adverse events were defined as adverse events that started before the first dose of study medication and either did not continue after or did not worsen in intensity (severity or frequency) after first dose of study medication.
- Posttreatment adverse events were defined as adverse events that started at least seven (7) days following last dose of study medication and either were considered "not related" to study medication by the investigator or the causality assessment was missing.
- On treatment adverse events were defined as adverse events that were not considered pretreatment or posttreatment adverse events. Note that adverse events occurring more than seven (7) days after the last dose of study medication and assessed by the investigator as possibly related to study medication are considered on treatment.

In addition, all on-treatment events were classified as treatment-emergent or nontreatment-emergent. The following definitions were used:

- Treatment emergent adverse events (TEAEs) include any ontreatment adverse event that was not present before treatment or was present before treatment and became more intense (increased in severity or frequency) during the treatment period, as determined by the investigator. The treatment period included the first day of study medication to 7 days after the last day of study medication. In addition, any on-treatment adverse event considered possibly related to study medication by the investigator, which led to permanent discontinuation of study medication, or resulted

in death was considered treatment-emergent. This group of adverse events is of primary interest.

- Possibly related treatment-emergent adverse events are those treatment-emergent adverse events the investigator reported as "possibly related" to study medication and those on-treatment adverse events with missing causality.

The primary determination of causality for adverse events was made by the investigator and was limited to "possibly related" or "not related" to study medication. These assessments of drug relatedness were individually reviewed by the sponsor for each serious adverse event. All assessments of serious adverse events presented in the safety tables of this report are those of the investigator.

Laboratory safety variables

The following definitions were used when screening all laboratory data to identify potentially important individual laboratory values:

- **Abnormal value**. Any value outside the normal or extended range defined, except for serum creatinine, for which local laboratory ranges are used. Where possible, predefined extended normal ranges were chosen rather than laboratory normal ranges. The extended normal ranges were adapted for laboratory analytes, which are commonly out of the normal range due to the underlying infectious disease. An extended normal range was used for hemoglobin, leukocytes, neutrophils, eosinophils, platelets, prothrombin time, INR, SGPT/ALT, SGOT/AST, alkaline phosphatase, bilirubin, creatinine clearance and potassium.

- **Predefined change abnormal (PCA).**

- A PCA increase is a laboratory value that is abnormally high **and** is an increase from pretherapy/entry of at least a predefined amount.

- A PCA decrease is a laboratory value that is abnormally low **and** is a decrease from pretherapy/entry of at least a predefined amount.

PCAs were derived from values of tests taken up to 7 days after last dose of study medication.

- **Last evaluation predefined change abnormal (LPCA).**

An LPCA is a PCA occurring at the subject's last evaluation on treatment. The LPCAs were determined for two different scenarios:

(1) LPCA1 - where "final evaluation on treatment" means last day of active study drug.

A time window of Day 3 until 5 days after the last day of active study drug was applied, and the laboratory evaluation in that window that was closest to the last day of active study drug was assessed as a potential LPCA. If two evaluations occurred the same number of days from the last day of active study drug, one before and one after, then the one before last day of active study drug was considered. Note that for subjects whose last day of active study drug was day 5 (i.e. most subjects in the HMR 3647 5-d group), the window would be Day 3 to Day 10. For subjects whose last day of active study drug was day 10 (i.e. most subjects in the HMR 3647 10-d group and in the AMC group), the window would be Day 3 to Day 15. LPCA1 enabled a comparison of laboratory values at the end of active study drug in each treatment group.
[However, it should be borne in mind that owing to the timing of visits in this trial, it was most frequently a comparison of the on-therapy laboratory assessment (Days 3-5) for the HMR 3647 5-d group with the end of therapy laboratory evaluation (Days 11-13) for the HMR 3647 10-d group and the AMC group].

(2) LPCA2 - where "final evaluation on treatment" means last day of study drug.

A time window of Day 3 until 7 days after the last day of study drug was applied, and the laboratory evaluation in that window that was closest to the last day of study drug was assessed as a potential LPCA. If two evaluations occurred the same number of days from the last day of active study drug, one before and one after, then the one after last day of active study drug was considered.
Note that for subjects whose last day of study drug was Day 10 (i.e. most subjects in each of the three treatment groups) the window would be Day 3 to Day 17.

- Clinically noteworthy abnormal laboratory values. These are PCA's or other abnormal laboratory values considered medically important by the sponsor according to predefined criteria (assessed during the period from day 1 until 7 days after the last intake of study medication).

Other safety variables

The primary ECG parameter of interest in the safety analysis was the QT interval corrected for heart rate (QTc).

The QTc interval was calculated by using the Bazett method as follows: Bazett's QTc = uncorrected QT long interval divided by the square root of the RR interval.

Based on the recommendation of Dr — , the ECG QTc analyses were performed using two methods for calculating QTc, the Bazett and Fridericia methods.

The Fridericia method is presented in the ECG analyses of this report as a comparative method for calculating QTc because it is considered to be a more accurate when the heart rate is high. The method for calculating the Fridericia QTc as follows: Fridericia QTc = uncorrected QT divided by the cubed root of the RR interval.

The Bazett and Fridericia QTc values used in the ECG analyses were calculated by using the original Bazett and Fridericia formulas to calculate two QTc values, once using the QT long interval in the original formulas and a second time using the QT short interval in the original formulas. The results from both of the Bazett calculations were added together and then divided by two to arrive at the Bazett QTc used in the ECG analyses. The same method was used to arrive at the Fridericia QTc used in the ECG analyses.

The Bazett and Fridericia QTc intervals (each using the QT long and short) and were examined for clinically relevant findings. Summary statistics (mean, standard deviation, median, maximum and minimum) were calculated at each visit, and evaluated for changes from pretherapy/entry.

Variable	Predefined change (PC)	Clinically noteworthy criteria
QTc interval	≥ 30 msec and < 60 msec (slight increase) ≥ 60 msec (clear increase)	≥ 500 msec

Clinically noteworthy QTc interval values identified from the Bazett QTc (using the QT long and short intervals) are described and discussed for each subject individually. The initial QTc interval as read by the cardiologist at — as well as the over-read QTc interval by the consultant cardiologist are included in the adverse event narrative for subjects who were discontinued due to a clinically noteworthy QTc value.

Study populations

Subject disposition was defined and documented prior to unblinding the database. Protocol deviations were evaluated on a case-by-case basis and disposition codes were assigned for all subjects. The following study populations were analyzed:

- **Modified intent-to-treat (mITT) populations:**

- mITT, defined as modified intent-to-treat population, all randomized subjects, as treated, who received at least one dose of study medication and had signs and symptoms of AMS and radiological findings supporting the diagnosis of AMS. Note that "received at least one dose of study medication" means study medication that had not expired or degraded – therefore subjects treated with study medication from packaging order PK01732 were excluded from the mITT population (see amendment no. 3, 7 December 1998).
- bmITT, defined as bacteriological modified intent-to-treat population, all mITT subjects with a bacteriological sample performed at pretherapy/entry and containing at least one pathogen that was considered by the investigator to be "responsible for infection".

- **Per-protocol (PP) populations:**

- PPc, defined as per protocol population for analysis of clinical outcome; all mITT subjects excluding those with major protocol violations (see below).

- PPb, defined as per protocol population for analysis of bacteriological outcome; all PPc subjects with a bacteriologically proven infection (isolation of a causative pathogen in an adequate pretreatment culture collected within 48 hours of the first dose of study medication), and who have a bacteriological sample collected in the TOC window (i.e., days 17 to 24 inclusive) that is classifiable (i.e., not indeterminate), except (i) subjects with unsatisfactory response that occur before day 17, as unsatisfactory response is carried forward, and (ii) subjects with no sample collected at TOC because of clinical resolution who had a causative pathogen isolated at pretherapy/entry.

- **Safety evaluable population:** all subjects, as treated, who received at least one dose of study medication and had at least one post pretherapy/entry safety assessment.

The primary analysis was based on the clinical outcome in the PPc population. Assignment of subjects to analysis populations was performed and documented before the database was unblinded.

As a supportive analysis, clinical outcome at posttherapy/TOC for the classic definition of the intent-to-treat (ITT) population, i.e., all randomized subjects analyzed as randomized, was also analyzed to confirm that the results were independent of the choice of mITT population.

Major protocol violations

Subjects who fell into any of the following categories (detailed in the final analysis plan prior to the unblinding of the database) were classified as subjects with major protocol violations and were not eligible for the PPc or PPb populations:

- Previous antimicrobial therapy
- Received treatment with other systemic (oral or parenteral) antibiotics within 7 days prior to enrollment.
- Received previous treatment with AMC for this infectious episode of AMS.
- Insufficient treatment duration:
- Missed the morning dose on day 1.
- Less than 2 days of complete dosing of study drug within the first 2 days (i.e., 6 consecutive doses during the first 2 days). Subjects whose first dose is on the morning of day 1 are expected to complete 6 consecutive doses (i.e., 12 capsules) on the evening of day 2.

Subjects whose first dose is on the afternoon or evening of day 1 will take the morning dose from day 1 and possibly the midday or evening dose from day 1; they are expected to complete 6 consecutive doses (12 capsules) by either the morning or midday of day 3, depending on how many doses were taken on day 1.

- Less than 5 days of complete dosing of study drug within the first 5 days (i.e., 15 consecutive doses during the first 5 days), except failures occurring before the 15th consecutive dose since for these subjects it's impossible to have complete dosing during the first 5 days.
- Compliance over the first 10 days less than 70%, except failures that occur before the last dose on the 7th day (i.e. before the 21st consecutive dose) since for these subjects it's impossible to be 70% compliant in the first 10 days. Compliance is defined as the number of capsules taken as a percentage of the number planned, and "over the first 10 days" is the period between the first intake of study drug and the expected time of completing the intake of 30 doses (i.e., 60 capsules). Subjects whose first dose is on the morning of day 1 are expected to complete 30 consecutive doses (i.e., 60 capsules) on the evening of day 10. Subjects whose first dose is on the afternoon or evening of day 1 will take the morning dose from day 1 and possibly the midday or evening dose from day 1; they are expected to complete 30 consecutive doses (60 capsules) by either morning or midday of day 10, depending on how many doses were taken on day 1.
- Wrong entry diagnosis:

- Signs and symptoms at entry insufficient to meet inclusion criteria (i.e., the absence of all the following signs and symptoms, or the presence for 28 days or more of at least one of them: (1) purulent nasal discharge visualized in the middle meatus - right or left side, (2) purulent post nasal discharge, (3) nasal congestion, (4) maxillary tenderness, (5) maxillary toothache, (6) maxillary pain at percussion, (7) facial pain, pressure or tightness).
- Maxillary sinus X-ray at pretherapy/entry insufficient to meet inclusion criteria (i.e., absence of each of (1) air fluid level, (2) total sinus opacity and (3) $\geq$ 6 mm mucosal thickening [the latter was added by amendment no. 2, 20 July 1998]).
- Maxillary sinus X-ray at pretherapy/entry done more than 48 hours before the initiation of study medication.
- More than three episodes of sinusitis that required antibiotic therapy within 12 months prior to entry.
- Chronic sinusitis with symptoms lasting more than 28 days.
- Concomitant sphenoidal sinusitis or odontological infection requiring antibiotic or surgical therapy.
- Need of immediate surgical intervention for maxillary sinusitis.
- Nosocomial sinusitis.
- Use of nasal catheters, or nasotracheal or nasogastric intubation during the study.
- Immotile cilia syndrome, cystic fibrosis, obstructive anatomic lesions in nasopharynx such as nasal polyps, tumor and severe septal deviation.
- Nonbacterial sinusitis.
- Concomitant respiratory infection at entry.

