
Edward M. Cox, M.D., M.P.H.
Medical Officer/HFD-590

cc: Division File
NDA 21-144

Concurrence Only:
HFD-520/ActingDivDir/JSoreth

HFD-520/MTL/JKorvick
HFD-520/MTL/DRoss
HFD-520/MTL/DMakhene
HFD-520/MO/ADavidson
HFD-520/MO/NMoledina
HFD-590/MO/ECox
HFD-520/PharmTox/BOsterberg
HFD-520/PharmTox/TPeters
HFD-520/Micro/ASheldon
HFD-520/Micro/FMarsik
HFD-520/BioPharm/FPelsor
HFD-520/BioPharm/JZheng
HFD-520/Stat/DLin
HFD-520/Stat/GRochester
HFD-520/CSO/JCintron

DFS Keywords
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Study type(s): study clin control active; study clin uncontrolled; study Phase 1; study Phase 3
Indication(s): indic pneumonia, CAP; indic sinusitis, acute; indic pharyngitis streptococcal; indic bronchitis ABECB
Special Populations: pop adult
Drug Class: class macrolide/ketolide

Appendix A.

Appendix A.1
A brief summary of the information on selected patients from the Phase I Studies with Hepatic AEs are provided below. Note that these summaries also include patients from phase I studies that involved telithromycin administration with other drugs. Hence the total number of cases described is more than is displayed in Table 3. In addition some subjects with elevated liver function tests from phase I studies who did not have hepatic AEs are also summarized.

Liver Damage
(Liver Damage refers to asymptomatic increases in transaminases)

Study 1030 Subject #10 was a 72-year old female healthy volunteer enrolled in this study of single escalating doses of telithromycin. She had a normal AST, ALT, and Bilirubin at Screening. She also had normal AST, ALT, GGT, Alk. Phos. and Bilirubin on Day 1 (5/12/98). She did not receive any concomitant medications during study. She received 1200 mg telithromycin on 5/12/98, followed by 1600 mg telithromycin on 5/19/98, placebo on 5/26/98, and 2000 mg telithromycin on 6/2/98. Her LFTs tested on Days 1, 2, and 5 of each dosing period were normal throughout the study until 8 days after receiving the 2000 mg telithromycin dose. Her LFTs were tested 9 times between 8 and 30 days after receiving the 2000 mg telithromycin dose. Serial LFTs demonstrate a curve of rising and falling transaminases over this time period between Day 8 and Day 30 (ALT>AST). Her ALT peaked at 184 IU/L (NR<40) 14 days post-therapy (6/16/98) and her AST peaked 13-days post-therapy at 99 IU/L (NR<40). Her GGT, Alk. Phos., and T.bili. were within the normal range on the 4 occasions that they were tested between Day 8 and Day 30 post-therapy. On Day 37 post-therapy her AST and ALT were normal. She did not develop eosinophilia.

The patient's evaluation for this episode of elevated transaminases included an ultrasound of the liver that was reportedly normal. A CMV serology done on 6/15/98 that was positive for IgM and IgG followed by a repeat CMV serology (7/1/98) positive for IgG and negative for IgM. She also had a positive EBV IgG (6/15/98), a positive serology for HSV IgG (6/15/98 and 7/1/98) and negative serologies for HBc, HCV, HAV, and toxoplasma.

The investigator's opinion was that this adverse event was reasonably associated with the study drug. The Applicant notes that *a reasonable possibility of a casual relationship between liver injury and the administration of the study drug cannot be excluded* (6:v111:p076). The Applicant also notes that the event occurred following the administration of a dose of 2000 mg of telithromycin – a dose greater than intended for therapeutic use and that CMV *(re)infection* could also be an alternative explanation.

> **MO Comment:** If the transaminase abnormalities observed in Pt. 1030/10 are due to the single dose of 2000 mg telithromycin, the onset of the abnormal ALT/AST in this patients was first noted 7 days post-therapy, peaked 14 days post-therapy, and resolved between Day 30 to Day 37 post-therapy. If this is in fact the time course for telithromycin associated transaminitis, the washout period may be insufficient for evaluating abnormal transaminases.

> **MO Comment:** If serum from study entry for Pt. 1030/10 had been tested for IgG and IgM to CMV at Screening, one might be able to provide additional information regarding the likelihood that the observed changes were possibly due to CMV infection. In a normal host with existing CMV immunity, one would expect CMV reinfection as a cause of transaminitis to be an uncommon event. A positive CMV IgG especially with a negative IgM at Screening would make CMV infection a less likely cause of the events observed.

Study 1030 Subject # 16 was a 69-year old male, healthy volunteer with a history of tinnitus, psoriasis, and arthritis who was enrolled in this study of single escalating doses of telithromycin. He had a normal AST and ALT at Screening. He also had normal AST, ALT, GGT, Alk. Phos., and Bilirubin on Day 1 (5/12/98). He received placebo on 5/12/98, followed by 1200 mg telithromycin on 5/19/98, 1600 mg

telithromycin on 5/26/98, and 2000 mg telithromycin on 6/2/98. He did not receive any concomitant medications. His AST, ALT, GGT, and alkaline phosphatase tested on Days 1, 2, and 5 of each dosing period were normal throughout the study. His bilirubin was normal on 8 of the 12 tests performed during the Day 1, 2, and 5 assessments. When elevated, the bilirubin elevations were only slight [22.3, 22.1, 22.2, 25.6 (NR 1.7 – 22.0 µmol/L)]. At his first re-testing on Day 8 (6/9/98) after receiving the 2000 mg telithromycin dose, his ALT, AST, GGT, alkaline phosphatase, and Bilirubin were normal. At his next follow-up re-testing on Day 18 (6/19/98) he had the following abnormalities: AST 141 IU/L (NR<51), ALT 199 IU/L (NR<57). His GGT, alkaline phosphatase, and bilirubin were normal at Day 8. Further follow-up testing of his AST and ALT showed a curve for transaminase increases that peaked at Day 21 (6/22/98) at AST 180 and ALT 260. His transaminases were tested 6 times between Day 18 and Day 37 (7/8/98) and gradually returned to within the normal range on Day 44 (7/15/98). During the period of increased transaminases no determinations for GGT, alkaline phosphatase, or bilirubin levels were done. A bilirubin level was reported for Day 44 which was within the normal range. He did not have eosinophilia on his CBC/Diff during the study (his final CBC/Diff was on Day 8 (6/9/98)).

The patient's evaluation for this episode of elevated transaminases included an ultrasound of the liver and biliary tract that was reportedly normal. An EBV serology done on 6/22/98 was negative for IgM and positive for IgG at 352 AU/mL. A repeat of the patient's EBV serology for IgG on 7/8/98 was negative and a serology for IgG antibody to EBV nuclear antigen was positive (EBNA IgG was not performed on 6/22/98). A serology for CMV was positive for IgG >250 AU/mL and negative for IgM. Re-testing for CMV IgG performed on 7/8/98 was reported as positive at 43 AU/mL. Serologic testing for HAV IgM Ab, HBcAb, HCV, HSV, and toxoplasma Ab was reported as negative.

The investigator's opinion was that this adverse event was reasonably associated with the study drug. The Applicant notes that a *reasonable possibility of a casual relationship between [ ] liver injury and the administration of the study drug cannot be excluded* (6:v111:p086). The Applicant also notes that the event occurred following the administration of a dose of 2000 mg of telithromycin – a dose greater than intended for therapeutic use. The Applicant also notes *acute EBV and CMV (re)infection were demonstrated to occur in two other subjects of this group, simultaneously institutionalized. A similar (re)infection could also be considered for this subject, which cannot be proven in the absence of sequential serologies* (6:v111:p086).

> **MO Comment:** The significance in the change in the results for the CMV serology are of unclear significance.
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> **MO Comment:** The hypothesis that this event is attributed to EBV based on the positive IgG from 6/22/98 and negative IgG from 7/8/98 is not well supported by this serologic pattern. One would have to postulate reinfection with EBV followed by a loss of a positive IgG titer within the period of two-weeks.
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> **MO Comment:** The first serum chemistries demonstrating elevated transaminases were obtained on Day 18 after single dose administration of 2000 mg of telithromycin on Day 1. The peak in transaminases occurred on Day 21 after the 2000 mg single dose of telithromycin. No liver function tests were performed between Day 8 and Day 18.

Study 1030 Subject # 12 (AE "liver damage" attributed to placebo) was a 62-year old healthy male volunteer enrolled in this study of single escalating doses of telithromycin. He had a normal AST and ALT at Screening. He also had normal AST, ALT, GGT, Alk. Phos. and Bilirubin on Day 1 (5/12/98). His reported medication use consisted of acetaminophen 1000 mg po qd from — /98 for left hip pain and Anusol cream beginning — 98 for hemorrhoids. He received 1200 mg of telithromycin on 5/12/98, followed by 1600 mg of telithromycin on 5/19/98, 2000 mg of telithromycin on 5/26/98, and 2000 mg of placebo on 6/2/98. His AST, ALT, GGT, alkaline phosphatase, and bilirubin were tested on Days 1, 2, and 5 of each dosing period and were normal throughout the study. At his first re-testing on Day 8 (6/9/98) after receiving placebo, his AST, and ALT were elevated and his GGT, alkaline phosphatase, and bilirubin were normal. His AST and ALT peaked on Day 15 (6/16/98) at the following levels: AST 211 IU/L (NR<51), ALT 383 IU/L (NR<57). Further follow-up testing of his AST and ALT showed a curve for

transaminase increases that peaked on Day 15/16 and then gradually resolved returning to the normal range on Day 44 (7/15/98). Transaminases (AST & ALT) were checked 13 times between Day 8 and 44. GGT, alkaline phosphatase, and bilirubin were checked less frequently during this same interval. Serum GGT, alkaline phosphatase, and bilirubin were checked on Day 8, 10, 15, and 18 and were within the normal range. Complete blood counts with a differential performed on 6/9/98 and 6/19/98 did not demonstrate eosinophilia.

The patient's evaluation for this episode of elevated transaminases included an ultrasound of the liver with findings consistent with fatty infiltration of the liver. An EBV serology done on 6/11/98 was positive for IgM and IgG. Follow-up serologic testing for EBV on 6/22/98 found a positive IgG antibody to EBV nuclear antigen, negative IgM antibodies to EBV, negative IgM to viral capsid antigen. Additional EBV serologies performed on 6/26/98 were negative for EBV IgG and IgM and weakly positive for EBNA IgG antibody. Other serologic results included a positive HAV IgG and negative HAV IgM (6/11/98). Negative serologies were also reported for CMV IgG, CMV IgM, HBc Ab, HCV, HSV, and toxoplasma.

The investigator's opinion was that this adverse event was reasonably associated with the study drug. The Applicant notes that a *reasonable possibility of a casual relationship between* [ ] l*iver injury and the administration of the study drug cannot be excluded* (6:v111:p086). The Applicant also notes that the event occurred following the administration of a dose of 2000 mg of telithromycin – a dose greater than intended for therapeutic use. The Applicant also notes *acute EBV (re)infection was serologically demonstrated to occur in this subject just before the documentation of liver injury. EBV infection can be an alternative explanation.* (6:v111:p083).

> **MO Comment:** The reported negative EBV IgG serology 15 days after the serology leading to the Applicant's diagnosis of acute EBV is an unexpected results and raises questions as to the accuracy of the serologic diagnosis. While there are always variabilities in how an individual patient will respond serologically to a viral infection, one should interpret the results in this particular case cautiously because of the less than characteristic pattern for acute EBV infection. In addition, while EBV and CMV infections do occur in older individuals, many older individuals are already seropositive to EBV and/or CMV. Unfortunately we do not have information regarding the patient's baseline serological status.

> **MO Comment:** While this event had its onset on Day 8 after placebo dosing, given the potential for variability in the interval between dosing and hepatic manifestations, the prior dose of 2000 mg of telithromycin cannot be excluded as the cause of these events. If the 2000 mg dose of telithromycin is attributed as the causal event, the time to first identification of the transaminase abnormality would be Day 15 post the 2000 mg dose and the time to peak enzymes would be Day 22 post the 2000 mg dose. This time course for events is not inconsistent with what was observed for subject 16 described above.

> **MO Comment:** The clustering of abnormal transaminases in elderly patients within Group C, the group of elderly patients that received a single dose of 2000 mg suggests the possibility that this effect is related to the higher dose of telithromycin of 2000 mg. While it is noted that the Applicant's proposed dose for telithromycin is 800 mg po qd, the results observed in this small number of elderly subjects receiving a single dose of 2.5 times the "recommended" dose provides information in assessing the potential toxicities of telithromycin. If the hepatic toxicity observed in this small group of patients is a signal of telithromycin's hepatotoxic potential, this information may provide a useful signal of what might be expected if a larger population were exposed to telithromycin. Even though these events occurred in the setting of higher doses of telithromycin in this small study, in a larger population one would expect that similar exposures and/or persons more susceptible to these potential effects would be present. Therefore this potential signal should not be dismissed because it was observed at a dose higher than the dose being sought for approval.

> **MO Comment:** Study 1030 was designed primarily to assess pharmacokinetics and really was not specifically designed to assess hepatotoxicity.

