serious adverse event. The event was associated with bradycardia and a QTc increase of 33.5 msec. The event did not lead to discontinuation of the study medication. Of the 4 (2.4%) subjects in the HMR 3647 10-d group with vertigo, the event was of mild intensity in all subjects. None of the events were reported as serious, none were associated with any QTc increase and none led to discontinuation of study medication.

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

Treatment-emergent adverse events possibly related to study medication

TEAEs occurring in 92 subjects were considered by the investigator as possibly related to study medication: 43 subjects (25.9%) in the HMR 3647 5-d group and 49 subjects (29.3%) in the HMR 3647 10-d group. There was no statistically significant difference between the two treatment groups in the number of subjects with possibly related TEAEs.

Distribution by body system of possibly related TEAEs 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%)

Most of the possibly related TEAEs were of mild intensity in both treatment groups: HMR 3647 5-d, 43 events; HMR 3647 10-d, 47 events.

All serious treatment-emergent adverse events

A serious TEAE was reported in four subjects (HMR 3647 5-d: 4 subjects (2.4%); HMR 3647 10-d: 0 subjects. Serious TEAEs displayed by seriousness criterion were as follows:

	Serious TEAEs by seriousness criterion			
	Number of subjects (%)			
Adverse event	**HMR 3647 5-d**		**HMR 3647 10-d**	
Total no. of subjects in safety population	166	(100.0%)	167	(100.0%)
Total with serious TEAEs	4	(2.4%)	0	(0.0%)
Death	0	(0.0%)	0	(0.0%)
Life-threatening	0	(0.0%)	0	(0.0%)
Required or prolonged hospitalization	2	(1.2%)	0	(0.0%)
Permanently or significantly disabling	0	(0.0%)	0	(0.0%)
Occurred with overdose	0	(0.0%)	0	(0.0%)
Involved cancer	0	(0.0%)	0	(0.0%)
Congenital abnormality	0	(0.0%)	0	(0.0%)
Medically important	1	(0.6%)	0	(0.0%)
Required medical intervention	1	(0.6%)	0	(0.0%)

No serious TEAEs that were life-threatening occurred in either treatment group.

In the HMR 3647 5-d group, the two serious TEAEs that required or prolonged hospitalization were infection (1 subject) and vertigo (1 subject). The medically important serious TEAE was infection (1 subject) and the serious TEAE that required medical intervention was accidental injury (1 subject).

The numbers of subjects with serious TEAEs by decreasing frequency were as follows:

	Serious TEAEs			
		Number of subjects (%)		
Adverse event	HMR 3647 5-d		HMR 3647 10-d	
Total no. of subjects in safety population	166	(100.0%)	167	(100.0%)
Total with serious TEAEs	4	(2.4%)	0	(0.0%)
Infection	2	(1.2%)	0	(0.0%)
Accidental injury	1	(0.6%)	0	(0.0%)
Vertigo	1	(0.6%)	0	(0.0%)

None of the serious TEAEs were considered by the investigator to be possibly related to the study medication. Case narratives for all subjects who had at least one serious adverse event, regardless of whether treatment emergent or not, were provided in the NDA and reviewed by the Medical Officer. The Medical Officer concurs with the applicant's conclusions that the serious TEAEs were not related to the study medication.

Deaths

There were no deaths in the study.

Other significant adverse events

There were 49 (14.7%) subjects (24 [14.5%] subjects in the HMR 3647 5-d group; 25 [15.0%] subjects in the HMR 3647 10-d group) who reported a TEAE that fulfilled the "other significant" criteria. Of these 49 subjects, 6 (3.6%) subjects in the HMR 3647 5-d group and 1 (0.6%) subject in the HMR 3647 10-d group had a TEAE that led to discontinuation of study medication. One subject in the HMR 3647 10-d group had therapy interrupted due to a TEAE compared with no subjects in the HMR 3647 5-d group. Twelve (7.2%) subjects in the HMR 3647 5-d group and 14 (8.4%) subjects in the HMR 3647 10-d group had a TEAE treated with counteractive medication, and 10 (6.0%) subjects in the HMR 3647 5-d group and 11 (6.6%) subjects in the HMR 3647 10-d group had TEAEs that were medically important laboratory abnormalities.

Adverse events leading to discontinuation

Treatment with study medication had to be discontinued due to adverse events in seven subjects (2.1%) (six subjects [3.6%] in the HMR 3647 5-d group; one subject [0.6%] in the HMR 3647 10-d group). The TEAEs leading to discontinuation of study medication were reported in a number of different body systems with the digestive system being the most frequently affected.