- Previously enrolled and randomized in the study.
- Missing appropriate posttreatment information:
- Missing clinical assessment at posttherapy/TOC, or posttherapy/TOC visit outside days 17 to 24 inclusive (except failures that occur by the end of day 24, since failures were carried forward).
- Missing maxillary sinus X-ray at posttherapy/TOC (except (1) failures that occur by the end of day 24, or (2) subjects with clinical outcome at posttherapy/TOC of "return to preinfection state" or "improved" and a maxillary sinus x-ray from either visit 2, 3 or 5 classified as "improved").
- Use of nonstudy systemic antimicrobials between pretherapy/entry and posttherapy/TOC evaluation (except failures).
- Treatment unblinded before posttherapy/TOC visit.
- Inability to determine treatment outcome at posttherapy/TOC (i.e., classified as indeterminate at posttherapy/TOC).

- Treatment discontinued *a posteriori* because of laboratory exclusion criteria at pretherapy/entry:
- Creatinine clearance ≤50 mL/min
- Liver enzymes (ALT or AST) >2 times upper limit of normal

Minor protocol violations

Subjects who fulfilled the following were classified as subjects with minor protocol violations; they were not excluded from the PPc population:

- QTc > 450 msec at entry
- impaired renal function as shown by creatinine clearance ≤ 50 mL/min at entry
- INR or PT ratio ≥ 1.3 times upper limit of reference range at entry
- ALT or AST ≥ 2 times upper limit of reference range at entry
- bilirubin > upper limit of reference range at entry (except for Gilbert's disease)
- alkaline phosphatase ≥ 1.25 times upper limit of reference range
- neutropenia (< 1500 neutrophils / mm^3) at entry
- maintenance corticosteroid therapy either inhaled nasal or systemic
- TOC visit between days 22 and 24 inclusive (except failures that occur by the end of day 21, as failures are carried forward)

Statistical methods

Analysis of baseline data

In each population described above, the pretherapy/entry (i.e., baseline) variables were summarized by treatment group using means, standard deviation, medians, minima and maxima for continuous variables, and frequencies and percentages for categorical variables.

Pretherapy/entry data were summarized separately for the invalidated subjects who received study medication from the second packaging order (PK01732) (amendment no. 3, 7 December 1998) and the one subject who was randomized to expired study medication from the first packaging order.

The continuous variables age, body mass index and weight recorded before treatment were compared for between-group homogeneity using analysis of variance (ANOVA) with treatment group as a factor. The Cochran-Mantel-Haenszel test (CMH) was used for the following categorical data: sex; age ≥ 65; race; smoking status; number of sinusitis episodes in last year; nasal septal deviation; history of asthma; history of allergic rhinitis; duration of current episode; AMS intensity; sinus X-ray findings; and concomitant use of corticosteroids, local vasoconstrictors and/or NSAIDs. In each case, all three treatment groups were compared in a single model.

Centers with less than 18 randomized subjects (i.e., six blocks) were pooled with other small centers in the same geographic region. If the number of subjects within a geographic region were less than 18, the geographic region was combined with the smallest centers in a second geographic region.

Analysis of efficacy data

For details of the statistical analyses, please refer to review by Dr. George Rochester.

The primary efficacy analysis was to demonstrate equivalence of the clinical cure rates at posttherapy/TOC in the PPc population. A similar analysis was also performed for the mITT population.

According to the protocol, the posttherapy/TOC visit was to be performed between days 17 and 24. During the first month of the study, this window was amended to days 17 to 21 for the purposes of study conduct (protocol amendment no. 2, 20 July 1998), in an attempt to improve the homogeneity of the subject population. However, for the PPc and PPb analyses, all data within the original 8-day window of days 17 to 24 were valid for the test of cure assessment, and therefore this window was used for the primary efficacy analysis. Likewise, the time window for the late posttherapy visit was changed by protocol amendment to days 31 to 36; however, an extended time window of days 31 to 45 was used for the PPc and PPb analyses. This wider interval was used to accommodate the more erratic visit timing at late posttherapy compared to posttherapy/TOC, and to ensure that relapses occurring later would be included in the per protocol analysis. There is no risk of bias by using this wider interval since it is applied to all three treatment groups. All data, including data outside the time windows, were used for the mITT and bmITT analyses.

The two treatments were considered equivalent if the lower limit was -15% or greater and the upper limit crossed zero.

The treatment difference between the HMR 3647 5-d group and the AMC group, and the associated confidence interval, were calculated in the same way.

A closed procedure was used to control for multiple comparisons. The first comparison in the closed procedure was a comparison of the HMR 3647 10-d group versus the AMC group. If the two-sided 95% confidence interval method did not conclude equivalence, then testing was stopped with the conclusion that neither 10 days nor 5 days of HMR 3647 were equivalent to AMC given for 10 days. If the first comparison concluded equivalence, then a second comparison of the HMR 3647 5-d group with the AMC group was

reported. Conclusions were drawn accordingly, with no adjustment to the Type I error rate (confidence interval coverage probability) required to maintain the overall probability of incorrectly concluding equivalence at less than or equal to 2.5%, one-sided.
The Breslow-Day test was used to test the homogeneity of treatment effect across centers.

The secondary analysis variables, including clinical outcome at late posttherapy in the PPc population, and clinical outcome at posttherapy/TOC and late posttherapy in the mITT population, were analyzed using the confidence interval approach similar to the analysis of the primary efficacy parameter. Bacteriological outcome was analyzed for the PPb and bmITT populations at posttherapy/TOC and late posttherapy, and confidence intervals of the difference in rates of satisfactory outcome were presented.

In addition, the bacteriological outcome at posttherapy/TOC was displayed for each causative pathogen separately (evaluation per pathogen: eradication, presumed eradication, persistence, presumed persistence, recurrence. Superinfection and colonization were reported irrespective of the eligibility status of the patient (e.g., appropriate pretherapy/entry sample performed and known to be sterile). Indeterminate outcomes were excluded from the analysis of bacteriological response by pathogen in the bmITT analyses. Development of antimicrobial resistance determined by susceptibility testing during treatment, and at posttherapy/TOC or late posttherapy including persistent pathogens was summarized. All statistical analyses were performed using a two-tailed 5% significance level.

The numbers of subjects with a positive therapeutic outcome (i.e., clinical outcome of cure and bacteriological outcome of satisfactory), were presented by treatment group.

Clinical outcome for the classic ITT population was shown at posttherapy/TOC.

Subjects whose posttherapy/TOC or late posttherapy visit was missing or out of the time window were handled as follows:

For subjects who had no posttherapy/TOC visit, clinical outcome was handled as follows:

- If the subject were considered by the investigator to be a clinical failure at any previous visit occurring up to day 24 (i.e., had a subsequent antibiotic started for AMS or any other RTI, had new clinical findings, or died due to AMS), the subject was considered a failure at posttherapy/TOC

- In all other cases where the posttherapy/TOC visit was missing, the subject was considered to have a clinical outcome of indeterminate at posttherapy/TOC.

Similarly, for subjects who had no late posttherapy visit, clinical outcome was handled as follows:

- If the subject were considered by the investigator to be a clinical failure at posttherapy/TOC, the subject was also considered a failure at late posttherapy
- In all other cases where the late posttherapy visit was missing, the subject was considered to have a clinical outcome of indeterminate at late posttherapy.

Thus, for the PPc analysis of clinical outcome, subjects with a missing posttherapy/TOC or late posttherapy visit and a previous outcome of failure were included in the PPc population, whereas indeterminate outcomes were excluded from the PPc population.

Subjects with the posttherapy/TOC visit outside the time window and an outcome of cure or indeterminate were also excluded from the PPc analysis since this was a protocol violation; subjects with outcome failure and with the posttherapy/TOC visit outside the time window were included as failure at posttherapy/TOC in the PPc analysis only if the visit was before the posttherapy/TOC time window, otherwise they were excluded. Similarly, subjects with the late posttherapy visit outside the time window and an outcome of cure or indeterminate at late posttherapy were excluded from the PPc analysis at late posttherapy, whereas subjects with outcome failure at late posttherapy outside the time window were included as failure at late posttherapy in the PPc analysis at late posttherapy only if the visit was before the late posttherapy time window, otherwise they were excluded.

For the mITT analysis, no reference was made to time windows, thus subjects with a posttherapy/ TOC or late posttherapy visit outside the time window were analyzed for clinical outcome as if the visit were within the time window, i.e., as the data appear in the study book.

For bacteriological response of subjects with the posttherapy/TOC visit missing or outside the time window of days 17 to 24, a classification could still be made if, prior to the last day of the posttherapy/TOC window, the subject received a new antibiotic for AMS or any other respiratory tract infection or the subject died due to AMS. In these cases, a bacteriological outcome of unsatisfactory was carried forward to posttherapy/TOC. In all other cases where the posttherapy/TOC visit was missing or outside the time window, the subject was excluded from the PPb analysis. For the bmITT analysis no reference to time windows was made; if the posttherapy/TOC

bacteriological sample was collected outside the time window then the bacteriological response was retained and analysed as if the visit were within the time window.

For bacteriological response of subjects with the late posttherapy visit missing or outside the time window of days 31 to 45, subjects with outcome unsatisfactory at posttherapy/TOC were classified as outcome unsatisfactory at late posttherapy. In addition, if prior to the last day of the late posttherapy window, the subject received a new antibiotic for AMS or any other respiratory tract infection or the subject died due to AMS, then a bacteriological response of failure at late posttherapy was assigned. In all other cases where the late posttherapy visit was missing or outside the time window, the subject was excluded from the PPb analysis. For the bmITT analysis no reference to time windows was made; if the late posttherapy bacteriological sample was collected outside the time window then the bacteriological response was retained and analysed as if the visit were within the time window.

The clinical outcome at posttherapy/TOC was summarized for subjects with pathogens of importance in AMS and across other subgroups of interest in the PPc population. The subgroups analyzed were as follows:

- Pathogens of importance in AMS: *Streptococcus pneumoniae* (total and according to sensitivity to penicillin or erythromycin), *Haemophilus influenzae* (total, according to sensitivity to azithromycin, beta-lactamase producers, beta-lactamase nonproducers and sensitivity to ampicillin), and *Moraxella catarrhalis*.
- Demographic characteristics: sex, age (<65 years, ≥65 years), race (white, black, Asian/Oriental, multiracial), smoking status (current/ex/never).
- General risk factors for morbidity: none, one, more than one.
- Characteristics of current infection and AMS-specific prognostic factors: number of sinusitis 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 or severe; or no = absent); ENT-related surgical history; duration of current AMS episode (1 to 3 days, 4 to 6, ≥7 days); previous antimicrobial medication (received systemic antibiotics within the 7 days prior to entry); investigator's assessment of intensity (mild/moderate/severe); fever (yes/no); sinus X-ray findings: unilateral/bilateral, mucosal thickening ≥6 mm (yes/no), air fluid level (yes/no) and total opacity (yes/no). An exploratory analysis of the influence of the following predefined characteristics of current infection and AMS-specific prognostic factors on clinical outcome was performed by logistic regression: age; sex; race; smoking status; body mass index; ENT-related

surgical history; AMS in last year; history of asthma; nasal septal deviation; duration of current AMS episode; intensity of current AMS infection; fever and sinus X-ray findings. A forward stepwise procedure was used, with a level of $p \leq 0.1$ for entry into the model and $p > 0.1$ for removal from the model. This regression analysis was performed comparing the HMR 3647 10-d group to the AMC group. In addition, if these two treatment groups were declared as equivalent by the primary efficacy analysis, then a separate logistic regression analysis was performed comparing the HMR 3647 5-d group to the AMC group.