Increased AST

Study 1001 Subject # 49 a 26-year-old male enrolled in Study 1001 a placebo controlled, tolerability, pharmacokinetic and food interaction study in healthy male volunteers with single oral doses (50 to 800 mg) of telithromycin. At study entry his CBC/Diff and serum chemistries were within normal limits including a normal AST, ALT, alkaline phosphatase, and bilirubin. He did not receive any concomitant medications. On 2/3/97 he received 200 mg of telithromycin. Following the 200 mg dose his liver function tests remained within normal limits. On 2/17/97 he received 800 mg of telithromycin. On follow-up labs he was noted to have an increase in AST (AST 69 IU/L (NR 16-50 IU/L) that occurred 72 hours after his prior dose of 800 mg of telithromycin. His other LFTs were normal [ALT 25 U/L (NR 10-60); GGT 21 U/L (NR 12-62); alkaline phosphatase 45 U/L (NR 42-114); bilirubin 11 umol/L (NR 3-17)] . The Applicant also states that, *elevated CPK levels were also observed in this subject which indicated concomitant strenuous activity* (6:v087:p072). Reportedly his AST returned to normal after one week. The subject's CPK levels and the follow-up AST level were not provided in the listing of laboratory values for subject 049 (6:v90:p053). The investigator considered this event to not be causally related to study medication and likely due to physical exercise.

Study 1005 Subject # 55 a 20 year-old male enrolled in Study 1005, a study of the pharmacokinetics of telithromycin in elderly male and female subjects compared to those in healthy young male subjects after single and repeated dose oral administration of telithromycin once a day for 10 days. He had normal LFTs at his initial visit AST 30 U/L (NR 5-40); ALT 29 U/L (NR 5-72); alkaline phosphatase 90 U/L (NR 25-160); bilirubin 27.1 umol/L (NR 6-30). His CPK was elevated at Screening [CPK 898 IU/L (NR 55-170)]. He received no concomitant medications during study. On 10/10/97 he received a single dose of 800 mg of telithromycin. On 10/15/97 he received his first of 10 doses of telithromycin 800 mg po qd (final day a dose was given was 10/24/97). On 10/25/97 the patient was noted to have an elevated AST and CPK and his bilirubin was also mildly elevated [AST 140 U/L; ALT 54; alkaline phosphatase 77; bilirubin 35.9; CPK 9100 (NR 55-170 IU/L)]. Follow-up labs on 11/19/97 were AST 29, ALT 33, CPK 188, T. Bili. 32.4. The investigator attributed these events to intensive sport practice.

Study 1030 Subject # 5 a 39 year-old female enrolled in Study 1030. She had normal AST, ALT, GGT, alkaline phosphatase, and bilirubin at study entry. Her concomitant medications were acetaminophen 1000 mg po bid from 4/13/98 to 4/14/98 for headache. She reported negligible alcohol intake (*1 unit/week, if that*) She received 1600 mg of telithromycin on 3/31/98 followed by placebo on 4/6/98. Her LFTs were normal during this time period. On 4/14/98 she received 2000 mg of telithromycin. She experienced vomiting one hour after receiving the 2000 mg dose of telithromycin. She then developed increased LFTs [AST 95 (NR<40 IU/L); ALT 94 (NR<40 IU/L)] beginning Day 2 (4/15/98). On Day 3 (4/16/98) her LFTs peaked at AST 101, ALT 148. Continued monitoring of her LFTs on an every other day basis demonstrated a return to normal on Day 11 (4/24/98). She was withdrawn from the last stage of the study because of her elevated AST and ALT. Her CBC/Diff did not demonstrate eosinophilia when checked on Days 1, 2, and 5, during each of the dosing periods (first, second, and third).

The patient's evaluation for this episode of elevated transaminases included an ultrasound of the liver (4/24/98) which was normal. Serologies for HBcAb, HBsAg and HCV which were negative (4/17/98). Serologies for EBV IgG and toxoplasma IgG were positive and both were negative for IgM, consistent with past infection. Serologies for CMV, HSV, Coxsackie virus, and *C. burnetii* were negative.

The investigator's opinion was that this adverse event was reasonably associated with the study drug. The Applicant notes that a *reasonable possibility of a casual relationship between the reported events (headache excepted) and the administration of study drug cannot be excluded* (6:v111:p074). The Applicant also notes that the event occurred following the administration of a dose of 2000 mg of telithromycin – a dose greater than intended for therapeutic use.

Study 1032 Subject # 2 a 22 year-old male was enrolled in Study 1032 a four-way crossover study to assess the effects of various doses of telithromycin on QT interval during rest and exercise in young healthy subjects. At study entry he had a normal AST, ALT, alkaline phosphatase, and bilirubin. He did not

receive any concomitant medications during study. He received 1600 mg of telithromycin on 4/12/99. His LFTs at Day 1, Day 2 and Day 7 (days post-dose) were normal. On 4/26/99 labs done pre-dose (for an 800 mg dose of telithromycin) showed an elevation in AST (AST 130 IU/L NR<30) and ALT (ALT 37 IU/L NR<35). He received his 800 mg dose of telithromycin on 4/26/99 and his transaminases peaked on 4/27/99 at AST 216 IU/L and ALT 61 IU/L. By the time of his period 3 (placebo) blood draw on 5/10/99 his transaminases had normalized. His bilirubin and alkaline phosphatase were not elevated at the time of his transaminase elevations. The patient reported a history of jogging and re-tests performed 7-days later showed an elevated CPK of 289 IU/L (normal range not provided). On 5/24/99, he received telithromycin 2400 mg x 1. Serum chemistries drawn up to 6-days after the 2400 mg dose did not reveal abnormal LFTs. He did not exhibit eosinophilia on his CBC/diffs that were drawn on Days 1 and 2 of the dosing period. The investigator did not consider this event related to study medication.

Increased ALT

Study 1030 Subject # 5 (see description above)

Study 1046 Subject # 56 was a 35 year-old female who received 2400 mg telithromycin in period I, 3200 mg telithromycin in period II, and placebo in period III. She experienced the TEAE of ALT increased after the 3200 mg dose of telithromycin. At the Screening visit and after period I, the ALT levels for this subject were within the normal range (10.0 IU/L to 30 IU/L). ALT (SGPT) started to increase on Day 2 after the 3200 mg telithromycin administration (40 IU/L) to reach a value greater than twice the upper limit of normal (77 IU/L) on Day 8, with an associated increase in AST (SGOT) of 37 IU/L (NR 16.0-31.0) (TEAE ALT increased). Alkaline phosphatase and GGT remained within the normal ranges. The patient had a mildly elevated total bilirubin at Screening [19.9 umol/L (NR 4.0-14.2)]. The investigator's opinion was that the subject had asymptomatic Gilbert's disease. The patient experienced chills and dizziness on Day 1 after taking 3200 mg telithromycin for which he took 1 gram of acetaminophen. The subject denied the consumption of alcohol or herbal tea. The subject recovered without sequelae.

Study 1047 Subject 006 a 26-year old male received treatment "A", telithromycin 800 mg with water and then after a 12-day washout period received treatment "B", telithromycin 800 mg PO x 1 with grapefruit juice. Three days after receiving Treatment B, he was noted to have an increase in ALT and AST that was reported as a TEAE (ALT increased). He had an ALT of 166 U/L and an AST of 119 U/L along with an LDH of 300 U/L. His alkaline phosphatase and bilirubin were within normal limits. The event resolved without sequelae.

Liver Function Test Abnormal

Study 1016 Subject 2012 a 55 year-old female enrolled in Study 1016, Pharmacokinetics of [telithromycin] Tablets in Patients with Renal Impairment. She had a history of allergy to mold and cedar. At Screening her AST and ALT were within the normal range [AST 30 U/L (NR 0-40); ALT 29 U/L (NR 0-45)] and her alkaline phosphatase was mildly elevated [Alk. Phos. 189 U/L (NR 25-140)]. She received no concomitant medications during study. She received 800 mg of telithromycin on Day 1 (9/19/98). Her LFT's on Day 4 were Alk. Phos. 241, AST 62, ALT 75 and T. Bili. 5.13 umol/L (NR typically 6-30 umol/L). The abnormal liver function tests were assessed by the investigator as possibly related to study medication. She had mild eosinophilia at study entry that persisted (absolute eosinophil count at baseline and post-study was 0.6 G/L). The event reportedly resolved without sequelae.

Study 1045 Subject 002 a 25-year old white male developed an increases in his ALT (TEAE - Liver function abnormal) after receiving placebo for 5 days during period 1 and prior to receiving active medication during his second period of this 4 period study. He was withdrawn from study with an ALT of 65 U/L (NR 0-50 U/L). On the 8th day after placebo his ALT was 63 U/L. The event was judged as not related to study medication.

Study 1045 Subject 014 a 40 yo white male received placebo for 5 days followed by telithromycin 800 mg po QD x 5 days and ketoconazole 400mg po QD x 7days, then by telithromycin 800 mg po QD x 5 days, and finally ketoconazole 400 mg po QD x 7 days. On day 8 of the telithromycin 800 mg po QD x 5 dosing

period, subject 14 had an ALT of 60 U/L (NR 0-50 U/L) (TEAE - Liver function abnormal). On day 8 of the ketoconazole 400 mg po QD x 7 days dosing period, his AST and ALT values increased from 34 and 50 U/L at baseline to 101 and 73 U/L, respectively. The event was considered possibly related to study medication. His alkaline phosphatase and T. bilirubin remained normal.

Increased Alkaline phosphatase

Study 1017 Subject # 391/014 a 19 year-old male enrolled in Study 1017, entitled Pivotal Bioequivalence of HMR 3647 [telithromycin] Proposed-For-Marketing 400 mg Tablet Formulation in Healthy Male Subjects. He had a mildly elevated alkaline phosphatase at Screening 155 U/L (NR 50-136) and an AST of 21 U/L (NR 15-37), ALT 32 U/L (30-65), T. Bili. 6.8 umol/L (NR 0.0-20.5) at Screening. He received no concomitant medications during the study. He received 800 mg of telithromycin on 2/20/99 and 2/27/99. On Day 3 following the second dose of telithromycin, his alkaline phosphatase was noted to be further elevated (Alk. Phos. 180 U/L and repeat 184 U/L. His AST, ALT, and T. Bili. remained within normal range. No further follow up LFTs were obtained beyond Day 3. His CBC/Diff at Screening and post-study did not show eosinophilia. The event was considered possibly related to study therapy.

Other Phase I Patients LFT Abnormalities

There are other patients from the phase I studies that manifested LFT abnormalities that fell short of the criteria for an Adverse Event. One such patient is described below.

Study 1008 Subject # 1 was a 29 year-old male enrolled in Study 1008, a dose proportionality study of telithromycin pharmacokinetics after single and multiple oral administration of 400, 800, and 1600 mg of telithromycin to healthy subjects. He received concomitant medications during the study including Augmentin (no dose designated) TID 10/12/98 thru 10/16/98 for pharyngitis and the following medications for nausea and vomiting, metoclopramide 10 mg po bid on 10/29/98, cyclizine lactate 50 mg po on 10/30/98, diclofenac sodium 75 mg IM once on 10/31/98, and prochlorperazine 12.5 mg IM on 10/31/98. He experienced an increase in his liver enzymes in the setting of serum levels of telithromycin 3 to 10 times higher than other subjects on the protocol. His AST and ALT increased (AST from 22 to 82 IU/L (NR 5-40) and ALT from 37 to 74 IU/L (NR 5-72) (re-testing showed an AST of 48 IU/L and ALT 81 IU/L) following the administration of telithromycin at the dose of 1600 mg po qd. Three weeks later his elevated AST and ALT returned to within the normal range. His T. Bili. and alkaline phosphatase remained normal throughout the study. He also experienced an adverse event of "gastrointestinal disorder" (nausea, vomiting, and diarrhea) of severe intensity from day 7 to day 9 of the multiple 1600 mg dose. Pharmacokinetic data was examined for this subject. After single dose administration of telithromycin, Cmax and AUC for Subject #1 was the highest among the subjects in Study 1008. Cmax was [redacted] mg/L and AUC was 48.54 mg*j/L for this subject. The mean Cmax and AUC0-z for the others were 3.929 mg/L and 23.30 mg*h/L, respectively. At the time when this subject experienced severe gastrointestinal discomfort (between the third and the fifth 1600 mg dose), telithromycin trough plasma concentrations were [redacted] mg/L after the third, fourth and fifth dose, respectively. The mean trough levels for the other subjects were 0.172 mg/L, 0.169 mg/L and 0.159 mg/L after the third, fourth and fifth dose, respectively. He did not exhibit eosinophilia during the study period. Subject # 1's renal function remained normal during the study.

Study 1046 Subject # 5 was a 29 year-old male enrolled in Study 1046 a study of the safety, tolerability and pharmacokinetics of single oral doses of telithromycin (2400 and 3200 mg) in healthy young male and female volunteers. He received 2400 mg of telithromycin in period I, 3200 mg telithromycin in period II and placebo in period III. At the Screening visit, and after period I and period II, his AST levels were within the normal range (17.0 IU/L to 39.0 IU/L). Fifteen days after the subject received placebo his AST increased to 82 IU/L. His AST increase was considered a CNALV but not a TEAE. No action was taken in response to the elevated AST. His AST levels returned to normal within 9 days of the noted elevation and there were no sequelae. The increased AST levels were considered by the investigator as attributable to a viral infection. The subject was also noted to have taken 1 gram of acetaminophen and also reported the AEs of sore throat, fever, rhinitis, and myalgia over the 2 days prior to the noted AST abnormalities.

Study 1043 Subject 10 a 70 year old male with carcinoma of the lung and diabetes mellitus did not experience a Hepatic AE, but did have a CNALV for SGPT and alkaline phosphatase. He received telithromycin 800 mg po QD for 4 days. On his Day 6 to 8 labs he was noted to have an ALT of 84 U/L and an alkaline phosphatase of 112 U/L.

Other Phase I Studies

Study 1049 examined the effects of telithromycin 800 mg, telithromycin 1600 mg, clarithromycin 500mg, or placebo on the QT interval. There were no hepatic TEAE's reported in this study nor were there hepatic CNALVs reported.

Study 1056 examined the effects of combined midazolam and telithromycin administration. The study enrolled twelve healthy male subjects. In this study there was a 23-year old white male who experienced elevations in CPK (1.9 xULN), AST (1.7 xULN), and ALT (1.7 xULN), on Day 9 of the telithromycin 800 mg po QD Days 2 to 7 and Midazolam 6 mg po on Day 1 and Day 6 period. This subject (subject No. 2) had an elevated CPK at baseline (1.6 x ULN). On follow-up testing 21-days after his last dose of telithromycin, the subject's lab values were CPK 4.6xULN, AST 1.4xULN, and ALT 2.5xULN.

Study 1048 studied the interaction of telithromycin and simvastatin. The treatment regimens for this study were telithromycin 800 mg po QD and simvastatin 40 mg po QD or simvastatin 40 mg po QD plus placebo. One subject (No. 2) experienced a CNALV for bilirubin at the end of the telithromycin and simvastatin treatment period. The subject's bilirubin value was already elevated before starting treatment (40.2 micromol/L) and also at screening (53.3 micromol/L). His increased bilirubin value was (61.2 micromol/L). The Sponsor notes that this change may be related to underlying Gilbert's disease.

Study 1057 was a study to assess the effects of combined sotalol and telithromycin administration on the QT interval. The two treatment regimens were telithromycin mg po and sotalol 160 mg po or sotalol 160 mg po and placebo. Twenty-five subjects were enrolled and received sotalol and placebo. Twenty-four of the 25 received telithromycin and sotalol (one patient was withdrawn after sotalol and placebo because of QT prolongation). There were no CNALVs or hepatic TEAEs reported.

Study 1060 was an on-going study as of the safety cut-off date of 7 February 2001. The study is designed to evaluate the pharmacokinetics and safety of telithromycin in-patients with hepatic impairment. Twelve patients with hepatic impairment and 12 healthy subjects were to receive telithromycin 800 mg po QD for 7 days. At the time of the safety cut-off date 3 patients with hepatic impairment and 2 healthy patients were enrolled. No hepatic TEAEs or CNALVs were reported in the study to date.

Appendix A.2

Table 38. All Hepatic TEAEs (coded terms) in Subjects Administered Telithromycin: All Completed Controlled Phase III Studies

Coded term	Phase III Studies by Indication									
	Number (%) of Subjects									
	CAP 3006		CAP 3009		CAP 3001		AECB 3007		AECB 3003	
	Telithro 10 d N=221	CLA 10 d N=222	Telithro 7-10 d N=108	TVA 7-10 d N=109	Telithro 10 d N=199	AMX 10 d N=205	Telithro 5 d N=180	CXM 10 d N=186	Telithro 5 d N=160	AMC 10 d N=160
LFT abnormal	4 (1.8)	6 (2.7)	3 (2.8)	0 (0.0)	9 (4.5)	9 (4.4)	1 (0.5)	2 (1.1)	3 (1.9)	3 (1.9)
SGPT/ALT increased	0 (0.0)	1 (0.5)	1 (0.9)	0 (0.0)	8 (4.0)	5 (2.4)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
Alk phos increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	4 (2.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SGOT/AST increased	0 (0.0)	0 (0.0)	2 (1.9)	0 (0.0)	2 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
LDH increased	0 (0.0)	1 (0.5)	1 (0.9)	0 (0.0)	3 (1.5)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver damage	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholestatic jaundice	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Jaundice	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bilirubinemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GGT Increased	0 (0.0)	1 (0.5)	1 (0.9)	1 (0.9)	4 (2.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver Tenderness	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total no. of Hepatic Events [a]	6	11	8	2	31	23	1	2	4	4
Total no. of Patients with Hepatic Events	6 (2.7)	11 (5.0)	5 (4.6)	1 (0.9)	22 (11.1)	17 (8.3)	1 (0.5)	2 (1.1)	4 (2.5)	4 (2.5)

Key: CAP=community acquired pneumonia; AECB=acute exacerbation of chronic bronchitis; AMS=acute sinusitis; TONS/PHAR=tonsillitis/pharyngitis

[a] A subject may have had more than one hepatic TEAE.

Adapted from Applicants Table from NDA 21-144 8:v251:p189 (Source: Table 8-281, 8:v253:p174 , Table 8-287, 8:v253:p277, Table 8-293, 8:v254:p054 and Table 8-299, 8:v254:p125), the Applicant's SAS.txp files for the each of the Phase III NDA Studies, and Tables q09/0000036t.1st 19 October 2000, q09/0000042t.1st 16 October 2000, q09/0000048t.1st 16 October 2000

CLA=clarithromycin, TVA=trovafloxacin, AMX=amoxicillin, CXM=cefuroxime axetil, AMC=amoxicillin/clavulanic acid

Table 38. (cont'd) All Hepatic TEAEs (coded terms) in Subjects Administered Telithromycin and Comparator: All Completed Controlled Phase III Studies

Coded Term	Phase III Studies by Indication								
	AMS 3005			TONS/PHAR 3008		TONS/PHAR 3004		AMS 3011	
	Telithro 5 d N=244	Telithro 10 d N=254	AMC 10 d N=245	Telithro 5 d N=229	CLA 10 d N=228	Telithro 5d N=198	PEN 10 d N=196	Telithro 5d N=252	CXM 10 d N=121
LFT abnormal	6 (2.5)	2 (0.8)	1 (0.4)	0 (0.0)	2 (0.9)	3 (1.5)	2 (1.0)	1 (0.4)	0 (0.0)
SGPT/ALT increased	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.5)	7 (3.6)	1 (0.4)	0 (0.0)
Alk phos increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
SGOT/AST increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
LDH increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver damage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholestatic jaundice	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Jaundice	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bilirubinemia	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GGT Increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver Tenderness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total no. of Hepatic Events[a]	8	3	1	3	2	5	11	2	1
Total no. of Patients with Hepatic Events	8 (3.3)	3 (1.2)	1 (0.4)	2 (0.9)	2 (0.9)	5 (2.5)	10 (5.1)	2 (0.8)	1 (0.8)

Key: CAP=community acquired pneumonia; AECB=acute exacerbation of chronic bronchitis;
AMS=acute sinusitis; TONS/PHAR=tonsillitis/pharyngitis

[a] A subject may have had more than one hepatic TEAE.

Adapted from Applicants Table from NDA 21-144 8:v251:p189 (Source: Table 8-281, 8:v253:p174 , Table 8-287, 8:v253:p277, Table 8-293, 8:v254:p054 and Table 8-299, 8:v254:p125), the Applicant's SAS.txp files for each of the Phase III NDA Studies, and Tables q09/0000036t.1" 19 October 2000, q09/0000042t.1" 16 October 2000, q09/0000048t.1" 16 October 2000, Table 170 from the Study 3011 Study Report

AMC=amoxicillin/clavulanic acid, CLA=clarithromycin, PEN=penicillin VK, CXM=cefuroxime axetil

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CLINICAL REVIEW OF NDA 21-144

ACUTE MAXILLARY SINUSITIS

MEDICAL REVIEWER: **Nasim Moledina, M.D.**
Medical Officer, DAIDP, FDA

APPLICANT: Aventis Pharmaceuticals Inc.,
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627.

DRUG: **Generic:** Telithromycin
Trade: Ketek™ Film-Coated tablets

PHARMACOLOGY
CATEGORY: **Ketolide - 14-membered ring**
Macrolide Antiinfective

DOSAGE FORM: Film-coated tablet
STRENGTH: 400 mg

SUBMISSIONS REVIEWED:

The Applicant submitted two studies – 3002 and 3005 with the original NDA submission in support of the acute sinusitis indication. An additional study – 3011 was submitted on February 20, 2001 as a major amendment to the NDA with additional case report forms submitted in March 2001.

The first part of the Medical Officer's Review dated December 19, 2000 includes review of safety and efficacy of two studies – 3002 and 3005. The second MOR (review of the amendment) dated May 08, 2001 includes review of study 3011 and the overall summary of all the three studies, conclusions and recommendations.

CLINICAL REVIEW OF NDA 21-144

ACUTE MAXILLARY SINUSITIS

TABLE OF CONTENTS

MEDICAL OFFICER'S REVIEW OF NDA 21-144

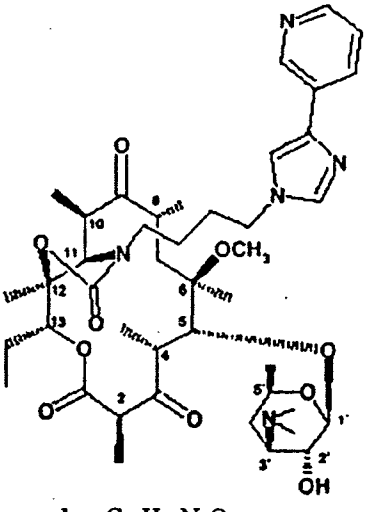
KETEK™ FILM-COATED TABLETS
ACUTE MAXILLARY SINUSITIS INDICATION

Date Submitted:	**February 28, 2000**
Diskette Received:	**June 01, 2000.**
MOR Initiated:	**October 5, 2000.**
MOR Completed:	**December 19, 2000.**
Executive Summary:	**May 16, 2001.**

APPLICANT: Aventis Pharmaceuticals Inc.,
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627.

DRUG: **Generic:** Telithromycin
Trade: Ketek™ Film-Coated tablets
Chemical Name: 11,12-dideoxy-3-de [(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl) oxy]6-O-methyl-3-oxo-12, 11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]erythromycin.

Chemical Structure:



Molecular Formula: $C_{43}H_{65}N_5O_{10}$
Molecular Weight: 812.03

Pharmacology Category:	Ketolide - 14-membered ring Macrolide Antiinfective
Dosage Form:	Film-coated tablet
Strength:	400 mg

PROPOSED INDICATIONS:

The applicant has requested the following indications for approval:

INDICATIONS AND USAGE

KETEK™ tablets are indicated for the treatment of infections caused by susceptible strains of the following designated common pathogens, including resistant strains of *S. pneumoniae,* and atypical pathogens in the specific conditions listed below for patients 18 years old and above, except in tonsillitis/pharyngitis in which KETEK™ is indicated for patients 13 years old and above:

Community-acquired pneumonia due to *S. pneumoniae,* including strains resistant to penicillin and erythromycin, *H. influenzae, H. parainfluenzae, M. catarrhalis, C. pneumoniae, L. pneumophila,* and/or *M. pneumoniae.*

Acute bacterial exacerbation of chronic bronchitis due to *S. pneumoniae, H. influenzae, H. parainfluenzae, M. catarrhalis, S. aureus, C. pneumoniae,* and/or *M. pneumoniae.*

Acute sinusitis due to *S. pneumoniae,* including strains resistant to penicillin and erythromycin, *H. influenzae, H. parainfluenzae, M. catarrhalis,* and/or *S. aureus.*

Tonsillitis/Pharyngitis due to *S. pyogenes* in patients 13 years old and above.

DOSAGE AND ADMINISTRATION

KETEK™ tablets can be administered with or without food.

Infection	*Daily dose And route of Administration*	*Frequency of Administration*	*Duration of Treatment*
Acute bacterial exacerbation of chronic Bronchitis	800 mg oral (2 tablets)	once daily	5 days
Acute sinusitis	800 mg oral (2 tablets)	once daily	5 days
Tonsillitis /Pharyngitis	—	—	—
Community-acquired pneumonia	800 mg oral (2 tablets)	once daily	7-10 days

Related Material: IND 55,283; DMF — DMF — DMF — DMF — DMF — DMF — DMF — DMF —

SUBMISSION REVIEWED:

This Medical Officer's review will address the safety and efficacy of telithromycin in patients with Acute Maxillary Sinusitis. The applicant has submitted the data in an electronic format with case report forms and integrated efficacy and safety summaries.

Chemistry, Manufacturing and Controls:

Refer to the chemistry review by Dr. Andrew Yu.

Pharmacology and Toxicology:

Refer to the toxicology review by Dr. Terry Peters.

Human Pharmacokinetics and Bioavailability:

Refer to the pharmacokinetics review by Dr. Jenny Zheng.

Microbiology:

Refer to the microbiology review by Dr. Fred Marsik.

Statistical:

Refer to the statistical review by Dr. George Rochester.

The Applicant submitted two studies – 3002 and 3005 with the original NDA submission in support of the acute sinusitis indication. An additional study – 3011 was submitted on February 20, 2001 as a major amendment to the NDA with additional case report forms submitted in March 2001.

The first part of the Medical Officer's Review dated December 19, 2000 includes review of safety and efficacy of two studies – 3002 and 3005. The second MOR (review of the amendment) dated May 08, 2001 includes review of study 3011 and the overall summary of all the three studies, conclusions and recommendations.