Exploratory analyses were also performed to verify consistency and robustness of results. These included repetition of the efficacy analysis using the narrower time windows of days 17 to 21 for the posttherapy/TOC visit and days 31 to 36 for the late posttherapy visit.

Analysis of safety data

Adverse events

All adverse events (AEs) emerging or worsening during the study period (i.e., from the time of informed consent to the late posttherapy visit) are included in the analysis. Events occurring after the late posttherapy visit that the investigator considered necessary to be reported as an AE are also included. Tables of all TEAEs, all possibly related TEAEs, all TEAEs classified by intensity, all serious TEAEs, and all other significant TEAEs are provided by body system for comparisons between the treatment groups. Corresponding subject listings are also provided. Whenever it was possible for the investigator to group the signs and symptoms as a syndrome or diagnosis, only the diagnosis/syndrome is evaluated in the adverse event summary tables.

Fisher's exact test was used as a descriptive measure to flag imbalances in frequency between treatment groups. This test was reported twice for each coded term, comparing the HMR 3647 5-d group to the AMC group and comparing the HMR 3647 10-d group to the AMC group.

Laboratory variables

Two approaches were used to summarize laboratory data.

First, summary statistics were determined (mean, standard deviation, median, minimum and maximum). These were calculated for all variables measured before, during and after treatment, and for changes from pretherapy/entry, using the following time windows:

Time window used in safety Visit	analysis
Pretherapy/entry	day –2 to day 2
On-therapy	day 3 to day 7
Last Observation Evaluable On-Therapy – LPCA1	day 3 to (LASTACT + 5)
Last Observation Evaluable On-Therapy – LPCA2	day 3 to (LASTDAY + 7)
Posttherapy/TOC (LASTDAY + 8) to	LPT visit date

LASTACT = the last day of *active* study drug LASTDAY = the last day of study drug

In the second, potentially important individual laboratory values (PCAs and LPCAs) were flagged. The numbers of subjects with PCAs and LPCAs were counted per variable, and the percentages of PCAs were compared between the treatment groups at on-therapy, last observation evaluable on-therapy (LPCA1 and LPCA2), and at last evaluation. Fisher's exact test was used as a descriptive measure to flag imbalances in frequency between treatment groups. This test was reported twice for each of the variables, once comparing the HMR 3647 5-d group to the AMC group and once comparing the HMR 3647 10-d group to the AMC group. Clinically noteworthy abnormal laboratory values were described and discussed for each subject individually.

Vital signs

Summary statistics are presented for selected vital signs (heart rate, blood pressure, RR interval of expert ECG reading) comparing the findings at pretherapy/entry and follow-up visits. Summary statistics (mean, standard deviation, median, minimum and maximum) were calculated for each variable using the same time windows as for laboratory variables (see 'Laboratory variables' in this section) and for changes from pretherapy/entry.

For heart rate and blood pressure (systolic and diastolic), frequencies of PCAs and LPCAs were compared between treatment groups using Fisher's exact test (2-tailed). This test will be reported twice for each PCA and LPCA, once comparing the HMR 3647 5-d group to the AMC group and once comparing the HMR 3647 10-d group to the AMC group. The P-values of these pairwise comparisons will be used as a descriptive measure to flag imbalances between treatment groups.

Twelve-lead ECG

The QTc findings are presented by treatment in summary statistics comparing the findings at pretherapy/entry and follow-up visits. Summary statistics (mean, standard deviation, median, minimum and maximum) were calculated for QTc at pretherapy/entry, on-therapy, and posttherapy and for changes from pretherapy/entry using the time windows described below. The results are displayed twice, once using a modified Bazett method, and once following a modified Fridericia method.

The time windows used in the safety analysis of ECGs were amended to better characterize the temporal relationship of the ECG variables with drug level. For the pretherapy/entry period, the latest ECG taken before the first dose of study medication was used (Day 1). However, if the Day 1 ECG was not available, then the ECG done on Day –1, or if not available, the ECG done on Day –2, or if not available, the ECG done on Day –3 was used in the analysis. For the on-therapy period, an ECG taken while the subject was on active treatment was used. If the patient had more than one ECG evaluation during the active treatment period, then the last assessment during the active treatment period was used in the descriptive statistics. For the posttherapy period, the ECG taken one day after the last dose of active treatment up to seven days after the last dose of study medication (including placebo) was used. If there were multiple ECG assessments during this period, the evaluation taken closest to the last dose of active study medication was used in the descriptive statistics.

The number of subjects with at least one predefined change (PC) for the QTc interval occurring on active treatment was compared between treatment groups using Fisher's exact test (2-tailed). All ECGs taken during the active treatment period were used in the analysis of PC. No LPCA comparison was performed. Clinically noteworthy abnormal laboratory values (CNALVs) for the QTc interval (Bazett and Fridericia) were presented for the on-therapy and posttherapy periods. All ECGs taken during these two periods were used in the analysis.

Pharmacokinetic data

The plasma HMR 3647 concentration-time data from this study were incorporated with plasma HMR 3647 concentration-time data from other multicenter trials into a pharmacokinetic/ pharmacodynamic (PK/PD) data set to allow for population PK/PD analysis. These results will be reported separately in a population pharmacokinetic/pharmacodynamic report. Detailed review of the pharmacokinetic data is done by Dr. Jenny Zheng.

RESULTS - STUDY SUBJECTS AND CONDUCT

Subject accounting

The first subject entered the study on 8 July 1998, and the last subject completed the study on 16 June 1999.

Subjects were enrolled at 69 centers in 5 countries; however 4 centers (165, 167, 193, and 395) enrolled but did not randomize any subjects. Center 189 enrolled the most subjects (73 subjects) and centers 193, 199 and 400 enrolled the least (1 subject each). For the efficacy analysis, centers were pooled by geographic region to give 24 pooled centers.

Subject disposition

Disposition of subjects	**Total**
Number of subjects enrolled	1244
Number of investigators (centers)	69
Number of investigators (centers) who randomized:	
less than 18 subjects randomized	56
18 or more subjects randomized	13
Number of investigator pools	24

Subject accounting

	HMR 3647 5-d	**HMR 3647 10-d**	**AMC**	**Total**
Enrolled	-	-	-	**1244 (100%)**
Randomized	258	270	263	**791 (100%)**
Treated	258	270	262	**790 (99.9%)**

Of the 1244 subjects enrolled (gave informed consent), only 791 (63.6%) were randomized. The primary reason for enrolled subjects not being randomized was lack of x-ray evidence of disease. The randomization sequence was not followed for 1 subject. Subject number 151/002 was enrolled at a site that also was enrolling subjects in study 3008 (HMR 3647 versus clarithromycin in GABHS pharyngitis/tonsillitis). This subject was accidently given drug meant for study 3008. The subject received clarithromycin. The subject is subsequently excluded from all tables in this report.

In total, 790 subjects were exposed to study medication (i.e., received at least one dose of HMR 3647 or AMC).

Completion of study

The numbers of subjects who actually completed study visits (as opposed to subjects whose missing outcome was carried forward from a previous visit) are given in the table below.

	Study completion status			
Subjects with:	**HMR 3647 5-d**	**HMR 3647 10-d**	**AMC**	**Total**
Actual pretherapy/entry visit	258 (100%)	270 (100%)	262 (100%)	**790 (100%)**
Actual on-therapy visit	255 (98.8%)	264 (97.8%)	254 (96.6%)	**773 (97.7%)**
Actual end of therapy visit	225 (87.2%)	242 (89.6%)	229 (87.1%)	**696 (88.0%)**
Actual posttherapy/TOC visit	210 (81.4%)	228 (84.4%)	200 (76.0%)	**638 (80.7%)**
Actual late posttherapy visit	176 (68.2%)	196 (72.6%)	173 (65.8%)	**545 (68.9%)**
Actual posttherapy/TOC and late posttherapy visits	175 (67.8%)	196 (72.6%)	173 (65.8%)	**544 (68.8%)**

Subjects who prematurely withdrew from the study or initiated subsequent antibiotic therapy for Acute Maxillary Sinusitis (AMS) were to complete the study visit procedures for the current or next scheduled visit (if the withdrawal or initiation occurred between visits) within 72 hours. In both cases, no other study visits were to be completed in the case report form. This resulted in fewer subjects actually completing the late posttherapy visit. Subjects who prematurely discontinued study medication and did not initiate subsequent antibiotic therapy for AMS were encouraged to continue with the remaining visits as scheduled in the protocol, even if they were clinical failures.

A total of 246 subjects (HMR 3647 5-d: 81; HMR 3647 10-d: 74; AMC: 91) withdrew after starting study medication.

Reason for withdrawal from study	Reasons for withdrawal from study Number of subjects HMR 3647 5-d		HMR 3647 10-d		AMC	
Total subjects treated	258	(100%)	270	(100%)	262	(100%)
Total subjects withdrawn from study [a]	81	(31.4%)	74	(27.4%)	91	(34.7%)
New adverse event or worsening of an existing adverse event	17	(6.6%)	19	(7.0%)	14	(5.3%)
Subject did not wish to continue in the study	2	(0.8%)	0	(0.0%)	7	(2.7%)
Subject lost to follow-up	5	(1.9%)	6	(2.2%)	7	(2.7%)
Administrative reasons	0	(0.0%)	0	(0.0%)	3	(1.1%)
Treatment failure/addition of subsequent antimicrobial	43	(16.7%)	40	(14.8%)	45	(17.2%)
X-ray findings insufficient to meet inclusion criteria [b]	9	(3.5%)	7	(2.6%)	8	(3.1%)
Exclusionary lab at pretherapy/entry [b]	4	(1.6%)	1	(0.4%)	5	(1.9%)
Other reasons	1	(0.4%)	1	(0.4%)	3	(1.1%)

[a] A subject could discontinue study medication but complete the study.
[b] One subject (168/002) met 2 exclusion criteria: exclusionary lab at pretherapy/entry and x-ray findings insufficient to meet inclusion criteria and is counted in both rows.

The numbers of subjects and the specific reasons for withdrawal due to "other reasons" were as follows: pregnancy-2 subjects, concomitant pneumonia at entry-1 subject, randomized to the second packaging order -1 subject (this subject was mistakenly categorized as "other" when all other discontinuations for this reason were categorized as "administrative"), and "husband threw away study medication"-1 subject.

Discontinuation of study medication

A total of 110 subjects discontinued study medication before completion of the assigned treatment duration (HMR 3647 5-d: 36; HMR 3647 10-d: 33; AMC: 41). Reasons for discontinuation of study medication were as follows:

Reasons for discontinuation of study medication Number of subjects							
Reason for discontinuation of study medication	**HMR 3647 5-d**		**HMR 3647 10-d**		**AMC**		**Total**
Total subjects treated	258	(100%)	270	(100%)	262	(100%)	**790 (100%)**
Total subjects discontinued study medication [a]	36	(14.0%)	33	(12.2%)	41	(15.6%)	**110 (13.9%)**
Efficacy reasons	2	(0.8%)	1	(0.4%)	3	(1.1%)	**6 (0.8%)**
Other Reasons	34	(13.1%)	32	(9.7%)	38	(14.5%)	**104 (13.2%)**
New adverse event or worsening of an existing adverse event	17	(6.6%)	19	(7.0%)	14	(5.3%)	**50 (6.3%)**
Pregnancy	1	(0.4%)	1	(0.4%)	0	(0.0%)	**2 (0.3%)**
Subject did not wish to continue in the study	1	(0.4%)	0	(0.0%)	6	(2.3%)	**7 (0.9%)**
Administrative reasons	0	(0.0%)	0	(0.0%)	2	(0.8%)	**2 (0.3%)**
X-ray findings insufficient to meet inclusion criteria	7	(2.7%)	7	(2.6%)	4	(1.5%)	**18 (2.3%)**
Lost to follow-up	3	(1.2%)	4	(1.5%)	5	(1.9%)	**12 (1.5%)**
Exclusionary labs at pretherapy/entry	4	(1.6%)	1	(0.4%)	5	(1.9%)	**10 (1.3%)**
Other reasons	1	(0.4%)	0	(0.0%)	2	(0.8%)	**3 (0.4%)**

[a] A subject may have had more than one reason for discontinuation.