Executive Summary of Acute Bacterial Sinusitis

The applicant submitted three clinical studies in support of the acute bacterial sinusitis indication for telithromycin (HMR 3647):

Protocol	Study Type	Dose/Frequency/Duration	Number of Patients	Geographic Location
Study 3002[1]	Multicenter, randomized, double-blind, controlled trial	Ketek 800 mg qd for 5 days Ketek 800 mg qd for 10 days	170 randomized 171 randomized	Austria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Sweden
Study 3005	Multicenter, randomized, controlled, three-arm trial	Ketek 800 mg qd for 5 days Ketek 800 mg qd for 10 days Augmentin®500/125 mg tid for 10 days	258 randomized (165 USA pts) 270 randomized (174 USA pts) 262 randomized (169 USA pts)	Argentina, Canada, Chile, S. Africa, USA **64.3% - USA patients**
Study 3011[1,2]	Multicenter, double-blind, 2:1 randomized, controlled	Ketek 800 mg qd for 5 days Cefuroxime axetil 250 mg bid for 10 days	252 randomized (145 USA pts) 122 randomized (66 USA pts)	France, S. America, S. Africa, USA **56.4% - USA patients**

[1]Studies were primarily intended to capture patients who had maxillary sinus punctures for bacteriologic studies.
[2]Submitted to the NDA as a major amendment on February 20, 2001. Additional case-report forms were submitted on March 05, 2001.

Study 3002:

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

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

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

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

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

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

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

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

The clinical cure rate at posttherapy/TOC was lower in the mITT population compared with the PPc population because indeterminate cases were classified as failures in the mITT analysis.

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

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

Safety:

Adverse Events:

Distribution by body system of possibly related TEAEs (Treatment-emergent Adverse Events) is shown below.

TEAEs possibly related to study medication, by body system

	Number of subjects (%)			
Body system	**HMR 3647 5-d**		**HMR 3647 10-d**	
Total in safety population	166	(100.0%)	167	(100.0%)
Total with possibly related TEAEs	43	(25.9%)	49	(29.3%)
Digestive system	29	(17.5%)	34	(20.4%)
Urogenital system	5	(3.0%)	3	(1.8%)
Nervous system	4	(2.4%)	6	(3.6%)
Special senses	4	(2.4%)	3	(1.8%)
Body as a whole	3	(1.8%)	4	(2.4%)
Metabolic and nutritional disorders	3	(1.8%)	3	(1.8%)
Cardiovascular system	2	(1.2%)	3	(1.8%)
Skin and appendages	2	(1.2%)	2	(1.2%)
Hemic and lymphatic system	0	(0.0%)	2	(1.2%)

TEAEs considered possibly related to the study medication and reported in at least 2% of subjects are summarized by treatment group below:

TEAEs possibly related to study medication in ≥2% of subjects

	Number of subjects (%)			
Adverse event	**HMR 3647 5-d**		**HMR 3647 10-d**	
Total in safety population	166	(100.0%)	167	(100.0%)
Total with possibly related TEAEs	43	(25.9%)	49	(29.3%)
Diarrhea	16	(9.6%)	21	(12.6%)
Nausea	8	(4.8%)	4	(2.4%)
Gastrointestinal pain	3	(1.8%)	7	(4.2%)
Vertigo	0	(0.0%)	4	(2.4%)

Deaths

There were no deaths in the study.

Study 3005:

FDA's Number of evaluable subjects in the populations analyzed for efficacy and safety – 3005

	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%)

* - The Division of Scientific Investigations inspected several sites to validate the data collected by the applicant. Data from two sites 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. This table and all the following tables with FDA analysis for study 3005 were generated with the help of our staff statistician, Dr. George Rochester.

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	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*

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*

Eradication rates at posttherapy/TOC – PPb population

Pathogen*	Eradication rate 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

Safety:

The Treatment-Emergent Adverse Events (TEAE) were as follows:

Study 3005 - TEAEs in ≥2% of subjects

Adverse event	Number of subjects (%)					
	Telithromycin 5 days		Telithromycin 10 days		Amoxicillin/ clavulanic acid	
Total in safety population	244	(100.0%)	254	(100.0%)	245	(100.0%)
Total with TEAEs	137	(56.1%)	164	(64.6%)	144	(58.8%)
Diarrhea	49	(20.1%)	55	(21.7%)	58	(23.7%)
Nausea	31	(12.7%)	28	(11.0%)	21	(8.6%)
Headache	16	(6.6%)	21	(8.3%)	19	(7.8%)
Dizziness	15	(6.1%)	14	(5.5%)	9	(3.7%)
Vomiting	8	(3.3%)	11	(4.3%)	7	(2.9%)
Flatulence	11	(4.5%)	5	(2.0%)	3	(1.2%)
Dyspepsia	8	(3.3%)	9	(3.5%)	7	(2.9%)
Asthenia	8	(3.3%)	6	(2.4%)	5	(2.0%)
Vaginal moniliasis	4	(1.6%)	8	(3.1%)	15	(6.1%)
Abdominal pain	9	(3.7%)	13	(5.1%)	7	(2.9%)
Gastrointestinal pain	4	(1.6%)	6	(2.4%)	9	(3.7%)
Liver function test abnormal	6	(2.5%)	2	(0.8%)	1	(0.4%)
Dry mouth	5	(2.0%)	5	(2.0%)	7	(2.9%)
Somnolence	5	(2.0%)	5	(2.0%)	1	(0.4%)
Rhinitis	6	(2.5%)	4	(1.6%)	6	(2.4%)
Sore throat	3	(1.2%)	4	(1.6%)	6	(2.4%)
Upper respiratory infection	2	(0.8%)	7	(2.8%)	3	(1.2%)
Rash	3	(1.2%)	3	(1.2%)	7	(2.9%)
Pharyngitis	4	(1.6%)	1	(0.4%)	5	(2.0%)
Vaginitis	2	(0.8%)	3	(1.2%)	6	(2.4%)

Medical Officer's Comments:

The most common adverse events were reported in the digestive system for both the Ketek groups and the comparator.

The TEAE possibly related to Ketek were as follows:

Study 3005 – TEAEs possibly related to study medication in ≥2% of subjects

Adverse event	Number of subjects (%)					
	Telithromycin 5 days		Telithromycin 10 days		Amoxicillin/ clavulanic acid	
Total in safety population	244	(100.0%)	254	(100.0%)	245	(100.0%)
Total with possibly related TEAEs	103	(42.2%)	119	(46.9%)	105	(42.9%)
Diarrhea	47	(19.3%)	52	(20.5%)	58	(23.7%)
Nausea	29	(11.9%)	24	(9.4%)	19	(7.8%)
Dizziness	13	(5.3%)	13	(5.1%)	5	(2.0%)
Flatulence	10	(4.1%)	5	(2.0%)	3	(1.2%)
Vomiting	5	(2.0%)	11	(4.5%)	5	(2.0%)
Abdominal pain	8	(3.3%)	13	(5.1%)	6	(2.4%)
Vaginal moniliasis	4	(1.6%)	8	(3.1%)	13	(5.3%)
Gastrointestinal pain	3	(1.2%)	5	(2.0%)	7	(2.9%)
Dyspepsia	6	(2.5%)	8	(3.1%)	3	(1.2%)
Dry mouth	4	(1.6%)	5	(2.0%)	4	(1.6%)
Liver function test abnormal	5	(2.0%)	2	(0.8%)	1	(0.4%)
Asthenia	5	(2.0%)	2	(0.8%)	2	(0.8%)
Headache	2	(0.8%)	10	(3.9%)	3	(1.2%)
Rash	1	(0.4%)	3	(1.2%)	5	(2.0%)
Vaginitis	2	(0.8%)	3	(1.2%)	6	(2.4%)
Abnormal stools	2	(0.8%)	5	(2.0%)	3	(1.2%)

Medical Officer's Comments:

The most common side effects observed in more than or equal to 2% of patients were diarrhea, vomiting and headache. In the 5-day and 10-day Ketek groups, dizziness was twice as common as in the comparator group. There were more patients with liver function abnormalities in the 5-day Ketek as compared to 10-day Ketek and Augmentin groups.

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

Lab parameter	Telithromycin(5 day)			Telithromycin (10 day)		
Hemoglobin	0 /	244	0.00%	0 /	254	0.00%
Platelets	0 /	244	0.00%	0 /	254	0.00%
PT INR	5 /	239	2.09%	12 /	252	4.76%
Leukocytes	3 /	244	1.23%	5 /	254	1.97%
Neutro (Abs.)	9 /	244	3.69%	7 /	254	2.76%
Eosino (Abs.)	0 /	244	0.00%	1 /	254	0.39%
SGOT/AST	3 /	244	1.23%	1 /	254	0.39%
SGPT/ALT	5 /	244	2.05%	4 /	254	1.57%
Alkaline phosphatase	1 /	243	0.41%	0 /	254	0.00%
Total Bilirubin	1 /	244	0.41%	0 /	254	0.00%
Creatinine clearance	0 /	244	0.00%	1 /	254	0.39%
Creatinine	0 /	244	0.00%	0 /	254	0.00%
Potassium	0 /	243	0.00%	2 /	254	0.79%

Lab parameter	Comparator		
Hemoglobin			
Platelets	0 /	245	0.00%
PT INR	0 /	244	0.00%
Leukocytes	8 /	240	3.33%
Neutro (Abs.)	0 /	245	0.00%
Eosino (Abs.)	5 /	245	2.04%
SGOT/AST	2 /	245	0.82%
SGPT/ALT	2 /	245	0.82%
Alkaline phosphatase	1 /	245	0.41%
Total Bilirubin	0 /	245	0.00%
Creatinine clearance	0 /	245	0.00%
Creatinine	0 /	245	0.00%
Potassium	0 /	245	0.00%
	0 /	245	0.00%

Medical Officer's Comments:

There were more SGOT/SGPT changes in the Ketek group as compared to Augmentin. All the abnormal laboratory values went back to baseline after therapy was completed. No discontinuations occurred because of the abnormal LFTs.

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

HMR3647

Criteria	On therapy			Post therapy		
QTc increase						
>=30, <60 msec	38 /	444	8.56%	30 /	418	7.18%
>=60 msec	0 /	444	0.00%	0 /	418	0.00%
QTc value						
>=450 msec men	0 /	196	0.00%	0 /	185	0.00%
>=470 msec women	0 /	253	0.00%	1 /	239	0.42%
>=500 msec	0 /	449	0.00%	0 /	424	0.00%

Comparator

Criteria	On therapy			Post therapy		
QTc increase						
>=30, <60 msec	19 /	231	8.23%	9 /	164	5.49%
>=60 msec	0 /	231	0.00%	0 /	164	0.00%
QTc value						
>=450 msec men	0 /	86	0.00%	0 /	56	0.00%
>=470 msec women	0 /	148	0.00%	0 /	109	0.00%

Medical Officer's Comments:

As mentioned above, all of the QTc changes are < 60 msec when on therapy and post therapy evaluations are made.

Deaths:

There were no deaths in this study.

Study 3011:

Number of subjects evaluable at posttherapy/TOC visit

Population	Number of subjects HMR 3647	Cefuroxime
MITT	240	116
PPc	189	89
BmITT	126	60
PPb	100	49

Clinical outcome at posttherapy/TOC – PPc population

Assessment	Number of subjects (%) HMR 3647		Cefuroxime		Difference	95% CI [a]
N	189		89			
Cure	161	(85.2%)	73	(82.0%)	3.2%	(-7.1; 13.4)
Returned to preinfection State	97		51			
Postinfectious stigmata [b]	64		22			
Failure	28	(14.8%)	16	(18.0%)		

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

Clinical outcome at posttherapy/TOC – PPb population

Assessment	Number of subjects (%) HMR 3647		Cefuroxime		Difference	95% CI [a]
N	100		49			
Cure	84	(84.0%)	38	(77.6%)	6.4%	(-8.8; 21.7)
Returned to preinfection State	48		29			
Postinfectious stigmata [b]	36		9			
Failure	16	(16.0%)	11	(22.4%)		

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

AMS Clinical outcome in subjects with pathogens of importance isolated as a single Pathogen – posttherapy/TOC in the PPb population

		Number of subjects					
		HMR 3647			Cefuroxime		
Pathogen	N	Cure	Failure		N	Cure	Failure
S. pneumoniae	19	16 (84.2%)	3	(15.8%)	8	8 (100.0%)	0 (0.0%)
H. influenzae	23	18 (78.3%)	5	(21.7%)	11	9 (81.8%)	2 (18.2%)
H. parainfluenzae	2	2 (100.0%)	0	(0.0%)	0	0 (0.0%)	0 (0.0%)
M. catarrhalis	3	3 (100.0%)	0	(0.0%)	3	3 (100.0%)	0 (0.0%)
S. aureus	10	10 (100.0%)	0	(0.0%)	4	3 (75.0%)	1 (25.0%)

AMS Clinical outcome in subjects with pathogens of importance isolated as single + multiple pathogens – posttherapy/TOC in the PPb population

		Number of subjects					
		HMR 3647			Cefuroxime		
Pathogen	N	Cure	Failure		N	Cure	Failure
S. pneumoniae	29	25 (86.2%)	4	(13.8%)	12	12 (100.0%)	0 (0.0%)
H. influenzae	32	26 (81.3%)	6	(18.8%)	14	12 (85.7%)	2 (14.3%)
H. parainfluenzae	6	3 (50.0%)	3	(50.0%)	1	1 (100.0%)	0 (0.0%)
M. catarrhalis	7	7 (100.0%)	0	(0.0%)	6	6 (100.0%)	0 (0.0%)
S. aureus	12	11 (91.7%)	1	(8.3%)	4	3 (75.0%)	1 (25.0%)

Bacteriological eradication and clinical cure rates at posttherapy/TOC for single *S. pneumoniae* resistant isolates – PPb population

	Bacteriological eradication [a]						Clinical cure					
	HMR 3647			Cefuroxime			HMR 3647			Cefuroxime		
Causative pathogen	N	N	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Total *S. pneumoniae* [b]	17	14	(82.4%)	7	7	(100%)	17	14	(82.3%)	7	7	(100%)
Total Pen-R or Ery-R [c]	12	10	(83.3%)	3	3	(100%)	12	10	(83.3%)	3	3	(100%)
Pen-R	**8**	**6**	**(75.0%)**	**1**	**1**	**(100%)**	**8**	**6**	**(75.0%)**	**1**	**1**	**(100%)**
Ery-R	10	8	(80.0%)	3	3	(100%)	10	8	(80.0%)	3	3	(100%)
Both Pen-R and Ery-R	6	4	(66.7%)	1	1	(100%)	6	4	(66.7%)	1	1	(100%)

a Eradication includes documented and presumed eradication.

b Total single *S. pneumoniae* Includes all strains isolated at pretherapy/entry and confirmed by CMI regardless Of sensitivity.

c Pen-R = penicillin G resistant (MIC ≥2.0 µg/mL); Ery-R = erythromycin A resistant (MIC ≥1.0 µg/mL).

Bacteriological eradication and clinical cure rates at posttherapy/TOC For *S. pneumoniae* isolates (single + mixed pathogens) resistant to penicillin G and/or erythromycin A – PPb population

	Bacteriological eradication [a]				Clinical cure			
	HMR 3647		Cefuroxime		HMR 3647		Cefuroxime	
Causative pathogen	**N**	**n (%)**	**N (%)**	**N**	**n**	**(%)**	**N**	**n**	**(%)**
Total *S. pneumoniae* [b]	27[d]	24 (88.9%)	11 (100%)	27[d]	23	(85.2%)	11	11	(100%)
Total Pen-R or Ery-R [c]	14	12 (85.7%)	6 (100%)	14	12	(85.7%)	6	6	(100%)
Pen-R	**9**	**7 (77.8%)**	**4 (100%)**	**9**	**7**	**(77.8%)**	**4**	**4**	**(100%)**
Ery-R	12	10 (83.3%)	5 (100%)	12	10	(83.3%)	5	5	(100%)
Both Pen-R and Ery-R	7	5 (71.4%)	3 (100%)	7	5	(71.4%)	3	3	(100%)

a Eradication includes documented and presumed eradication.
b Total *S. pneumoniae* includes all strains isolated at pretherapy/entry and confirmed by CMI regardless of Sensitivity.
c Pen-R = penicillin G resistant (MIC ≥2.0 µg/mL); Ery-R = erythromycin A resistant (MIC≥1.0µg/mL)
D Subject 735/001 had a mixed infection, at posttherapy/TOC the *S. pneumoniae* isolate was eradicated, However, the *H. influenzae* was persistent and subsequent antimicrobial therapy was given. As such this Subject is represented in this table as eradication for *S. pneumoniae* but had an overall clinical outcome of Failure.

Safety:

TEAEs possibly related to study medication, by body system

	Number of subjects (%)			
Body system		**HMR 3647**		**CXM**
Total safety population	252	(100%)	121	(100%)
Total with possibly related TEAEs	56	(22.2%)	20	(16.5%)
Digestive system	41	(16.3%)	16	(13.2%)
Nervous system	14	(5.6%)	5	(4.1%)
Body as a whole	5	(2.0%)	0	(0.0%)
Urogenital system	4	(1.6%)	2	(1.7%)
Special senses	4	(1.6%)	1	(0.8%)
Musculoskeletal system	2	(0.8%)	0	(0.0%)
Metabolic and nutritional disorders	1	(0.4%)	1	(0.8%)
Hemic and lymphatic system	1	(0.4%)	0	(0.0%)
Skin and appendages	0	(0.0%)	2	(1.7%)
Cardiovascular system	0	(0.0%)	1	(0.8%)
Respiratory system	0	(0.0%)	1	(0.8%)

TEAEs possibly related to study medication in ≥2% of subjects In either treatment group

	Number of subjects (%)			
Adverse event	**HMR 3647**		**CXM**	
Total safety population	252	(100%)	121	(100%)
Total with possibly related TEAEs	56	(22.2%)	20	(16.5%)
Nausea	17	(6.7%)	5	(4.1%)
Diarrhea	15	(6.0%)	6	(5.0%)
Dizziness	7	(2.8%)	0	(0.0%)
Vomiting	5	(2.0%)	3	(2.5%)

Laboratory adverse events

Subjects with medically important TEAE laboratory abnormalities

Treatment/ Subject number	Coded term	Relationship to study med.	Intensity	Serious TEAE
HMR 3647				
629/008	Creatine phosphokinase incr.	None	Mild	No
659/001	SGPT/ALT increased	Possibly	Mild	No
712/006	Thrombocytosis	Possibly	Mild	No
727/008	LFT abnormal	None	Mild	No

(h): high with respect to the normal range.

- HMR 3647 Subject 659/001 (a 41-year old man) experienced a TEAE of elevated SGPT/ALT levels from day 5 of the study. This event was considered to be mild in intensity and possibly related to study medication, but was not categorized as serious. Related laboratory variables in this subject are summarized below:

Hepatic laboratory variables in HMR 3647 Subject 659/001

Analyte (units)	Normal range	Value			
		Day 1	**Day 5**	**Day 18**	**Day 168**
SGOT/AST (U/L)	11–36 U/L	49 (h)	57 (h)	63 (h)	62 (h)
SGPT/ALT (U/L)	6–43 U/L	80 (h)	118 (h)	123 (h)	78 (h)
Alkaline phosphatase (U/L)	31–110 U/L	126 (h)	133 (h)	105	120 (h)
LDH (U/L)	53–234 U/L	157	167	190	184
Total bilirubin (µmol/L)	3–21 µmol/L	5	7	10	9

(h): high with respect to the normal range.

Deaths

There were no deaths in this study.

OVERALL SUMMARY:

The clinical efficacy rates are displayed below for the mITT and PPc analysis. The Division of Scientific Investigations (FDA) inspected two sites to validate the data collected by the applicant. Data from these sites could not be validated at the time of this review. Due to data integrity issues a total of 37 patients were omitted from the data analyses in study 3005.

Clinical Efficacy of HMR 3647and Comparators in Acute Sinusitis (per Medical Officer)

Study #	Telithromcyin (5 day)	Telithromcyin (10 day)	Comparator	95% C.I.
PPc				
3002	91.1%(112/123)	91%(121/133)		(-7.7, 7.9)
3005 (augmentin)	75.3%(110/146) ---	--- 72.9%(102/141)	74.5%(102/137) ---	(-9.9, 11.7) (-12.7, 9.5)
3011 (cefuroxime)	85.2% (161/189)	---	82%(73/89)	(-7.1, 13.4)
MITT				
3002	82.6% (138/167)	87.5% (147/168)	---	(-13.1, 3.3)
3005 (augmentin)	69.7%(140/201) ---	--- 68.6%(140/204)	68.3%(138/202) 68.3%(138/202)	(-8.2, 10.9) (-9.2, 9.8)
3011 (cefuroxime)	80.4%(193/240)	---	72.4%(84/116)	(-2.2, 18.2)

A review of the PPc analysis reveals evidence supporting the efficacy of telithromycin for treatment of sinusitis. Studies 3002 and 3011 were intended to collect information regarding baseline isolates by performing maxillary sinus taps. Both studies had similar cure rates. Study 3005 was more difficult to analyze since it was mainly a clinical study and about 15% of patients enrolled had a history of allergic rhinitis. Therefore, the efficacy of telithromycin for the treatment of bacterial sinusitis may not have been studied. However, the clinical study did demonstrate equivalence to the Comparator.

Some of the reasons the patients in the mITT population were excluded from the PPc populations were: (These were equally distributed among the active and controlled groups)

- Previous antibiotic therapy
- Insufficient treatment duration
- Wrong entry diagnosis
- Lost to follow-up
- No x-ray within 2 days of entry into study
- Baseline laboratory abnormality, so treatment discontinued

The bacteriological evaluation is displayed in the following table. This table includes selected pathogens of clinical importance in acute bacterial sinusitis. It includes patients who had single and mixed isolates. The number of specific isolates is small among the control groups when compared with

telithromycin; however, the cure rates are similar to the overall cure rates observed in the clinical trails.

Clinical Outcome (Cure) in subjects with pathogens of importance in ABS - PPb population at postherapy/TOC

Pathogen	Telithromycin 5 days	Telithromycin 10 days	Augmentin	Cefuroxime
S. pneumoniae	49/55 (89.1%)	24/26 (92.3%)	2/4 (50%)	12/12 (100%)
H. influenzae	36/42 (85.7%)	12/12 (100%)	1/1 (100%)	12/14 (85.7%)
M. catarrhalis	12/13 (92.3%)	3/4 (75%)	1/1 (100%)	6/6 (100%)

The applicant is requesting the acute bacterial sinusitis indication due to S. pneumoniae including penicillin and erythromycin resistant strains. The following table reviews the efficacy of telithromycin across the three studies in the PPb population.

The definition of the breakpoints for *S. pneumoniae* was as follows:

Penicillin		Erythromycin	
Sensitive	< 0.6 ug/mL	Sensitive	≤ 0.25 ug/mL
Intermediate ug/mL	$0.12 \leq$ MIC ≤ 1 ug/mL	Intermediate	$0.25 <$ MIC < 1
Resistant	> 1 ug/mL	Resistant	≥ 2 ug/mL

APPEARS THIS WAY
ON ORIGINAL

Summary of Outcomes by Resistance patterns for *Streptococcus pneumoniae* from all three studies for Acute Bacterial Sinusitis – Telithromycin (PPb population)

Study #	Outcome- Cured					
	Pen-S	PRSP[@]	Ery-S	Ery-R	Pen-S + Ery-S	PRSP+ EryR
3002	32/37 (86.5%)	3/3 (100%)	30/34 (88%)	7/8 (87.5%)	30/34 (88%)	3/3 (100%)
3005	2/2 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)
3011	10/12 (83%)	7/9 (77.8%)	9/11 (82%)	10/12 (83.3%)	9/11 (82%)	5/7 (71.4%)
TOTAL	44/51 (86.3%) *12 mixed** *10/12 (83.3%)*	11/13 (84.6%) *2 mixed* *2/2 (100%)*	41/47 (87%) *12 mixed* *9/12 (75%)*	18/21 (85.7%) *5 mixed* *5/5 (100%)*	41/47 (87%) *11 mixed* *10/11 (91%)*	9/11 (82%) *2 mixed* *2/2 (100%)*

*mixed- cultures which contained bacterial pathogens in addition to *S. pneumoniae*

[@] In study 3002, only one patient was in the 5-day Ketek® treatment arm, and none in study 3005. ***Since the applicant is requesting a 5-day treatment regimen in the labeling for this indication, the total # of PRSP cured in the 5-day arm was 8/10 – 80%.***

There were 4 PRSP in the cefuroxime axetil group in study 3011, and all were cures.

Eight (8) PRSP isolates were from the United States, 4 from France and one from South Africa.

There were 14 *S. pneumoniae* isolates classified as intermediate penicillin sensitivity. All of these patients were cured.

CONCLUSION:

Based upon the analyses of clinical data submitted in the NDA, telithromycin is effective in treating acute bacterial sinusitis due to selected susceptible organisms. On the contrary, data submitted for treating resistant organisms, especially penicillin-resistant *S. pneumoniae* (PRSP) was insufficient, but the outcome in these patients was similar to patients with Pen-S organisms. There were more patients with erythromycin-resistant *S. pneumoniae(ERSP),* but since we do not have enough knowledge regarding the Public Health impact of ERSP at this time, adequate clinical study of this entity is required before this indication can be granted. The patient population in these studies had mild to moderate sinus infection, thus the benefit of telithromycin must be weighed against it's risk of potential hepatic and cardiac toxicity.

The data from this application was presented to the Anti-Infective Advisory Committee on April 26, 2001. The majority of members voted against granting the indication of acute sinusitis citing that there were not enough resistant organisms, and that they were concerned about the potential hepatic and cardiac toxicity.

RECOMMENDATIONS:

The applicant has requested the following in the INDICATIONS AND USAGE section of the label:

INDICATIONS AND USAGE

Acute sinusitis due to *S. pneumoniae,* including strains resistant to penicillin and erythromycin, *H. influenzae, H. parainfluenzae, M. catarrhalis,* and/or *S. aureus.*

Based upon the data submitted and the recommendations made by the committee members at the Anti-infective Advisory Committee, and all the reasons cited in my conclusions, the indication of Acute Sinusitis due to *S. pneumoniae,* including strains resistant to penicillin and erythromycin, *H. influenzae, H. parainfluenzae, M. catarrhalis,* and/or *S. aureus.* is not recommended for approval.

MEDICAL OFFICER'S REVIEW OF INDICATION – ACUTE MAXILLARY SINUSITIS:

The applicant has conducted two studies in support of this indication:

Study 3002:

"A multicenter, randomized, double-blind, comparative study, evaluation of Safety and Efficacy of Oral HMR 3647 (Ketek™) 800 mg once a day for 5 days versus HMR 3647 800 mg once a day for 10 days in the treatment of Acute Maxillary Sinusitis in adults."