Protocol deviations

Major protocol violations

There were 204 subjects with major protocol violations in 638 subjects in the mITT population. These subjects were excluded from the PPc population. Of the 790 subjects treated, 152 were excluded from the mITT population due to lack of x-ray findings of the disease or treatment with expired or degraded study medication. The major protocol violations were as follows:

Summary of major protocol violations and reasons for exclusion from mITT

Major protocol violations	HMR 3647 5-d	HMR 3647 10-d	AMC	TOTAL
Total treated	**258**	**270**	**262**	**790**
Total excluded from mITT analysis	**46**	**55**	**51**	**152**
Subjects without X-ray findings consistent with the indication	18	20	20	58
Treated with expired/degraded study medication	32	38	36	106
Total subjects in mITT analysis	**212 (100%)**	**215 (100%)**	**211 (100%)**	**638 (100%)**
Total excluded from PPc analysis	**63 (29.7%)**	**68 (31.6%)**	**73 (34.6%)**	**204 (32.0%)**
Previous antimicrobial therapy	2	0	1	3
Insufficient treatment duration	46	41	45	132
Wrong entry diagnosis	5	9	9	23
Missing appropriate posttreatment information	1	9	11	21
Concomitant antimicrobial therapy between pretherapy/entry and posttherapy/TOC visits (except failure)	1	3	2	6
Treatment unblinded before posttherapy/TOC	1	2	0	3
Inability to determine treatment outcome at posttherapy/TOC	6	4	8	18
Treatment discontinuation a posteriori due to baseline lab exclusion	3	1	3	7
Without x-ray within 2 days of entry	2	3	2	7
Total subjects in PPc analysis	**149 (70.3%)**	**147 (68.4%)**	**138 (65.4%)**	**434 (68.0%)**

Note: A 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 434 subjects eligible for the primary analysis (PPc) population:

- QTc > 450 msec at entry was observed in 3 subjects (all from HMR 3647 10-d group)
- maintenance corticosteroid therapy either inhaled nasal or systemic was observed in 25 subjects (HMR 3647 5-d: 8; HMR 3647 10-d: 8; AMC: 9)
- TOC visit between days 22 and 24 inclusive (except failures that occur by the end of day 21, as failures are carried forward) was observed in 37 subjects (HMR 3647 5-d: 14; HMR 3647 10-d: 12; AMC: 11)

Administration of study medication

Dosage and duration

There was no dosage adjustment allowed by protocol in this study.

Treatment duration in the mITT population was as follows:

Duration of treatment for the mITT population
Number of subjects (%)

Duration of treatment	HMR 3647 5-d Duration of Study(placebo) Medication	HMR 3647 5-d Duration of active study med	HMR 3647 10-d Duration of study medication	AMC Duration of Study Medication
Total subjects	212 (100%)	212 (100%)	215 (100%)	211 (100%)
<2 days	2 (0.9%)	2 (0.9%)	2 (0.9%)	3 (1.4%)
2 days	7 (3.3%)	7 (3.3%)	5 (2.3%)	0 (0.0%)
3 days	4 (1.9%)	4 (1.9%)	4 (1.9%)	4 (1.9%)
4 days	1 (0.5%)	1 (0.5%)	2 (0.9%)	6 (2.8%)
5 days	4 (1.9%)	196 (92.5%)	3 (1.4%)	5 (2.4%)
6 days	1 (0.5%)	0 (0.0%)	3 (1.4%)	0 (0.0%)
7 days	1 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
8 days	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
9 days	0 (0.0%)	0 (0.0%)	3 (1.4%)	0 (0.0%)
10 days	77 (36.3%)	0 (0.0%)	68 (31.6%)	63 (29.9%)
11 days	100 (47.2%)	0 (0.0%)	115 (53.5%)	114 (54.0%)
>11 days	12 (5.7%)	0 (0.0%)	9 (4.2%)	11 (5.2%)
Unknown	2 (0.9%)	2 (0.9%)	1 (0.5%)	2 (0.9%)
Median (days)	11.0	5.0	11.0	11.0
Range (days)	1 – 13	1 – 5	1 – 14	1 – 15
Mean + SD (days)	**9.9 ± 2.3**	**4.8 ± 0.7**	**10.0 ± 2.2**	**10.1 ± 2.2**

The median treatment duration was equal to 11 days in the HMR 3647 10-day group and the active control arm for subjects in the mITT population. Treatment duration was calculated as first day of treatment to last day of treatment inclusive. A treatment duration of 11 days occurred most frequently when the subject started treatment at midday or later on day 1 and continued until the medication finished on day 11. Note that the median duration of active treatment was necessarily shorter in the HMR 3647 5-d group.

In the PPc population the treatment duration was as follows:

Duration of treatment for the PPc population
Number of subjects (%)

Duration of treatment	HMR 3647 5-d Duration of Study(placebo) Medication	HMR 3647 5-d Duration of active study med	HMR 3647 10-d Duration of study medication	AMC Duration of study medication
Total subjects	149 (100%)	149 (100%)	147 (100%)	138 (100%)
2 days	1 (0.7%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
3 days	3 (2.0%)	3 (2.0%)	2 (1.4%)	0 (0.0%)
4 days	0 (0.0%)	0 (0.0%)	1 (0.7%)	2 (1.4%)
5 days	2 (1.3%)	145 (97.3%)	1 (0.7%)	3 (2.2%)
6 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
8 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
9 days	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
10 days	67 (45.0%)	0 (0.0%)	57 (38.8%)	48 (34.8%)
11 days	70 (47.0%)	0 (0.0%)	83 (56.5%)	79 (57.2%)
>11 days	6 (4.0%)	0 (0.0%)	2 (1.4%)	6 (4.3%)
Median (days)	11.0	5.0	11.0	11.0
Range (days)	2 – 12	2 – 5	3 – 12	4 – 13
Mean + SD (days)	**10.3 ± 1.5**	**4.9 ± 0.4**	**10.4 ± 1.2**	**10.5 ± 1.3**

The median treatment duration was equal to 11 days in both the HMR 3647 10-day treatment and AMC groups in the PPc population. The subjects in the PPc population who received less than 5 days of treatment were clinical failures (HMR 3647 5-d: 4 subjects; HMR 3647 10-d: 3 subjects; and, AMC: 2 subjects).

The median number of doses of active treatment in the PPc population was 5 in the HMR 3647 5-d group, 10 in the HMR 3647 10-d group and 30 in the AMC group. For clinically cured subjects in the PPc population, the mean number of active doses was 5, 10, and 29.8 in the HMR 3647 5-d, HMR 3647 10-d, and AMC groups, respectively.

In the PPc population, the cumulative number of days of active treatment, derived from the number of doses of active treatment divided by the number of planned doses per day, was 5 days for the HMR 3647 5-d group, 10 days for the HMR 3647 10-d group, and 10 days for the AMC treatment group. In the mITT population, the cumulative number of days of active treatment were 5, 10, and 10 for the HMR 3647 5-d, HMR 3647 10-d, and AMC groups, respectively.

Compliance

Compliance was measured by capsule counts at the on-therapy visit (days 3 to 5) and the end-of-therapy visit (days 11 to 13). In the mITT population,

76.0% of subjects (HMR 3647 5-d: 75.9%; HMR 3647 10-d: 78.6%; and AMC: 73.5%) took 100% of their medication during the first 5 days of treatment. During the first 10 days of treatment, 89.5% of subjects (HMR 3647 5-d: 89.2%; HMR 3647 10-d: 90.2%; and AMC: 89.1%) took at least 70% of their medication. *(Numbers include treatment with placebo.)*

Drug accountability

The investigator or pharmacist inventoried and acknowledged receipt of all shipments of study medication. Study medication was to be stored in accordance with the manufacturer's instructions, in a locked area with access restricted to designated study personnel. At the end of the study, all unused study medication and all medication containers were to be returned to the sponsor. The sponsor prepared and provided to the investigator a final report of drug accountability to the unit dose level.

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, bmITT, PPc and PPb populations. 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	AMC	Total
Total treated	258	270	262	790
mITT	212	215	211	638
bmITT	9	9	11	29
PPc	149	147	138	434
PPb	7	7	8	22
Safety	257	266	255	778

Of the subjects treated, 80.8% (HMR 3647 5-d: 82.2%; HMR 3647 10-d: 79.6%; and AMC: 80.5%) were included in the mITT analysis. The most common reasons for subjects to be excluded were lack of x-ray findings of disease when over-read by an expert radiologist and treatment with the second packaging order which included expired or degraded study medication.

Of the mITT subjects, 434 were included in the PPc analysis (HMR 3647 5-d: 149; HMR 3647 10-d: 147; AMC: 138). The most common reason for exclusion

from the PPc analysis was insufficient treatment duration (missed Day 1 morning dose, compliance less than 100% during first five days or compliance less than 70% during first 10 days). This reason accounted for the exclusion of 132 of the 204 subjects excluded from the PPc population. Forty-one subjects (HMR 3647 5-d: 15; HMR 10-d: 11; and, AMC: 15), predominantly from two centers (0150 and 0171, 25 subjects total), were excluded specifically for missing the morning dose on Day 1. As stated before, subjects who were 100% compliant in the first 48 hours and who were classified as clinical failures before the end of day 5 were retained in the PPc. The other common reasons for exclusion from the PPc analysis were wrong entry diagnosis (mostly sphenoidal sinusitis) and missing posttreatment information.

Sinus punctures were only performed at designated study centers. Of the 45 PPc subjects who underwent a sinus puncture procedure, 48.9% were included in the PPb analysis (HMR 3647 5-d group 46.7%, HMR 3647 10-d group 43.8%, and AMC 57.1%). The only reason for exclusion of a PPc subject from the PPb analysis was lack of a valid causative pathogen at study entry.

Of the subjects treated, 98.5% (HMR 3647 5-d group 99.6%, HMR 3647 10-d group 98.5%, and AMC 97.3%) were included in the safety analysis. Subjects were only excluded from the safety analysis if they did not have a post pretherapy/entry safety assessment.

MEDICAL OFFICER'S COMMENTS:

The Division of Scientific Investigations inspected several sites to validate the data collected by the applicant. Data from two sites (centers 150 and 191) could not be validated at the time of this review, so patients enrolled at those two sites have been excluded from all analyses performed by FDA. Through out this review, I will point out essential differences between the two data sets, and make appropriate comments if they are significant. The table below shows the number of patients that have been excluded from the FDA analysis. This table and all the following tables with FDA analysis were generated with the help of our staff statistician, Dr. George Rochester.