Study 3005:

"A multicenter, randomized, double-blind, active-controlled, comparative three-arm study, evaluation of Safety and Efficacy of Oral HMR 3647 (Ketek™) 800 mg once a day for 5 days versus HMR 3647 800 mg once a day for 10 days versus amoxicillin/clavulanic acid 500/125 mg three times a day for 10 days in the treatment of Acute Maxillary Sinusitis in adults."

Medical Officer's Review of Study 3005:

Background Information on Ketek™ (As provided by the Applicant):

HMR 3647 belongs to the family of ketolides representing a new class of 14-membered ring macrolide antibacterial antibiotics. Ketolides are characterized by a ketone function in position three of the macrolactone ring instead of the cladinose moiety, a sugar long thought to be essential for antibacteriologic activity.

HMR 3647 possesses well-balanced antibacteriologic activity against all relevant pathogens involved in respiratory tract infections (RTI). Its spectrum of activity includes gram-positive aerobic organisms such as *Streptococcus pneumoniae,* Group A beta-hemolytic streptococci, and *Staphylococcus aureus*; gram-negative bacteria such as *Moraxella catarrhalis* and *Haemophilus influenzae* regardless of the resistance antibiophenotypes; and atypical bacteria, such as *Chlamydia* spp, *Mycoplasma* spp, and *Legionella* spp.
HMR 3647 is active against multiresistant pneumococci, including penicillin-resistant and macrolide constitutively-resistant strains whose prevalence is currently increasing and could lead to a notable public health problem in the near future in many countries worldwide. In addition, unlike macrolides, HMR 3647 does not induce so-called macrolide lincosamine streptogramine-B resistance (MLSB), thereby exhibiting potent activity against all macrolide inducibly resistant strains. Conforming to its *in vitro* profile, HMR 3647 displays potent therapeutic efficacy in animals challenged with the main pathogens involved in human respiratory tract infections (RTIs).

Toxicity studies indicated that the toxicologic profile of the drug was similar to that of other macrolides. Studies in the rat and rabbit have not shown any evidence of a potential teratogenic effect. Based on preclinical studies, adverse events potentially anticipated with HMR 3647 were similar to those observed with the macrolide family of antibiotics, namely gastrointestinal side effects (nausea, vomiting, gastric pain, diarrhea), an increase in hepatic enzymes, and under rare circumstances, hypersensitivity reactions and pancreatic disorders.

In clinical pharmacology studies, HMR 3647 has been administered orally over a dose range of 50 to 1200 mg (single and multiple doses) in more than 500 subjects, including elderly subjects and subjects with renal or hepatic impairment. Following a single oral dose, HMR 3647 is rapidly absorbed with the median time to maximum plasma concentration (t_{max}) ranging from 1.0 to 3.0 hours. The pharmacokinetics of HMR 3647 appear to be dose dependent, with plasma concentrations increasing slightly more than the dose in healthy subjects. C_{max} is approximately 2 mg/L for the 800

mg per day regimen. Steady state is reached after 2 to 3 days of dosing. The plasma elimination of HMR 3647 is biphasic with a half-life of approximately 2 hours for the initial phase and about 10 hours for the terminal phase at the 800-mg doses. The percentage of drug excreted unchanged in the urine increases with the dose and represents approximately 13% of the dose following a dose of 800 mg. Penetration into respiratory tissues is good. Mean concentrations 8 hours after the last dose of a 5-day treatment with 800 mg HMR 3647 once daily were as follows: epithelial lining fluid 4.2 mg/L, bronchial tissue 2.2 mg/L, alveolar macrophages 100 mg/L. These concentrations are higher than the minimum inhibitory concentrations (MICs) for HMR 3647 of the main pathogens encountered in acute maxillary sinusitis.

Based on preclinical and initial tolerance and pharmacokinetic data obtained in healthy volunteers, a dosing regimen of 600 to 800 mg/day produces a plasma concentration that ensures adequate coverage of the main respiratory pathogens, including strains of *S. pneumoniae* resistant to penicillin G and/or erythromycin A. A dosage of 800 mg once daily, which gives a better ratio of plasma level to minimum inhibitory concentration (MIC) of respiratory pathogens, and was well tolerated in young and elderly subjects in phase I studies, has been selected for the clinical trials conducted in subjects with respiratory tract infections (RTIs).

Acute maxillary sinusitis (AMS) is an infection of one or more paranasal sinuses. AMS is usually a complication of the common cold or viral infections of the upper respiratory tract and occurs in approximately 0.5% to 2% of these subjects. The infectious agents responsible for most cases of acute sinusitis are *S. pneumoniae* (20% to 35%), *H. influenzae* (6% to 26%), concomitant presence of both of them (1% to 9%), and *S. aureus* (0% to 8%). These percentages can vary depending on the country. *S. pyogenes*, *M. catarrhalis*, gram-negative bacteria, and anaerobic bacteria can also cause sinus infections. A sinus puncture with aspiration of the sinus material is the most reliable method to establish the diagnosis and bacterial etiology.

Antibiotics are used for treatment because they shorten disease duration and prevent complications. They are usually chosen on an empirical basis, since sinus puncture is not routinely performed in a clinical setting. The antibiotics must be active against the most common causative pathogens. The most frequently used compounds for treatment of sinusitis are beta-lactams, second and third generation cephalosporins, and macrolides.

Treatment duration for RTIs varies between 7 and 14 days; however, current medical trends favor a reduction in treatment duration for RTIs. The scientific rationale is that this could improve compliance and lead to a lower rate of adverse effects. The efficacy of shorter treatment durations has been

demonstrated in previous trials with different classes of antibiotics. Current cost constraints also justify studies with a shorter antibiotic treatment period that can potentially lower costs.

HMR 3647 is more active against *S. pneumoniae* than macrolides, regardless of *S. pneumoniae* resistance to penicillin or erythromycin and does not induce MLSB resistance. HMR 3647 is active against strains of *S. pneumoniae* resistant to penicillin G; it has also been shown that HMR 3647 is active against strains of *S. pneumoniae* resistant to tetracycline, chloramphenicol and quinolones. HMR 3647 should therefore represent a valuable first-line treatment for subjects with AMS due to its outstanding and well-balanced activity against the majority of pathogens involved in RTIs, including the resistant strains mentioned above.

This study (3005) was performed to compare the efficacy and safety of HMR 3647 800 mg once daily for 5 days versus HMR 3647 800 mg once daily for 10 days versus amoxicillin/clavulanic acid (AMC) 500/125 mg three times daily for 10 days in subjects with AMS.

The dosage used for HMR 3647 in this study (800 mg once daily for 5 or 10 days) has been established based on the preclinical data described above and on the pharmacokinetic profile in young and elderly subjects. This approach takes into account the susceptibility of different bacterial strains. In pharmacokinetic studies, HMR 3647 was found in high concentrations in white blood cells, with significant levels 48 hours after the last dose. From these data, it is expected that high and sustained levels of the drug will reach the infection site. A treatment duration of 5 days should ensure adequate drug levels at the infection site for at least 2 days after the end of treatment. The combination of AMC was selected as the comparator in this study due to its proven efficacy and activity against the most common causative pathogens for acute bacterial sinusitis. A standard dosage regimen of AMC 500/125 mg three times a day for 10 days was used for this study.

Study Title

A multicenter, randomized, double-blind, active-controlled, comparative three-arm study, evaluation of the efficacy and safety of oral HMR 3647 800 mg once a day for 5 days versus HMR 3647 800 mg once a day for 10 days versus amoxicillin/clavulanic acid 500/125 mg three times a day for 10 days in the treatment of acute maxillary sinusitis (AMS) in adults.

Investigator(s), Study site(s)

Multicenter study at 69 centers: Argentina (2), Canada (11), Chile (2), South Africa (3), and United States (51).

Phase 3

Indication

Acute maxillary sinusitis (AMS)

Objectives

Primary objective:

The primary objective was to demonstrate clinical equivalence in clinical efficacy and assess the safety of HMR 3647 given for 5 days versus HMR 3647 given for 10 days versus amoxicillin/ clavulanic acid given for 10 days in the treatment of AMS at posttherapy/test of cure (TOC).

Secondary objective:

The secondary objective was to assess the bacterial efficacy of HMR 3647 at posttherapy/TOC.

INVESTIGATIONAL PLAN

Study design

This was a prospective, multicenter, randomized, double-blind, active-controlled, three-arm parallel-group (1:1:1) comparative study conducted at 69 centers.

At the pretherapy/entry visit (day 1), subjects were randomized to one of the following three treatment groups: HMR 3647 800 mg orally once daily for 5 days or HMR 3647 800 mg orally once daily for 10 days or AMC 500/125 mg orally three times daily for 10 days. An on-therapy visit was to be performed at days 3 to 5. After the end of treatment, subjects were to complete further visits at end of therapy (days 11 to 13), posttherapy/TOC (days 17 to 21) and late posttherapy (days 31 to 36).

The time windows for the posttherapy/TOC and late posttherapy visits were changed by protocol amendment for the purposes of study conduct, to ensure that visits fell within a short time window for the majority of subjects (protocol amendment no. 2, 20 July 1998). 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.

Subjects lost to follow-up or who withdrew from the study 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 from the first packaging order. Amendment no. 3 (dated 7 December 1998) allowed replacement of 106 subjects to achieve the planned number of 120 per treatment arm of evaluable subjects and increased the number of centers to approximately 65 centers.

Subjects who prematurely withdrew from the study or initiated subsequent antibiotic therapy for 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. 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.

Selection of subjects

Number of subjects

Approximately 516 subjects were to be enrolled and treated with study medication at approximately 50 centers. The number of subjects was increased to approximately 624 and the number of centers was increased to approximately 65 due to degraded AMC tablets found during routine stability testing (changed by amendment no. 3, 7 December 1998).

Routine stability testing at the 3-month time point of the blinded AMC tablets used in the second packaging order of study medication (PK01732) revealed that a fraction of the blinded tablets was degraded. As a result, all investigative centers were notified to stop enrollment of subjects and to return unused study medication immediately. For those subjects who were participating in the study the center was to unblind the study medication. Subjects who had been randomized to AMC were to be discontinued from study medication, switched to an appropriate antibiotic at the discretion of the investigator, and scheduled for study exit procedures immediately. Subjects who had been randomized to either the HMR 3647 5-d group or HMR 3647 10-d group could be continued per scheduled study visits at the investigator's discretion.

All of the data for the subjects who had been treated with the AMC tablets in packaging order PK01732 were invalidated. In addition, the data from the subjects randomized to HMR 3647 were not evaluable for the efficacy analysis in the PPc and mITT populations. All of the subjects in all three treatment groups were included in the efficacy analysis for the ITT population and included in the safety population. One hundred-five (105) enrolled subjects were excluded for this reason. Therefore it was necessary to amend the protocol to allow replacement of these subjects to achieve the planned number (120 per arm) of evaluable subjects. It was also necessary to increase the number of centers to approximately 65 centers (changed by amendment no.3, 7 December 1998).

Medical Officer's Comments:

The Inclusion and Exclusion criteria summarized below are acceptable and the study was conducted according to the draft guidelines proposed by the division.

Inclusion criteria

Subjects meeting all of the following criteria were to be considered for admission to the study:

- Subjects, male and female, aged 18 years or greater
- For female subjects, the following criteria were to be met:
- postmenopausal for at least 1 year, or
- surgically incapable of bearing children, or
- of childbearing potential, and all of the following conditions applied: normal menstrual flow within 1 month before study entry

and

- negative pregnancy test (serum β-subunit HCG) immediately before study entry (i.e., before the start of treatment or any other study procedure that could potentially harm the fetus). If obtaining, the serum pregnancy test result would have caused a delay in treatment, the subject was to be entered on the basis of a negative urine pregnancy test sensitive to at least 50 mU/mL, pending results of the serum pregnancy test.

Subsequently, if the result of the serum test was positive, the subject was to be discontinued from study medication, and every attempt was to be made to follow such subjects to term

and

- agreed to use an accepted method of contraception (i.e., oral or implanted contraceptive with a barrier method, spermicide and barrier method, or

IUD). The subject must have agreed to continue with the same method throughout the study

Clinical criteria

At least one of the following signs and symptoms lasting less than 28 days:

- purulent nasal discharge visualized in the middle meatus or postnasal discharge
- maxillary tenderness
- maxillary pain at percussion
- maxillary toothache
- facial pain, pressure, or tightness
- nasal congestion with poor response to nasal decongestants **and**

Radiological Criteria

Abnormal maxillary sinus X-ray, three views, (taken within 48 hours before initiation of study medication) with:

- presence of air fluid level and/or total sinus opacity and/or
- ≥6 mm mucosal thickening (added by amendment no. 2, 20 July 1998).

Note: The radiological criteria could have been based on the investigator's assessment and then confirmed by a radiologist after enrollment.

Informed consent was to be obtained for all subjects before enrollment in the study.

Exclusion criteria

Subjects meeting any of the following criteria were not to be included in the study:

- A history of recurrent sinusitis defined as more than three episodes of sinusitis in the preceding 12 months which required antibiotic therapy
- A history of chronic sinusitis defined as symptoms lasting greater than 28 days
- Suspected concomitant sphenoidal sinusitis
- Nosocomial acquired sinusitis (e.g., hospitalization or nonambulatory institutional confinement, including nursing homes within 2 weeks)
- Obstructive anatomic lesions in nasopharynx like nasal polyps, tumor, severe septal deviation, etc.

- Needed immediate surgery for maxillary sinusitis
- Use of nasal catheter, nasogastric or nasotracheal intubation
- Suspected nonbacterial infections
- Immotile cilia syndrome
- Cystic fibrosis
- Concomitant odontological infection that would require antibiotic therapy or surgery
- A microbiologically documented infection with a pathogen known prior to inclusion to be resistant to the study medications
- Female subjects who were breast-feeding or were pregnant, as demonstrated by serum or urine pregnancy tests carried out before exposure to study medication or the start of any study procedure that could pose a risk to the fetus
- Were receiving other medications, including systemic antimicrobial agents, or who had other disease conditions or infections that could interfere with the evaluation of drug efficacy or safety
- Suspected or known hypersensitivity to, or a suspected or known serious adverse reaction to the study medications, beta-lactam or macrolide antibiotics
- Required on-study treatment with medications known to have contraindicated drug interactions with the study medication and/or macrolides, in general, including but not limited to:
- Ergot alkaloid derivatives, terfenadine, cisapride, astemizole, pimozide, cholinesterase inhibitors (e.g., tacrine, donepezil, physostigmine), ketamine, and quinidine (changed with amendment no. 5, 22 February 1999)
- On maintenance corticosteroid therapy either inhaled nasal or systemic
- Required treatment with probenecid
- Received treatment with other systemic (oral or parenteral) antibiotics within 7 days prior to enrollment
- Received prior therapy with AMC for this infectious episode
- Received any other investigational drug within 1 month prior to study entry or such treatment planned for the study period
- A progressively fatal disease; life expectancy ≤3 months
- Any concomitant condition, including clinically relevant cardiovascular, neurologic, endocrine, or other major systemic disease that could have made implementation of the protocol or interpretation of the study results difficult
- Subjects with known long QT syndrome or severe hypokalemia (changed with amendment no. 5, 22 February 1999).
- Recent (within the previous 3 months) history of drug or alcohol abuse
- Impaired hepatic function, as shown by any of the following:
- AST ≥2 times the upper limit of the reference range

- ALT ≥2 times the upper limit of the reference range
- Bilirubin >upper limit of reference range (except for Gilbert's disease)
- Alkaline phosphatase ≥1.25 times the upper limit of reference range
- Prothrombin time (PT) ratio of ≥1.3 times the control or international normalization ratio (INR) of ≥1.3 times the control when the ISI is 1.0, except for subjects receiving oral anticoagulants (changed with amendment no. 2, 20 July 1998)
- Encephalopathy.
- Impaired renal function, as shown by creatinine clearance ≤50 mL/min (creatinine clearance could have been estimated by formula or nomogram).

- Immunocompromised subjects, such as:

- HIV infection and either had an AIDS-defining condition (e.g., Kaposi's sarcoma, *Pneumocystis carinii* pneumonia or has a CD4 + T-lymphocyte count of <200/μL.
- Neutropenia (<1500 neutrophils/mm^3) not attributable to the acute infectious disease.

- Metastatic or hematologic malignancy.
- Splenectomized subjects or subjects with known hyposplenia or asplenia.
- A mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
- Unlikely to comply with the protocol, e.g., uncooperative attitude, inability to return for follow-up visits, and unlikelihood of completing the study.

Any waiver of these inclusion and exclusion criteria was to have been approved by the investigator and the sponsor on a case-by-case basis prior to enrolling the subject. This was to be documented by both the sponsor and the investigator.

Subjects were not allowed to enroll in this study more than once.

No subjects who were previously treated with HMR 3647 were to be enrolled in this study.

Study treatments

The identity of the treatment regimen was blinded by encapsulating active study medication tablets or placebo (lactose filler) in opaque (00) capsules. With the exception of batch RJ9804, which was recalled from the field, the encapsulation of active study medication in these opaque (00) capsules was not shown to alter the in vitro dissolution or stability of the medication. This

batch had been manufactured using
The initial stability batches of encapsulated AMC and the first clinical batch used in the study had not used a It appeared that the use of accelerated the degradation process of the AMC tablets.
Future batches of encapsulated AMC were not
The investigator or pharmacist was to inventory and acknowledge all shipments of study medication. All study medication was to be kept in a locked area with access restricted to designated study personnel. The study medication was to be stored in accordance with the manufacturer's instructions. At the conclusion of the study, all unused study medication and all medication containers were returned to the sponsor.

Dosage schedule

All subjects in the study were randomized to receive one of the following treatments:

HMR 3647 800 mg (400 mg capsules x 2) once daily in the morning and two matched placebo capsules twice daily at midday and evening for 5 days followed by two placebo capsules three times a day for 5 days. This treatment group is also referred to throughout the clinical study report as HMR 3647 5-d group.

HMR 3647 800 mg (400 mg capsules x 2) once daily in the morning and two matched placebo capsules twice daily at midday and evening for 10 days. This treatment group is also referred to throughout the clinical study report as HMR 3647 10-d group.

Amoxicillin one matched capsule of 250 mg and AMC one matched capsule of 250/125 mg three times daily in the morning, midday and evening for 10 days. This treatment group is also referred to throughout the clinical study report as AMC group.

The time of first dose of study medication administration and the treatment assignment number on the study medication unit dose cards were to be documented on the case report form.

The randomization schedule was prepared by the RANDO (randomization) administrator at Hoechst Marion Roussel The schedule was maintained and stored with the responsible Clinical Quality Assurance function at Hoechst Marion Roussel

For analysis of drug levels, the bioanalyst responsible was unblinded prematurely. The bioanalyst, however, confirmed in writing that he or she

would not disclose the randomization schedule or the analytical results to anybody before the official opening of the randomization schedule. This document was included in the trial master file.

Compliance

Subjects were instructed to bring their study medication unit dose cards with them to the on-therapy (days 3 to 5) and end of therapy (days 11 to 13) visits. Compliance was assessed by unused capsule counts. Details were to be recorded on the case report form.

Prior and concomitant illnesses and treatments

Prior and concomitant illnesses

Additional illnesses present at the time informed consent was given were regarded as concomitant illnesses and were to be documented on the appropriate pages of the case report form.

Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, were to be documented as adverse events on the appropriate pages of the case report form.

Most of the prior and concomitant illnesses (underlying diseases) are presented as general risk factors for morbidity.

Prior and concomitant treatments

All additional treatments being taken by the subject on entry to the study or at any time during the study were regarded as concomitant treatments and were documented on the case report form.

No oral or parenteral concomitant antimicrobial treatments were permitted for the duration of study medication. Subjects who required antimicrobial treatments other than the study medication during the study were to be discontinued from study medication and withdrawn from the study.

Concomitant nonantimicrobial treatments were to be kept to a minimum during the study. However, if concomitant nonantimicrobial treatments were considered to be necessary for the subject's welfare and were unlikely to

interfere with the study medication, they could be given at the discretion of the investigator.

Subjects were permitted to use a nasal decongestant like oxymetazoline 0.05% and could also use nonsteroidal anti-inflammatory drugs, if use was considered to be necessary. The use of nasal decongestants and/or nonsteroidal anti-inflammatory drugs was to be documented on the case report form.

Subjects were not permitted to use maintenance corticosteroid therapy either inhaled, nasal or systemic.

The following medications were contraindicated: ergot alkaloid derivatives, terfenadine, astemizole, cisapride, pimozide, cholinesterase inhibitors (e.g., tacrine, donepezil, physostigmine), ketamine, ketoconazole, itraconazole, fluconazole, disopyramide, quinidine, cardiac glycosides (e.g., digoxin), procainamide, bretylium and sotalol. Protocol amendment no. 5 (22 February 1999) removed the contraindication for the following: ketoconazole, itraconazole, fluconazole, disopyramide, procainamide, bretylium and sotalol. In addition, amendment no. 5 removed cardiac glycoside (e.g., digoxin) from the list of contraindicated medications, added digoxin to the list of precautioned medications, monitored throughout the study for the occurrence of serious adverse events (or any relevant finding of digoxin toxicity) and for plasma levels of digoxin.

Co-administration of probenecid was not allowed because probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with AMC could have resulted in increased and prolonged blood levels of amoxicillin.

Subjects who were taking concomitant mineral antacids or any oral iron preparations were not to take these substances within 2 hours before or after administration of HMR 3647 to avoid potential drug interactions. Preliminary data available at the time of protocol preparation indicated that food intake did not significantly affect the rate and extent of absorption of HMR 3647, these data were later confirmed.

Interactions between macrolide antibiotics and the following drugs have been reported:

- Theophylline
- Amiodarone
- Bromocriptine
- Cyclosporine
- Carbamazepine
- Triazolam
- Midazolam

- Oral anticoagulants (warfarin)
- HIV protease inhibitors
- Reverse transcriptase inhibitors
- Cardiac glycosides (e.g., digoxin) (added by amendment no.5, 22 February 1999).

In subjects who had taken one of these drugs concomitantly, a blood sample was to be taken before receiving study medication drugs (at pretherapy/entry visit) for the future determination of the serum levels of these drugs. Additionally, blood samples were to be taken for future determination of serum levels of these drugs plus HMR 3647, in cases of serious adverse events that occurred while the subject was receiving study medication. Details of the dose of these treatments, the time of blood sampling, and the times of last intake of these treatments and the study medication were to be entered on the case report form.

Additional monitoring was necessary at the pretherapy/entry, on-therapy, and end of therapy visits for the following drugs:

- Cyclosporine - plasma creatinine levels
- Amiodarone - ECG monitoring
- Warfarin – PT or INR.

If abnormal or adverse changes occurred from pretherapy findings for these parameters, the subject could be discontinued from study medication at the investigator's discretion.

Any subject undergoing surgical treatment(s) incompatible with the aims of the study was not to be enrolled. The use of nasal catheters, and nasotracheal or nasogastric intubation were not permitted during the study. Surgical procedures that were planned prior to enrollment in the study could be performed if they did not interfere with the treatment or evaluation of the sinusitis as judged by the investigator and the sponsor, and did not need to be reported as adverse events. For subjects who needed to undergo unplanned surgical procedures during the study, the reason for surgery was to be documented as an adverse event on the case report form. The surgical procedure was to be documented in the "comments" section of the adverse event form.

Study procedures and schedule

Overview of data collection

The **primary efficacy data** were clinical outcome at the posttherapy/TOC visit. According to the protocol, this visit was to be performed between days 17 and 24. During the study, this window was amended to days 17 to 21 for

the purposes of study conduct in an attempt to improve the homogeneity of the subject population (amendment no. 2, 20 July 1998). However, for the primary efficacy analysis, all data within the original 8-day window of days 17 to 24 are valid for the assessment of test of cure, and it is therefore this window that is used for the primary efficacy analysis. The primary assessment of clinical efficacy was based on the investigator's evaluation of clinical response (cure or failure) at posttherapy/TOC, using the following criteria:

- Clinical signs and symptoms: documentation of signs and symptoms of AMS listed in the case report form according to a scale from 0 to 3 at each visit **AND**
- Sinus x-ray: record of findings overreads by a radiologist and evaluation of improvement, no change or worsening of radiological signs of AMS.

That is, based on his/her clinical judgment, the investigator was asked to use the clinical signs and symptoms and the sinus x-ray findings to classify the clinical outcome of the subject as either cure, failure or indeterminate.

In addition, among the subjects classified as cure at posttherapy/TOC, the investigator was asked to distinguish between subjects who had returned to their preinfection state (classified as cure – returned to preinfection state), and those with residual symptoms which in the investigator's opinion represented a normal course of clearance of the inflammation process (classified as cure –improved/postinfectious stigmata). Residual symptoms requiring subsequent antibiotics in the opinion of the investigator were classified as failure.

The **secondary efficacy data** were clinical outcome at the late posttherapy visit (either by phone contact or actual visit), bacteriological outcome at posttherapy/TOC visit and at late posttherapy. The time window for the late posttherapy visit was also changed by protocol amendment no. 2, to days 31 to 36; however, an extended time window of days 31 to 45 was used for the per-protocol analyses, in an attempt to improve the homogeneity of the subject population. 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 treatment groups.

The secondary assessment of bacteriological efficacy was based on bacteriological culture and testing of isolates obtained by sinus puncture. If the subject had a total clinical recovery, eradication was presumed and there was no indication to perform a new sinus puncture.

Safety was evaluated using the following criteria: adverse events reported, laboratory safety data, 12-lead ECG recordings, physical examinations, and vital signs.

Additional assessments included the following: compliance with study medication, assessed by counting unused capsules at the on-therapy and the end of therapy visits, and population pharmacokinetics. The pharmacokinetic data obtained in this study was reported separately.

For analysis of HMR 3647 drug levels, the bioanalyst responsible was unblinded prematurely. The bioanalyst however, confirmed in writing that he would not disclose the randomization schedule or the analytical results to anybody before the official opening of the randomization schedule. The analysis for the plasma HMR 3647 concentration-time data from this study was incorporated and analyzed with plasma HMR 3647 concentration-time data from other multicenter trials and reported separately in a population pharmacokinetic/ pharmacodynamic report.