FDA's Number of evaluable subjects in the populations analyzed for efficacy and safety

	HMR-3647 5-Days	HMR-3647 10-Days	AMC 10-Days	Total
As Treated-Sponsor's	258	270	262	790
As treated – FDA	**245**	**257**	**251**	**753 (100%)**
MITT	202	204	202	608 (80.9 %)
PPc	147	141	137	425 (56.4%)
BmITT	9	9	11	29 (3.9%)
PPb	7	7	8	22 (2.9%)
Safety	244	253	244	741 (98.4%)

Demographics and baseline characteristics

The demographics and pretherapy/entry (i.e., baseline) characteristics of subjects eligible for the mITT population are summarized by treatment group in the following table:

Applicant's Demographics and pretherapy/entry characteristics – mITT Population

Characteristic	HMR 3647 5-d	HMR 3647 10-d	AMC
Total treated	212 (100%)	215 (100%)	211 (100%)
Sex:			
Male N (%)	101 (47.6%)	92 (42.8%)	78 (37.0%
Female N (%)	111 (52.4%)	123 (57.2%)	133 (63.0%)
Age (years):			
Median (range)	38 (18 – 69)	39 (18 – 84)	39 (16 – 79)
<65 years N (%)	201 (94.8%)	200 (93.0%)	205 (97.2%)
≥65 years N (%)	11 (5.2%)	15 (7.0%)	6 (2.8%)
BMI (kg/m^2):			
Mean ± SD	26.9 ± 5.7	27.2 ± 6.0	26.6 ± 5.4
Weight (kg):			
Mean ± SD	78.0 ± 17.7	78.2 ± 18.6	75.5 ± 17.3
Race:			
White N (%)	187 (88.2%)	191 (88.8%)	182 (86.3%)
Black N (%)	13 (6.1%)	19 (8.8%)	17 (8.1%)
Asian/Oriental N (%)	10 (4.7%)	3 (1.4%)	10 (4.7%)
Multiracial N (%)	2 (0.9%)	2 (0.9%)	2 (0.9%)
Smoking status:			
Smoker	58 (27.4%)	53 (24.7%)	52 (24.6%)
Ex-smoker	42 (19.8%)	44 (20.5%)	30 (14.2%)
Nonsmoker	112 (52.8%)	118 (54.9%)	129 (61.1%)

FDA's Demographic and baseline characteristics at the pre-therapy/entry visit for the mITT population

Characteristic	HMR-3647 5-Days	HMR-3647 10-Days	AMC 10-Days
Total	**202 (100%)**	**204 (100%)**	**202 (100%)**
Gender			
Male N (%)	93 (46.0%)	86 (42.0%)	70 (35.0%)
Female N (%)	109 (54.0%)	118 (58.0%)	132 (65.0%)
Age (years)			
Median (range)	37 (18-69)	39 (18-84)	38 (16-79)
< 65 years N (%)	191 (94.5%)	189 (92.6%)	196 (97.0%)
≥ 65 years N(%)	11 (5.5%)	15 (7.4%)	6 (3.0%)
Weight (Kg)			
Mean ± SD	77.7 ± 17.3	77.6 ± 17.8	75.1 ± 17.3
Race			
White N(%)	186 (92.1%)	187 (91.7%)	180 (89.1%)
Black N(%)	4 (2.0%)	12 (5.9%)	10 (5.0%)
Other N (%)	12 (5.9%)	5 (3.4%)	12 (5.9%)
Smoking Status			
Current smoker N (%)	49 (24.3%)	47 (23.0%)	45 (22.3%)
Ex-smoker N (%)	42 (20.7%)	42 (20.6%)	29 (14.4%)
Nonsmoker N(%)	109 (55.0%)	116 (56.9%)	128 (63.3%)

There were no differences between treatment groups in demographic and pretherapy/entry characteristics.

Primary disease

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

Applicant's Characteristics of current infection and AMS specific prognostic factors – mITT population

	Number of subjects					
	HMR 3647		HMR 3647			
Characteristics/prognostic factors:		**5-d**		**10-d**		**AMC**
Total number of subjects	**212**	**(100%)**	**215**	**(100%)**	**211**	**(100%)**
AMS episodes in the last year	70	(33.0%)	82	(38.1%)	79	(37.4%)
Number of AMS episodes requiring antibiotic treatment in last 12 months						
0	4	(5.7%)	2	(2.4%)	2	(2.5%)
1-3	66	(94.3%)	80	(97.6%)	77	(97.5%)
>3	0	(0.0%)	0	(0.0%)	0	(0.0%)
History of asthma?	30	(14.2%)	33	(15.3%)	27	(12.8%)
Episodes of allergic rhinitis in last 30 days?	34	(16.0%)	33	(15.3%)	37	(17.5%)
Nasal septal deviation:	51	(24.1%)	44	(20.5%)	41	(19.4%)
ENT related surgical history:	38	(17.9%)	39	(18.1%)	28	(13.3%)
Duration of current episode:						
1 to 3 days	22	(10.4%)	30	(14.0%)	23	(10.9%)
4 to 6 days	62	(29.2%)	56	(26.0%)	58	(27.5%)
7-14 days	87	(41.0%)	94	(43.7%)	104	(40.3%)
> 15 days	41	(19.3%)	35	(16.3%)	26	(12.3%)
Previous antibiotic therapy within 7 days prior to entry?	2	(0.9%)	0	(0.0%)	1	(0.5%)
Investigator assessment of current AMS episode:						
Mild	9	(4.2%)	13	(6.0%)	15	(7.1%)
Moderate	181	(85.4%)	172	(80.0%)	163	(77.3%)
Severe	22	(10.4%)	30	(14.0%)	33	(15.6%)
Fever:	5	(2.4%)	2	(0.9%)	3	(1.4%)
Sinus X-ray findings:						
Air fluid level						
Yes	59	(27.8%)	75	(34.9%)	86	(40.8%)
No	153	(72.2%)	140	(65.1%)	125	(59.2%)
Total opacity						
Yes	57	(26.9%)	51	(23.7%)	35	(16.6%)
No	155	(73.1%)	164	(76.3%)	176	(83.4%)
Mucosal thickening >= 6 mm						
Yes	151	(71.2%)	140	(65.1%)	145	(68.7%)
No	61	(28.8%)	75	(34.9%)	66	(31.3%)
Unilateral/Bilateral						
Unilateral	120	(56.6%)	132	(61.4%)	119	(56.4%)
Bilateral	92	(43.4%)	83	(38.6%)	92	(43.6%)
X-ray severity						
Air fluid level/total opacity with mucosal thickening >= 6 mm	51	(24.1%)	44	(20.5%)	50	(23.7%)
Air fluid level/total opacity without mucosal thickening >= 6 mm	61	(28.8%)	74	(34.4%)	66	(31.3%)
Mucosal thickening >= 6 mm only	100	(47.2%)	96	(44.7%)	95	(45.0%)
Other	0	(0.0%)	1	(0.5%)	0	(0.0%)

The duration of the current AMS episode was at least seven days for the majority of subjects.

Among the subjects in the mITT population, 3 subjects (0.5%) (HMR 3647 5-d: 2 [0.9%]; HMR 3647 10-d: 0 [0%]; AMC: 1 [0.5%]) had received a previous antimicrobial treatment in the 7 days before pretherapy/entry. Subjects who had antimicrobial treatment in the 7 days before pretherapy/entry were excluded from the PPc analysis. The remaining subjects did not receive any previous antimicrobial treatment. The antimicrobials during the 7 days prior

to pretherapy/entry were metronidazole for yeast infection, minocycline for acne rosaceae and clarithromycin for sinusitis.

Concomitant illnesses

In the mITT population, 43 (6.7%) subjects had at least one general risk factor for morbidity and 7 (1.1%) subjects had two or more risk factors for morbidity. The most common general risk factors in the mITT population were diabetes mellitus (14 subjects) and chronic obstructive pulmonary disease and allied conditions (13 subjects).

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

Concomitant medication

Overall, 460 subjects in the mITT population (HMR 3647 5-d group: 150 [70.8%]; HMR 3647 10-d group: 149 [69.3%]; AMC: 161 [76.3%]) received concomitant medication during treatment with study medication.

Concomitant nonantimicrobial medication

In the mITT population, 460 subjects (HMR 3647 5-d group: 150 [70.8%]; HMR 3647 10-d group: 149 [69.3%]; AMC: 161 [76.3%]) received concomitant nonantimicrobial medication during the treatment with study medication. The most commonly prescribed concomitant nonantimicrobial medication class was analgesics, taken by 184 (28.8%) subjects. With the exception of antihistamines for systemic use which were used in a higher percentage of subjects in the HMR 3647 5-d group (14.2%) than the HMR 3647 10-d group (7.9%), and AMC group (8.1%), the usage of concomitant medications which could affect sinusitis symptoms (i.e. analgesics, anti-inflammatory products, corticosteroids for systemic use, nasal preparations, and cough and cold preparations) was balanced between the 3 treatment groups.

Concomitant antimicrobial medication

No subjects in the mITT population received concomitant antimicrobial medication for AMS. There were no concomitant antimicrobial medications in the PPc, PPb or safety populations.

RESULTS – EFFICACY

Analyses of primary efficacy variable

Number of subjects included in analyses

The primary efficacy variable was clinical outcome 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:

Applicant's Number of subjects evaluable at posttherapy/TOC

	Number of subjects		
	HMR 3647	HMR 3647	
Population	**5-d**	**10-d**	**AMC**
PPc	149	147	138
mITT	212	215	211

FDA's Number of subjects evaluable at posttherapy/TOC

	Number of subjects		
	HMR 3647	HMR 3647	
Population	**5-d**	**10-d**	**AMC**
PPc	147	141	137
mITT	202	204	202

Applicant's Clinical outcome - assessment at posttherapy/TOC visit in the PPc population

The clinical outcome comparing HMR 3647 10-d with AMC at posttherapy/TOC in the PPc population is summarized in the table shown below:

Applicant's Clinical outcome at posttherapy/TOC – PPc population Number of subjects (%) HMR 3647						
Assessment	**10-d**		**AMC**		**Difference**	**95% CI [a]**
N	147		138			
Cure	109	(74.1%)	103	(74.6%)	-0.5	(-11.3, 10.4)
Returned to preinfection state	72		75			
Improved or postinfectious stigmata [b]	37		28			
Failure	38	(25.9%)	35	(25.4%)		

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

The response rates were 74.1% in the HMR 3647 10-d group and 74.6% in the AMC group, a difference between the groups of -0.5%. The 95% confidence interval of the difference was (-11.3%, 10.4%) – that is, the lower bound was greater than –15% and the upper bound was greater than 0, thereby demonstrating that the two treatment regimens were equivalent.
Among the 212 subjects assessed as cure in these two treatment groups, 72 subjects in the HMR 3647 10-d group and 75 subjects in the AMC group were classified as "returned to preinfection state", and 37 in the HMR 3647 10-d group and 28 in the AMC group were classified as "improved or postinfectious stigmata".

Of the 38 failures in the HMR 3647 10-d group and the 35 failures in the AMC group, 4 (10.5%) of the 38 in the HMR 3647 10-d group and 3 (8.6%) of the 35 in the AMC group failed secondary to discontinuation due to an adverse event not related to deterioration of clinical status, 3 (7.9%) and 4 (11.4%) failed due to development of another RTI which required treatment with a subsequent antimicrobial, 0 (0.0%) and 2 (5.7%) failed at the on therapy visit, 5 (13.2%) and 8 (22.9%) failed at the end of therapy visit, and 26 (68.4%) and 18 (51.4%) failed at the posttherapy/TOC visit, with 4 and 3 of these failures not receiving a subsequent antimicrobial for treatment of AMS. As previously noted, 5 (4.6%) HMR 3647 10-d subjects and 3 (2.9%) of the AMC subjects who were cures at posttherapy/TOC failed (relapsed) at late posttherapy.