Description of study days

Pretherapy/entry visit (day 1):

Subjects were assessed for eligibility for inclusion into the study based on inclusion/exclusion criteria. Medical/surgical history was taken and a physical examination was performed. Eligible subjects were randomized after signing informed consent forms. Demographic data were recorded. Vital signs were measured and a 12-lead ECG was performed. Sinusitis-related signs and symptoms were assessed. Sinus X-rays from three separate views (i.e., occipitomental, occipitofrontal, and lateral) were taken and assessed. The radiological diagnosis could have been based on the investigator's assessment and then confirmed by a radiologist after enrollment. For selected sites listed in the sinus puncture amendments, sinus puncture samples were taken for Gram staining and culture. The positive radiological diagnosis was to be made **before** a sinus puncture was performed. Subjects were to be dispensed study medication **after** sinus puncture and **before** the bacteriological results were available, at the selected sites listed in the sinus puncture amendments. For women of childbearing potential, serum and urine pregnancy tests were performed. Blood and urine samples were taken for laboratory safety testing, and a blood sample was to be taken as a pretherapy/entry comparison for measuring plasma HMR 3647 concentration. Data on prior and concomitant treatments were collected. Study medication was dispensed. Subjects were instructed to bring all unused study medication to their next visit for compliance verification. An appointment was made for days 3 to 5 (on-therapy visit).

Any adverse events that occurred since signing the informed consent form were documented.

On-therapy visit (days 3 to 5) and end of therapy visit (days 11 to 13):

Infection-related signs and symptoms and overall clinical status were assessed. If there were a worsening of clinical signs/symptoms and a change in antibiotic therapy was necessary, the subject was to have a sinus X-ray (three views: occipitomental, occipitofrontal, and lateral). In addition, if the subject were from a site listed in the sinus puncture amendments, a sinus puncture sample was to be done for Gram staining. Blood and urine samples were taken for laboratory safety testing and a blood sample was taken for measuring plasma HMR 3647 concentration. A physical examination was performed at the on-therapy visit. Vital signs were measured and a 12-lead ECG was carried out. Concomitant medication, adverse events and compliance were documented. At the on-therapy visit, subjects were instructed to bring all unused study medication to their next visit for compliance verification. An appointment was made for the next study visit.

Posttherapy/TOC visit (days 17 to 21):

Infection-related signs and symptoms were assessed and overall clinical outcome was evaluated. A sinus X-ray (three views: occipitomental, occipitofrontal, and lateral) was performed. For selected sites listed in sinus puncture amendments, a sinus puncture sample for bacteriological exams was done only in case of clinical failure with need for additional antibiotic therapy. Blood and urine samples were taken if samples were not collected at the end of therapy visit (days 11 to 13), or any abnormal results from the end of therapy visit required additional follow-up. For women of childbearing potential, a blood sample was taken for serum pregnancy testing. A physical examination was performed, vital signs were measured, and a 12-lead ECG was carried out if not performed or abnormal at the end of therapy visit. Concomitant medication and adverse events were documented. All study medication was to be collected and counted, if not done previously. An appointment was made for days 31 to 36 (telephone call late posttherapy visit).

Late posttherapy visit (days 31 to 36):

If the subject were not seen at the posttherapy/TOC visit, all of the posttherapy/TOC visit procedures were to be performed. All subjects assessed as clinically cured at the posttherapy/TOC visit received a telephone visit. The subject was to be questioned regarding: reoccurrence of infection-related signs and symptoms, concomitant treatment, any additional antibiotic therapy for AMS or complications resulting from AMS since posttherapy/TOC, and adverse events were documented. If AMS or related

symptoms returned or worsened after the posttherapy/TOC visit, the subject was to have an office visit with the following assessments performed: assessment of infection-related signs and symptoms, vital signs, physical examination, a sinus X-ray (three views: occipitomental, occipitofrontal, and lateral), and for selected sites listed in the sinus puncture amendments, a sinus puncture sample for bacteriological exams, in case of treatment failure or need for additional antibiotic therapy. For females of childbearing potential, a serum pregnancy test was to be performed if a serum pregnancy test was not performed at the posttherapy/TOC visit. If clinically significant abnormal ECG results were obtained at the end of therapy visit and the ECG was not performed at the posttherapy/TOC visit, a 12-lead ECG was to be performed. If clinically significant abnormal clinical laboratory results were obtained at the end of therapy visit or posttherapy/TOC visit, clinical laboratory assessments were to be performed. The investigator was to assess the clinical outcome for all subjects based on the study evaluations performed.

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 (changed by amendment no. 5, 22 February 1999).

The specific changes in visit schedule and data collection outlined in amendment no. 5 (22 February 1999) were as follows:

Premature discontinuation of study medication and no subsequent antibiotic therapy for AMS: If a subject was prematurely discontinued from study medication at a scheduled visit and a subsequent antibiotic was not initiated, the subject was to continue with the study schedule as outlined above. If a subject prematurely discontinued study medication between visits, the subject was to complete the next scheduled visit within 72 hours and continue with the study schedule as outlined above.

Premature withdrawal from the study: If a subject prematurely withdrew from the study at a scheduled visit, all procedures for that visit were to be completed. If a subject prematurely withdrew from the study between visits, the subject was to complete the next scheduled visit within 72 hours. In either situation, a physical exam and pregnancy test (for females of childbearing potential) was also to be done even if it were not scheduled for that visit. Any abnormal findings observed on physical exam that emerged or worsened since a previous physical exam were to be reported as adverse events. The pregnancy test result was to be documented on a report to the site from the central laboratory.

Initiation of subsequent antibiotic therapy for AMS:

If subsequent antibiotic therapy for AMS were initiated at a scheduled visit, all procedures for that visit were be completed. If subsequent antibiotic therapy were initiated between visits, the subject was to complete the next scheduled visit within 72 hours. In both cases, no other visits were to be completed in the case report form. In addition, a physical examination and pregnancy test (for females of childbearing potential) was to be completed and documented in the subject's medical record even if not scheduled for that visit. Any abnormal findings observed on physical exam that emerged or worsened since a previous physical exam were to be reported as adverse events. The pregnancy test result was to be documented on a report to the site from the central laboratory. The investigator was to assess the outcome of the subsequent antibiotic therapy and document any adverse events, which occurred when this therapy was completed. This could have been done either by phone or office visit. The investigator was to determine the timing of the assessment. The outcome was to be entered in the comment field on the "Completion of Study" page in the case report form. The assessment categories were "Cure," "Failure," or "Unknown." The assessment visit or phone call was considered the withdrawal visit for the subject.

Note: If subsequent antibiotic therapy was started at the late posttherapy visit, follow-up on the outcome was not done. The late posttherapy visit was to be completed as planned, ending the subject's participation in the study.

Methods of data collection

Efficacy data

Infection-related signs and symptoms

The following clinical signs and symptoms were recognized as indicators of AMS infections:

- purulent nasal discharge visualized in the middle meatus; purulent postnasal discharge; maxillary tenderness; maxillary pain at percussion; maxillary toothache; facial pain, pressure or tightness; nasal congestion; cough; headaches; hyposmia; and fever.

Investigators were to document the presence or absence of these items on the case report form. These clinical signs and symptoms of AMS were monitored at every visit and were recorded on a scale of 0 to 3, where 0=absent; 1=mild; 2=moderate; and 3=severe, and the improvement or disappearance of each was documented on the case report form. Fever was recorded as present or absent only. If possible, the clinical signs and symptoms of the disease were to be assessed by the same investigator within each study center.

Sinus X-ray

A three-view sinus X-ray (occipitomental, occipitofrontal, and lateral) was to be performed before inclusion to confirm the presence of an air fluid level and/or total opacity and/or ≥6 mm mucosal thickening (added by amendment no. 2, 20 July 1998). The subject could be enrolled based on the investigator's evaluation of the sinus X-ray and then the sinus X-ray was to be reviewed by a radiologist to confirm the diagnosis of AMS. The sinus X-ray was to be repeated at posttherapy/TOC (days 17 to 21), for the clinical efficacy evaluation. The X-rays were intended to be scored according to the radiographic scoring system by the computer. However, this was not done because it was not possible for this scoring system to be used by the investigators.

Microbiology

For selected sites, if the sinus X-ray confirmed the diagnosis of AMS, a sinus puncture with sinus fluid aspiration was to be performed before starting the administration of the study medication. Appropriate pretreatment specimens were to be obtained by sinus puncture for isolation, identification, and sensitivity testing of the causative pathogen(s) within 48 hours before the start of therapy. During and after treatment, sinus puncture samples were to be done prior to any subsequent antibiotic treatment or during the course of the study if a new antibiotic were needed.

A Gram stain was to be performed on the sinus puncture sample by a local lab and then evaluated for the presence of bacteria and polymorphonuclear cells (PMNs). These findings were to be documented on the case report form. If bacteria were detected on microscopic examination, the investigator was to document the morphotype observed (i.e., gram positive diplococci, other gram positive cocci, other gram positive bacteria, gram negative cocci, gram negative bacilli, or mixed flora). In addition, susceptibility testing was to be completed.

Organisms isolated in the cultures (primary isolates) were tested for susceptibility by the disk diffusion method to HMR 3647, the comparator and selected other antibiotics. The following compounds were to be tested locally in order to establish a minimal resistance profile on the pathogen isolated during the study: penicillin G, clindamycin, erythromycin A, ampicillin, and cefuroxime.

In addition, 1-microgram oxacillin disks were to be used for the detection of penicillin resistance (zone ≤19 mm) among *S. pneumoniae*, and the nitrocephin test was to be used to detect beta-lactamase. Penicillin minimum

inhibitory concentrations (MICs) were to be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm. Isolates were not to be reported as penicillin resistant or intermediate based solely on oxacillin zone diameter ≤19mm.

The disks for the susceptibility testing and the interpretative criteria for the inhibition zone were provided by the sponsor (tentative inhibition zone criteria for HMR 3647 and NCCLS inhibition zone criteria for all other antibiotics). The susceptibility results based on the disk zone inhibition from the local laboratory were used to summarize the susceptibility pattern of organisms isolated. The investigators were to record the results of the direct microscopy, Gram-stained smears and the culture results in the CRF. If an organism were isolated, the investigator was to record whether the isolate(s) was responsible for the current infection or colonization or normal flora. Subcultures of the primary isolates were then sent to a central microbiology laboratory (CMI) for: 1) identification, 2) simultaneous testing of the disk zone inhibition and minimal inhibitory concentration to HMR 3647, the comparator and selected other antibiotics and 3) quality control strain testing by NCCLS recommended criteria and methodology. If the subculture were not viable (no growth observed) or a different organism were grown at the central laboratory, the local laboratory was asked to send another subculture. If the difference persisted or the isolate was again not viable, the attempt to recover that particular isolate was terminated.

Reconciliation of minor discordances between the central and local laboratory (e.g., *H. influenzae* vs *H. parainfluenzae*) was sometimes possible and these were entered in the CRF through a correction log form. Where no consensus was reached, the local laboratory identification was kept in the CRF.

Safety data

Adverse events

The investigator observed subjects for adverse events (local or systemic) and instructed subjects to report any events that occurred during the study. For the purposes of the study, the period of observation for each individual subject extended from the time the subject gave informed consent until the late posttherapy visit.

The definitions used in the study for the terms "adverse event", "serious adverse event", and "nonserious adverse event" are given below.

The term **adverse event** covered any sign, symptom, syndrome, or illness that appeared or worsened in a subject during the period of observation in the clinical study and that may impair the well-being of the subject. The

term also covered laboratory findings or results of other diagnostic procedures that were considered to be clinically relevant (e.g. that required unscheduled diagnostic procedures or treatment measures, or resulted in withdrawal from the study).

The adverse event may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- An effect of a comparator drug
- Unrelated to participation in the clinical study
- A combination of one or more of these factors.

Adverse events will have been reported by the investigator as serious or nonserious.

A **serious adverse event** is any adverse event that, at any dose of study medication or at any time during the period of observation, meets one of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires or prolongs hospitalization
- Results in persistent or significant disability or incapacity
- Occurs with overdose
- Involves cancer
- Involves congenital anomaly
- Is medically important
- Requires medical intervention to prevent permanent impairment or damage.

A **nonserious adverse event** is any adverse event not meeting the serious adverse event criteria.

Adverse events were to be documented by the investigator on two different forms:

- All serious adverse events were to be documented on a "Serious adverse event" form and reported immediately.
- All nonserious adverse events were to be documented on a "Nonserious adverse event" form.

Only selected data were collected for pretreatment nonserious events, e.g., diagnosis/syndrome, end date, date of onset, and intensity of event.

No alert terms for immediate reporting to the sponsor were specified for this study.

In all cases, the investigator was to make every attempt to describe the adverse event in terms of a diagnosis, listing component symptoms below the diagnosis as appropriate. If only nonspecific signs or symptoms were present, these were each to be recorded as a diagnosis.

In addition, the investigator assessed causality as either possibly related or not related, by answering the following question: "Is there a reasonable possibility that the event is associated with the study medication? [No or Yes]".

Laboratory safety data

The following laboratory tests were performed using standard methods:

- Hematology: hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC; total and differential), platelet count, prothrombin time (PT), partial thromboplastin time (PTT), and INR.

Biochemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase, creatinine, total bilirubin, total protein, glucose, albumin, blood urea nitrogen (BUN), uric acid, inorganic phosphorus, calcium, sodium, potassium, chloride, carbon dioxide.

- Urinalysis: semiquantitative glucose, protein, leukocytes, erythrocytes, and urinary pH.

Routine laboratory safety assessments for study sites in Canada and the United States were performed according to standard laboratory procedures at a central laboratory, [redacted] The study sites in Argentina and Chile used [redacted], as the central laboratory. In South Africa, routine laboratory safety assessments were performed by [redacted], and through an exclusive agreement with [redacted]

Abnormal values were flagged and sent to the investigator for assessment of clinical relevance. Persistent clinically relevant abnormal values were to be followed up, if possible, until the test results returned to the premedication value. Laboratory abnormalities considered to be clinically relevant were to be reported as adverse events and monitored accordingly.