FDA's Clinical response at the test-of-cure visit (TOCV) in patients treated with 10-Day HMR 3647 versus 10-Days of AMC

Assessment of Outcome	Number of Subjects (%) HMR-3647 10-Days	AMC 10-Days	% Difference	2-Sided 95% Confidence Interval
PPc population				
N	141	137		
Cure N (%)	102 (72.9%)	102 (74.5%)	-1.6 %	(-12.7%, 9.5%)
Failure N (%)	38 (27.1%)	35 (25.5%)		
mITT population				
N	204	202		
Cure N (%)	140 (68.6%)	138 (68.3%)	0.3%	(-9.2%, 9.8%)
Failure N (%)	64 (31.4%)	64 (31.7%)		
PPb[1] population				
N	7	8		
Cure N (%)	6 (85.7%)	6 (75.0%)	10.7 %	
Failure N (%)	1 (14.3%)	2 (25.0%)		

[1] *Confidence intervals not presented for PPb population since there is sparse data*

Owing to the equivalence between HMR 3647 10-d and AMC, the comparison between HMR 3647 5-d with AMC was also made. The clinical outcome comparing HMR 3647 5-d with AMC at posttherapy/TOC in the PPc population is summarized in the table shown below:

Applicant's Clinical outcome at posttherapy/TOC – PPc population Number of subjects (%)

Assessment	HMR 3647 5-d		AMC		Difference	95% CI [a]
N	149		138			
Cure	113	(75.8%)	103	(74.6%)	1.2	(-9.5, 11.9)
Returned to preinfection State	74		75			
Improved or postinfectious stigmata [b]	39		28			
Failure	36	(24.2%)	35	(25.4%)		

[a] Two-sided 95% confidence interval

[b] No nonstudy antimicrobial therapy started

The response rates were 75.8% in the HMR 3647 5-d group and 74.6% in the AMC group, a difference between the groups of 1.2%. The 95% confidence interval of the difference was (-9.5%, 11.9%) – that is, the lower bound was greater than –15% and the upper bound was greater than 0, thereby demonstrating that the two treatment regimens were equivalent.

Among the 216 subjects assessed as cure, 74 subjects in the HMR 3647 5-d group and 75 subjects in the AMC group were classified as "returned to pre-infection state", and 39 in the HMR 3647 5-d group and 28 in the AMC group were classified as "improved or postinfectious stigmata".

Of the 36 failures in the HMR 3647 5-d group, 4 (11.1%) of these 36 subjects failed secondary to discontinuation due to an adverse event not related to deterioration of clinical status, 2 (5.6%) failed due to development of another RTI which required treatment with a subsequent antimicrobial, 2 (5.6%) failed at the on therapy visit, 3 (8.3%) failed at the end of therapy visit, and 25 (69.4%) failed at the posttherapy/TOC visit, with 5 of these failures not receiving a subsequent antimicrobial for treatment of AMS. As noted previously, 5 (4.4%) of the subjects who were cures at posttherapy/TOC failed (relapsed) at late posttherapy.

FDA's Clinical response at the test-of-cure visit (TOCV) for the HMR 5-Day versus AMC 10-Day

Assessment of Outcome	Number of Subjects (%) HMR-3647 5-Days	Number of Subjects (%) AMC 10-Days	% Difference	2-Sided 95% Confidence Interval
PPc population				
N	146	137		
Cure N (%)	110 (75.3%)	102 (74.5%)	0.8%	(-9.9%, 11.7%)
Failure N (%)	36 (24.7%)	35 (25.5%)		
mITT population				
N	201	202		
Cure N (%)	140 (69.7%)	138 (68.3%)	1.4%	(-8.2%, 10.9%)
Failure N (%)	61 (30.3%)	64 (31.7%)		
PPb[1] population				
N	7	8		
Cure N (%)	6 (85.7%)	6 (75.0)	10.7%	
Failure N (%)	1 (14.3%)	2 (25.0%)		

[1] *Confidence intervals not presented for PPb population since there are sparse data*

Applicant's Clinical outcome – assessment at posttherapy/TOC in the mITT population

The clinical outcome comparing HMR 3647 10-d with AMC at posttherapy/TOC in the mITT population is summarized in the table shown below.

Applicant's Clinical outcome at posttherapy/TOC – mITT population Number of subjects (%)

Assessment	HMR 3647 10-d		AMC		Difference	95% CI [a]
N	215		211			
Cure	149	(69.3%)	144	(68.2%)	1.1	(-8.2, 10.3)
Returned to preinfection state	96		99			
Improved or postinfectious stigmata [b]	53		45			
Failure	66	(30.7%)	67	(31.8%)		
Failure	50		45			
Indeterminate	16		22			

[a] Two-sided 95% confidence interval

[b] No nonstudy antimicrobial therapy started

The response rates were 69.3% in the HMR 3647 10-d group and 68.2% in the AMC group, a difference between the groups of 1.1%. The 95% confidence interval of the difference was (-8.2%, 10.3%) – that is, the lower bound was greater than –15% and the upper bound was greater than 0, 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 38 subjects at posttherapy/TOC were: lost to follow-up (HMR 3647 10-d group – 5 subjects; AMC - 4 subjects); discontinued due to AE (with less than 48 hours of treatment or without subsequent antimicrobial for AMS or due to an AE present at pretherapy/entry) (HMR 3647 10-d group – 4 subjects; AMC - 5 subjects); discontinued *a posteriori* for laboratory exclusion criteria (HMR 3647 10-d group – 1 subject; AMC - 3 subjects); new antibiotic given to treat indication other than AMS or related infection (HMR 3647 10-d group –4 subjects; AMC - 2 subjects); subject did not wish to continue in the study (HMR 3647 10-d group –0 subjects; AMC - 4 subjects); no x-ray at TOC (HMR 3647 10-d group – 0 subjects; AMC - 2 subjects); positive pregnancy test (HMR 3647 10-d group – 1 subject; AMC - 0 subjects); discontinued due to a concomitant respiratory condition at entry (HMR 3647 10-d group – 1 subject; AMC - 1 subject); subject lost study drug (HMR 3647 10-d group – 0 subjects; AMC - 1 subject).

Of the 50 failures in the HMR 3647 10-d group and the 45 failures in the AMC group, 10 (20%) of the 50 failures in the HMR 3647 10-d group and 4 (8.9%) of the 45 failures in the AMC group failed secondary to discontinuation due to an adverse event not related to deterioration of clinical status, 3 (6%) and 5 (11.1%), respectively, failed due to development of another RTI which required treatment with a subsequent antimicrobial, 0 (0.0%) and 2 (4.4%) failed at the on therapy visit, 7 (14%) and 10 (22.2%) failed at the end of therapy visit, and 30 (60%) and 24 (53.3%) failed at the posttherapy/TOC visit, with 5 and 4 of these failures not receiving a subsequent antimicrobial for treatment of AMS. As noted previously, 8 (5.4%) and 5 (3.5%) of the subjects who were cures at posttherapy/TOC failed (relapsed) at late posttherapy.

The clinical outcome comparing HMR 3647 5-d with AMC at posttherapy/TOC in the mITT population is summarized in the table shown below:

Applicant's Clinical outcome at posttherapy/TOC – mITT population Number of subjects (%)

Assessment	HMR 3647 5-d		AMC		Difference	95% CI [a]
N	212		211			
Cure	148	(69.8%)	144	(68.2%)	1.6	(-7.7, 10.8)
Returned to preinfection state	95		99			
Improved or postinfectious Stigmata [b]	53		45			
Failure	64	(30.2%)	67	(31.8%)		
Failure	47		45			
Indeterminate	17		22			

[a] Two-sided 95% confidence interval

[b] No nonstudy antimicrobial therapy started

The response rates were 69.8% in the HMR 3647 5-d group and 68.2% in the AMC group, a difference between the groups of 1.6%. The 95% confidence interval of the difference was (-7.7%, 10.8%) – that is, the lower bound was greater than –15% and the upper bound was greater than 0, thereby providing further evidence that the two treatment regimens were equivalent. This result further supports the primary efficacy outcome in the PPc analysis.

Again, 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 17 subjects at posttherapy/TOC in the HMR 3647 5-d group were: lost to follow-up (5 subjects); discontinued due to AE (4 subjects); discontinued *a posteriori* for laboratory exclusion criteria (3 subjects); new antibiotic given to treat indication other than AMS or related infection (2 subjects); subject did not wish to continue in the study (1 subject); no X-ray at TOC (1 subject); positive pregnancy test (1 subject).

Of the 47 failures in the HMR 3647 5-d group, 9 (19.1%) failed secondary to discontinuation due to an adverse event not related to deterioration of clinical status, 3 (6.4%) failed due to development of another RTI which required treatment with a subsequent antimicrobial, 2 (4.3%) failed at the on therapy visit, 6 (12.8%) failed at the end of therapy visit, and 27 (57.4%) failed at the posttherapy/TOC visit, with 5 of these failures not receiving a subsequent antimicrobial for treatment of AMS. As noted previously, 6 (4.1%) of the subjects who were cures at posttherapy/TOC failed (relapsed) at late posttherapy.

Clinical outcome – other populations at posttherapy/TOC

Clinical outcome in the PPb population at posttherapy/TOC was cure for 6/7 subjects (85.7%) in the HMR 3647 5-d group, 6/7 subjects (85.7%) in the HMR 3647 10-d group and 6/8 subjects (75.0%) in the AMC group.

Of the 4 subjects classified as clinical failure at posttherapy/TOC in the PPb population, one subject in the HMR 3647 5-d group (396/017) had *Pseudomonas aeruginosa* isolated at pretherapy/entry, one subject in the HMR 3647 10-d group (174/049) had *Streptococcus bovis,* and two subjects in the AMC group (175/020, 181/005) had *Streptococcus pneumoniae* isolated at pretherapy/entry.

Clinical outcome in the ITT population was slightly lower than that observed in the mITT population. Clinical outcome of cure at posttherapy/TOC in the ITT population was as follows: 170/258 subjects (65.9%) in the HMR 3647 5-d group, 187/270 subjects (69.3%) in the HMR 3647 10-d group, and 164/263 subjects (62.4%) in the AMC group.

The lower response rates were due primarily to the high proportion of indeterminates, primarily due to lack of X-ray evidence of disease in the additional 153 subjects (that is, there were 153 subjects in the ITT that were excluded from the mITT population).

Applicant's Clinical outcome at posttherapy/TOC of subjects who belong to the ITT population only			
	Number of subjects (%)		
Population	HMR 3647 5-d	HMR 3647 10-d	AMC
Cure	22 (48%)	38 (69%)	20 (38%)
Failure	8 (17%)	6 (11%)	9 (17%)
Indeterminate	16 (35%)	11 (20%)	23 (44%)

Of the 8 failures in the HMR 3647 5-d group, 6 failures in the HMR 3647 10-d group, and the 9 failures in the AMC group, 0 (0.0%) of the 8 in the HMR 3647 5-d group, 1 (16.7%) of the 6 in the HMR 3647 10-d group, and 0 (0.0%) of the 9 in the AMC group failed secondary to discontinuation due to an adverse event not related to deterioration of clinical status; no subject in any treatment group failed due to development of another RTI which required treatment with a subsequent antimicrobial, 0 (0.0%), 0 (0.0%), and 1 (11.1%), respectively, failed at the on therapy visit, 4 (50%), 1 (16.7%), and 3 (33.3%) failed at the end of therapy visit, and 4 (50.0%), 4 (66.7%), and 5 (55.6%) failed at the posttherapy/TOC visit, with 0, 1, and 1, respectively, of these failures not receiving a subsequent antimicrobial for treatment of AMS.

Analyses of secondary efficacy variables

Applicant's Clinical outcome – assessment at late posttherapy

The comparison of clinical outcome at late posttherapy for the HMR 3647 10-d group and the AMC group was as follows.

Assessment	Applicant's Clinical outcome at late posttherapy Number of subjects (%) HMR 3647 10-d		AMC		Difference	95% CI [a]
PPc population						
N	140		131			
Cure	97	(69.3%)	93	(71.0%)	-1.7	(-13.3, 9.9)
Failure	43	(30.7%)	38	(29.0%)		
Failure at posttherapy/TOC	38		35			
Relapse/reinfection	5		3			
mITT population						
N	215		211			
Cure	141	(65.6%)	138	(65.4%)	0.2	(-9.3, 9.7)
Failure	74	(34.4%)	73	(34.6%)		
Failure at posttherapy/TOC	50		45			
Relapse/reinfection	8		5			
Indeterminate	16		23			

[a] Two-sided 95% confidence interval

The response rates at the late posttherapy visit were slightly lower than those at posttherapy/TOC. The main reason for this was that all failures at posttherapy/TOC were carried forward to late posttherapy, whereas cures at posttherapy/TOC must have been confirmed at late posttherapy (by telephone contact or office visit) otherwise they were classified as indeterminate at late posttherapy. The rate of relapse was similar between HMR 3647 10-d (8/215) and AMC (5/211).
Relapse/reinfection occurred both in subjects with assessments at posttherapy/TOC of Return to Preinfection State (4/8 for HMR 3647 10-d and 0/5 for AMC) and Improved or Postinfectious Stigmata (4/8 for HMR 3647 10-d and 5/5 for AMC).

The 95% confidence interval of the difference in cure rates provided further evidence of equivalence between HMR 3647 10-d and AMC in both the PPc and mITT populations, with in each case a lower bound greater than -15% and an upper bound greater than 0.

FDA's Clinical response at the late-posttherapy visit (LPTV) for patients on HMR-3647 for 10-Days versus AMC for 10-Days

Assessment of Outcome	Number of Subjects (%) HMR-3647 10-Days	AMC 10-Days	% Difference	2-Sided 95% Confidence Interval
PPc population				
N	136	130		
Cure N (%)	90 (67.7%)	92 (70.8%)	-3.1%	(-15.0%, 8.8%)
Failure N (%)	43 (32.3%)	38 (29.2%)		
Relapse/Re-infection	8	5		
mITT population				
N	204	202		
Cure N (%)	132 (64.7%)	132 (65.3%)	-0.6%	(-10.4%, 9.1%)
Failure N (%)	72 (35.3 %)	70 (34.7%)		
Relapse/Re-infection	8	5		
PPb population				
N	7	7		
Cure N (%)	5 (71.4%)	5 (71.4%)	0.0%	
Failure N (%)	2 (28.6%)	2 (28.6%)		
Relapse/Re-infection	1 (14.3%)	0 (0.0%)		

[1] *Confidence intervals not presented for PPb population since there is sparse data*

The comparison of clinical outcome at late posttherapy for the HMR 3647 5-d group and the AMC group was as follows:

	Applicant's Clinical outcome at late posttherapy Number of subjects (%) HMR 3647					
Assessment	**5-day**		**AMC**		**Difference**	**95% CI [a]**
PPc population						
N	139		131			
Cure	98	(70.5%)	93	(71.0%)	-0.5	(-12.1, 11.1)
Failure	41	(29.5%)	38	(29.0%)		
Failure at Posttherapy/TOC	36		35			
Relapse/reinfection	5		3			
MITT population						
N	212		211			
Cure	140	(66.0%)	138	(65.4%)	0.6	(-8.9, 10.2)
Failure	72	(34.0%)	73	(34.6%)		
Failure at Posttherapy/TOC	47		45			
Relapse/reinfection	6		5			
Indeterminate	19		23			

[a] Two-sided 95% confidence interval

Cure rates at the late posttherapy were slightly lower than at posttherapy/TOC. Of the 6 HMR 3647 5-d subjects who were relapse/reinfection, 2 had been assessed as Return to Preinfection State at the posttherapy/TOC visit and 4 had been assessed as Improved or Postinfectious Stigmata. The numbers for the AMC group were given above.

The two-sided 95% confidence interval for the difference in cure rates indicates equivalence between the HMR 3647 5-d group and the AMC group since the lower bound of the confidence interval was greater than –15% and the upper bound was greater than 0 in both the PPc and mITT populations.

FDA's Clinical response for the 5-Day HMR-3647 compared to 10-Day of AMC at late posttherapy visit (LPTV) for the PPc population

Assessment of Outcome	Number of Subjects (%) HMR-3647 5-Days	Number of Subjects (%) AMC 10-Days	% Difference	2-Sided 95% Confidence Interval
PPc population				
N	136	130		
Cure N (%)	95 (69.9 %)	92 (70.8%)	0.9%	(-12.7%, 10.8%)
Failure N (%)	41 (30.1%)	38 (29.2%)		
Relapse/Re-infection	5	5		
mITT population				
N	201	202		
Cure N (%)	132 (65.7%)	132 (65.3%)	0.4%	(-9.5%, 10.1%)
Failure N (%)	69 (34.3%)	70 (34.7%)		
Relapse/Re-infection	6	5		
PPb[1] population				
N	7	7		
Cure N (%)	5 (71.4%)	5 (71.4%)	0.0%	
Failure N (%)	2 (28.6%)	2 (28.6%)		
Relapse/Re-infection	1 (14.3%)	0 (0.0%)		

[1] *Confidence intervals not presented for PPb population since there are sparse data*

Clinical outcome in the ITT population was somewhat lower than that in the mITT population. Clinical outcome of cure at late posttherapy was as follows: 161/258 subjects (62.4%) in the HMR 3647 5-d group, 179/270 subjects (66.3%) in the HMR 3647 10-d group, and 158/263 subjects (60.1%) in the AMC group.

Clinical outcome by investigator pool at posttherapy/TOC

The treatment effect was consistent across investigator pools at posttherapy/TOC in the PPc population. The Breslow-Day test did suggest some heterogeneity, with the comparison between the HMR 3647 5-d group and AMC yielding a p-value of 0.038, and between HMR 3647 10-d group and

AMC, a p-value of 0.082. However, further investigation using an adjusted Breslow-Day test to enable all of the investigator pools to be included in the analysis, and an additional statistical test by Lipsitz, led to the conclusion that there was no evidence of a difference in treatment effect across the centers.

Causative pathogens and in vitro susceptibility

Causative pathogens at pretherapy/entry

Only a subset of the investigational sites performed sinus puncture at the pretherapy/entry visit, such that there were a total of 29 subjects in the bmITT population. From these 29 subjects, a total of 33 pathogens were considered by the investigator to be causative for AMS (HMR 3647 5-d: 9 pathogens from 9 subjects; HMR 3647 10-d: 11 pathogens from 9 subjects; AMC: 13 pathogens from 11 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	AMC	Total
TOTAL	**9**	**11**	**13**	**33 (100%)**
S. pneumoniae	3	3	5	11 (33.3%)
H. influenzae	3	3	1	7 (21.2%)
H. parainfluenzae	1	0	1	2 (6.0%)
M. catarrhalis	0	0	2	2 (6.0%)
Other	2	5	4	11 (33.3%)

The distribution of causative pathogens isolated at pretherapy/entry was similar across the three treatment groups.

The following table summarizes all the causative pathogens isolated at pretherapy/entry in the PPb population.

Causative pathogens isolated at pretherapy/entry – PPb population

Pathogen	HMR 3647 5-d	HMR 3647 10-d	AMC	Total
TOTAL	**7**	**7**	**10**	**24 (100%)**
S. pneumoniae	2	2	4	8 (33.3%)
H. influenzae	2	3	1	6 (25.0%)
H. parainfluenzae	1	0	0	1 (4.2%)
M. catarrhalis	0	0	1	1 (4.2%)
Other	2	2	4	8 (33.3%)

Again, the distribution of causative pathogens was similar across the three treatment groups.

Susceptibility based on local laboratory testing (disk diffusion method)

Susceptibility test results to HMR 3647 are available for 27 of the 33 pathogens isolated in the bmITT population. Susceptibility test results to AMC are available for 15 of these 33 pathogens. Of the 27 isolates tested against HMR 3647, 3 (11.1%) isolates were resistant to HMR 3647. Of the 15 isolates tested against AMC, 0 (0.0%) were resistant to AMC.

Susceptibility based on central laboratory testing (disk diffusion and MIC methods)

In vitro susceptibility was determined by MIC and by disk susceptibility testing at the central laboratory, and for the pathogens concordant between the local and central laboratories in the bmITT and PPb populations.

Bacteriological outcome by subject – assessment at posttherapy/TOC

The bacteriological outcome comparing HMR 3647 10-d with AMC at posttherapy/TOC in the PPb population is summarized in the table shown below.

Bacteriological outcome by subject at posttherapy/TOC – PPb population

	Number of subjects (%)				
	HMR 3647				Difference
Assessment	10-d		AMC		
N	7		8		
Satisfactory [a]	6	(85.7%)	6	(75.0%)	10.7
Unsatisfactory [b]	1	(14.3%)	2	(25.0%)	

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

The bacteriological outcome rates at posttherapy/TOC are comparable between the HMR 3647 10-d group and the AMC group; however small sample sizes preclude any firm conclusions.

In the bmITT population, bacteriological outcome was satisfactory for 7/9 subjects (77.8%) in the HMR 3647 10-d group and 7/11 subjects (63.6%) in the AMC group. Indeterminate outcome was categorized as unsatisfactory in the bmITT analysis: of the unsatisfactory outcomes, only one subject (from the AMC group) had an outcome of indeterminate. This subject (153/002) was lost to follow-up following the end of therapy visit.

The comparison of bacteriological outcome at posttherapy/TOC in the PPb population for the HMR 3647 5-d group with the AMC group is as follows:

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Bacteriological outcome by subject at posttherapy/TOC – PPb population

	Number of subjects (%)				
	HMR 3647				
Assessment	**5-d**		**AMC**		**Difference**
N	7		8		
Satisfactory [a]	6	(85.7%)	6	(75.0%)	10.7
Unsatisfactory [b]	1	(14.3%)	2	(25.0%)	

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

The bacteriological outcome rates at posttherapy/TOC are comparable between the HMR 3647 5-d group and the AMC group; however, small sample sizes again preclude any firm conclusions.

In the bmITT population, bacteriological outcome was satisfactory for 8/9 subjects (88.9%) in the HMR 3647 5-d group and 7/11 subjects (63.6%) in the AMC group. Indeterminate outcome was categorized as unsatisfactory in the bmITT analysis: of the unsatisfactory outcomes, only one subject (from the AMC group) had an outcome of indeterminate. This subject (153/002)was noted above.

Bacteriological outcome by pathogen – assessment at posttherapy/TOC

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*	**HMR 3647 5-d**	**HMR 3647 10-d**	**AMC**
TOTAL	6/7 (85.7%)	6/7 (85.7%)	8/10 (80.0%)
S. pneumoniae	2/2 (100%)	2/2 (100%)	2/4 (50.0%)
H. influenzae	2/2 (100%)	3/3 (100%)	1/1 (100%)
H. parainfluenzae	1/1 (100%)	-	-
M. catarrhalis	-	-	1/1 (100%)
Other	1/2 (50.0%)	1/2 (50.0%)	4/4 (100%)

* Single and multiple pathogen infections

Eradication rates at posttherapy/TOC for the principal RTI pathogens were comparable in the 3 treatment groups. There were no cases of recurrence or documented persistence in any of the three treatment groups. There were

four pathogens classified as presumed persistence (HMR 3647 5-d group: 1 [illegible] resistant to HMR 3647); HMR 3647 10-d group: [illegible] (susceptible to HMR 3647); AMC group: 2 *Streptococcus pneumoniae* (both susceptible to AMC).

In the bmITT population, these results were confirmed and the eradication rates (documented or presumed eradication) were 8/9 (88.9%) for HMR 3647 5-d group, 7/11 (63.6%) for HMR 3647 10-d group and 9/13 (69.2%) for the AMC group. The distribution of eradicated pathogens was similar to that seen in the PPb population.

Bacteriological outcome by subject – assessment at late posttherapy

The bacteriological outcome at late posttherapy in all subjects with clinical signs and symptoms of AMS and bacteriologically proven infection (isolation of a causative pathogen) as treated in the PPb population is shown in the tables below.

The comparison of bacteriological outcome at late posttherapy in the PPb population for the HMR 3647 10-d group and the AMC group is as follows.

Bacteriological outcome at late posttherapy – PPb population

	Number of subjects (%)				
	HMR 3647				
Assessment	**10-d**		**AMC**		**Difference**
N	7		7		
Satisfactory	5	(71.4%)	5	71.4%)	0
Unsatisfactory[a]	2		2		

[a] Includes unsatisfactory at posttherapy/TOC and satisfactory at posttherapy/TOC with secondary failure (reinfection at late posttherapy, new antimicrobial during follow-up and recurrence at late posttherapy).

The comparison of bacteriological outcome at late posttherapy between HMR 5-d and AMC is as follows:

Bacteriological outcome at late posttherapy – PPb population

	Number of subjects (%)				
	HMR 3647				
Assessment	**5-d**		**AMC**		**Difference**
N	7		7		
Satisfactory	5	(71.4%)	5	(71.4%)	0
Unsatisfactory[a]	2		2		

[a] Includes unsatisfactory at posttherapy/TOC and satisfactory at posttherapy/TOC with secondary failure (reinfection at late posttherapy, new antimicrobial during follow-up and recurrence at late posttherapy).

The bacteriological outcome rates in the 3 treatment groups in the PPb population are comparable.

In the PPb population, 1 subject (174/050) in the AMC group was included in PPb at posttherapy/TOC but not at late posttherapy due to the visit being one day out of the window. Thus, there were only 7 subjects evaluable for bacteriological response at late postherapy in the AMC group.

The 6 subjects in the PPb population with an unsatisfactory response at late posttherapy included subjects with unsatisfactory response at posttherapy/TOC carried forward to late posttherapy (HMR 3647 10-d: 1 subject; HMR 3647 5-d: 1 subject; and, AMC: 2 subjects) and subjects with a satisfactory response at posttherapy/TOC (HMR 3647 10-d: 1 subject and HMR 3647 5-d: 1 subject). Both of these latter 2 subjects received an antimicrobial at late posttherapy for a recurrence of AMS symptoms.

In the bmITT population, bacteriological outcome was satisfactory for 7/9 subjects (77.8%) in the HMR 3647 5-d group, for 6/9 subjects (66.7%) in the HMR 3647 10-d group and for 7/11 subjects (63.6%) in the AMC group.

Bacteriological outcome by pathogen - assessment at late posttherapy

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

Eradication rates at late posttherapy – PPb population

Pathogen*	Eradication rate HMR 3647 5-d	HMR 3647 10-d	AMC
TOTAL	5/7 (71.4%)	5/7 (71.4%)	5/7 (71.4%)
S. pneumoniae	2/2 (100%)	1/2 (50%)	2/4 (50.0%)
H. influenzae	2/2 (100%)	3/3 (100%)	1/1 (100%)
H. parainfluenzae	1/1 (100%)	-	-
M. catarrhalis	-	-	1/1 (100%)
Other	0/2 (0.0%)	1/2 (50.0%)	1/1 (100%)

* Single and multiple pathogen infections

The one subject in the AMC group (174/050) who was included in PPb at posttherapy/TOC but not at late posttherapy had 3 causative pathogens isolated at pretherapy/entry. Thus there were only 7 pathogens evaluable for bacteriological response at late posttherapy in the AMC group.

There were no cases of recurrence or documented persistence in any of the three treatment groups. There were 6 pathogens classified as presumed persistence, 2 in each treatment group (HMR 3647 5-d group: [redacted], subject 177/019 (susceptible to HMR 3647) and 1 [redacted] subject 396/017(resistant to HMR 3647); HMR 3647 10-d group: [redacted], subject 174/049 and 1 *S. pneumoniae,*

subject 177/020 (both susceptible to HMR 3647); AMC group: 2 *S. pneumoniae,* subjects 175/020 and 181/005 (both susceptible to AMC).

In the bmITT population, these results were confirmed and the eradication rates (documented or presumed eradication) were 7/9 (77.8%) for HMR 3647 5-d group, 6/11 (54.5%) for HMR 3647 10-d group and 9/13 (69.2%) for the AMC group. The distribution of eradicated pathogens was similar to that seen in the PPb population.

Clinical outcome by isolated pretherapy/entry causative pathogen

Clinical outcome at posttherapy/TOC for subjects in the PPb population with a single pathogen of *S. pneumoniae, H. influenzae, H. parainfluenzae* or *M. catarrhalis* isolated at pretherapy/entry is shown in the tables below. Note that no subjects had either *Group A Streptococcus* (*S. pyogenes*) or *S. aureus* isolated.

Clinical outcome in subjects with single pathogens of importance in AMS based on local laboratory results– PPb population at posttherapy/TOC – HMR 3647 treatment groups

Subgroup	Clinical outcome Number of subjects (%)					
		HMR 3647 5-d			HMR 3647 10-d	
	N	Cure	Failure	N	Cure	Failure
Any pathogen	7	6 (85.7%)	1 (14.3%)	7	6 (85.7%)	1 (14.3%)
Pathogens of importance	5	5 (100.0%)	0 (0.0%)	5	5 (100.0%)	0 (0.0%)
Streptococcus pneumoniae	2	2 (100.0%)	0 (0.0%)	2	2 (100.0%)	0 (0.0%)
Haemophilus influenzae	2	2 (100.0%)	0 (0.0%)	3	3 (100.0%)	0 (0.0%)
Haemophilus parainfluenzae	1.	1 (100.0%)	0 (0.0%)	0	-	-
Moraxella catarrhalis	0	-	-	0	-	-

Clinical outcome in subjects with single pathogens of importance in AMS based on local laboratory results– PPb population at posttherapy/TOC – AMC group

Subgroup	Clinical outcome Number of subjects (%)		
		AMC	
	N	Cure	Failure
Any pathogen	10	8 (80.0%)	2 (20.0%)
Pathogens of importance	6	4 (66.7%)	2 (33.3%)
Streptococcus pneumoniae	4	2 (50.0%)	2 (50.0%)
Haemophilus influenzae	1	1 (100.0%)	0 (0.0%)
Haemophilus parainfluenzae	0	-	-
Moraxella catarrhalis	1	1 (100.0%)	0 (0.0%)

Clinical outcome and eradication rates according to MIC for isolated pretherapy/entry causative pathogens

Clinical outcome and eradication rates were analyzed separately for subjects with the following pathogens of importance for AMS (single pathogen infections). Only isolates with concordant results from the central laboratory and the local laboratory were taken into account.

- *Streptococcus pneumoniae* (susceptible, not susceptible, intermediate or fully resistant to penicillin; susceptible or resistant to erythromycin) as determined by MIC in the central laboratory
- *Haemophilus influenzae* (total, beta-lactamase non-producers, beta-lactamase producers according to ampicillin susceptibility) as determined by MIC in the central laboratory

Clinical and bacteriological outcome in these subjects in the PPb population is shown below:

Clinical outcome in subjects with single pathogens of importance in AMS according to their Susceptibility pattern determined by MIC– PPb population at posttherapy/TOC

	Clinical outcome Number of subjects								
		HMR 3647 5-d			HMR 3647 10-d			AMC	
Subgroup	N	Cure	Fail	N	Cure	Fail	N	Cure	Fail
Streptococcus pneumoniae									
Total	2	2	0	2	2	0	4	2	2
Penicillin sensitivity [MIC]									
Susceptible [≤0.06 µg/mL]	1	1	0	1	1	0	4	2	2
Not susceptible [a] [≥0.12 µg/mL]:									
Intermediate [0.12 - 1.0 µg/mL]	1	1	0	0			0		
Resistant [≥2.0 µg/mL]	0			1	1	0	0		
Erythromycin sensitivity [MIC]									
Susceptible [≤0.25 µg/mL]	2	2	0	1	1	0	4	2	2
Resistant [≥1.0 µg/mL]	0			1	1	0	0		
Haemophilus influenzae									
Total	2	2	0	3	3	0	1	1	0
Beta-lactamase producers	1	1	0	2	2	0	0		
Beta-lactamase non-producers	1	1	0	1	1	0	1	1	0

[a] Total not susceptible = (number Intermediate + number resistant)

Eradication rates in subjects with single pathogens of importance in AMS according to their Susceptibility pattern determined by MIC– PPb population at posttherapy/TOC

Subgroup	Clinical outcome Number of subjects HMR 3647 5-d Eradication rate (%)	HMR 3647 10-d Eradication rate (%)	AMC Eradication rate (%)
Streptococcus pneumoniae			
Total	2/2 (100%)	2/2 (100%)	2/4 (50%)
Penicillin sensitivity [MIC]			
Susceptible [≤0.06 µg/mL]	1/1 (100%)	1/1 (100%)	2/4 (50%)
Not susceptible [a] [≥0.12 µg/mL]:			
Intermediate [0.12 - 1.0 µg/mL]	1/1 (100%)	0	0
Resistant [≥2.0 µg/mL]	0	1/1 (100%)	0
Erythromycin sensitivity [MIC]			
Susceptible [≤0.25 µg/mL]	2/2 (100%)	1/1 (100%)	2/4 (50%)
Resistant [≥1.0 µg/mL]	0	1/1 (100%)	0
Haemophilus influenzae			
Total	2/2 (100%)	3/3 (100%)	1/1 (100%)
	1/1 (100%)		
Beta-lactamase producers		2/2 (100%)	0
Beta-lactamase non-producers	1/1 (100%)	1/1 (100%)	1/1 (100%)

[a] Total not susceptible (= number intermediate + number resistant)

The majority of PPb subjects with *S. pneumoniae* susceptible to penicillin G or erythromycin A or with *H. influenzae* susceptible to azithromycin or ampicillin had a clinical outcome of cure and the pathogen was eradicated, regardless of whether the subject received HMR 3647 or AMC. One subject in the HMR 3647 10-d group (177/020) had *S. pneumoniae* resistant to penicillin G and erythromycin A: the pathogen was eradicated and the subject was a clinical cure at posttherapy/TOC. This subject was a relapse, clinical failure, at the late posttherapy visit. None of the subjects with *H. influenzae,* which were beta-lactamase non-producers, were resistant to ampicillin.

The results in the bmITT population showed similar trends to the PPb analyses. One subject in the HMR3647 10-d group (153/001) had *S. pneumoniae* intermediately resistant to penicillin G: the pathogen was eradicated and the subject was a clinical cure. One subject in the AMC group (176/023) had *S. pneumoniae* resistant to penicillin G: the subject was a clinical failure at posttherapy/TOC due to new clinical findings of Strep throat.