TEAEs leading to discontinuation of study medication

	Number of subjects (%)			
Adverse event	**HMR 3647 5-d**		**HMR 3647 10-d**	
Total no. of subjects in safety Population	166	(100.0%)	167	(100.0%)
Total with TEAEs leading to Discontinuation of study medication	6	(3:6%)	1	(0.6%)
Diarrhea	1	(0.6%)	0	(0.0%)
Nausea	1	(0.6%)	0	(0.0%)
Vomiting	1	(0.6%)	0	(0.0%)
Cholelithiasis	1	(0.6%)	0	(0.0%)
Gastrointestinal pain	0	(0.0%)	1	(0.6%)
Face edema	1	(0.6%)	0	(0.0%)
Infection	1	(0.6%)	0	(0.0%)
Alkaline phosphatase increased	1	(0.6%)	0	(0.0%)

The numbers in each column are not additive because a subject may have had more than one TEAE leading to discontinuation of study medication

Events leading to discontinuation of study medication in the HMR 3647 5-d group were diarrhea and nausea (both in subject 1903/009), vomiting (705/006), cholelithiasis (1502/007), face edema (503/001), infection (701/010), and alkaline phosphatase increased (201/004). In the HMR 3647 10-d group, subject 501/015 had a TEAE of gastrointestinal pain that led to discontinuation of study medication. Of subjects with TEAEs leading to discontinuation of study medication, 3/6 subjects in the HMR 3647 5-d group and 1/1 subject in the HMR 3647 10-d group had TEAEs that were possibly related to the study medication.

Laboratory adverse events

Abnormal laboratory values in 21 subjects (of a total of 114 subjects with at least one TEAE) were reported as TEAEs by the investigators: 10 subjects in the HMR 3647 5-d group and 11 subjects in the HMR 3647 10-d group. The most frequently reported laboratory adverse event was ALT (SGPT) increased (HMR 3647 5-d: 4; HMR 3647 10-d: 1) followed by liver function test abnormal (HMR 3647 5-d: 2; HMR 3647 10-d: 1), hematuria (HMR 3647 5-d: 2; HMR 3647 10-d: 1), hyperglycemia (HMR 3647 5-d: 1; HMR 3647 10-d: 2) and AST (SGOT) increased (HMR 3647 5-d: 0; HMR 3647 10-d: 3). All three hematuria events were microscopic and were diagnosed by the DIPSTICK method. In addition, all three subjects had signs of hematuria at pretherapy/entry. None of the hematuria events were considered by the investigator to be possibly related to the study medication. One subject recovered without sequelae and for the other two subjects, no further control was deemed necessary by the investigator.

Laboratory safety data

Hematology, blood chemistry, and urinalysis data were examined for changes that occurred during treatment and within 7 days after study drug was discontinued. Mean and median pretherapy/entry, endpoint, and change from pretherapy/entry values were reviewed. In addition, laboratory data were analyzed using predefined changes (PCA) from pretherapy/entry to identify subjects with laboratory values of potential medical concern. The majority of laboratory variables showed no noteworthy findings, although 17 subjects in the HMR 3647 5-d group and 20 subjects in the HMR 3647 10-d group had a shift in random glucose values from normal at pretherapy/entry to high at last observation available on-therapy.

Criteria for extended normal ranges, PCA, and clinically noteworthy abnormal laboratory values

Variable	Unit [a]	Extended normal range	Predefined Change (PC)	Clinically noteworthy value
Hemoglobin	mmol/L	≥6.206 mmol/L	-1.2412 mmol/L	PCA
	g/dL	≥10 g/dL	-2 g/dL	PCA
Leucocytes	G/L	3 - 25 G/L	-2 G/L	<3 G/L
	/mm^3	3000 - 25,000 /mm^3	-2000 /mm^3	<3000 /mm^3
Neutrophils	G/L	≥1.5 G/L	-20% [b]	<1.5 G/L
	/mm^3	≥1500 /mm^3	-20% [b]	<1500 /mm^3
Eosinophils	G/L	≤1.0 G/L	+20% [b]	>1.0 G/L
	/mm^3	≤1000 /mm^3	+20% [b]	>1000 /mm^3
Platelets	G/L	≥100 G/L	-100 G/L	<100 G/L
	/mm^3	≥100,000 /mm^3	-100,000 /mm^3	<100,000 /mm^3
Prothrombin time	sec	≤14 sec	+2 sec	+2 sec and >16 sec
Prothrombin time ratio	%	≥80%	-20%	<70%
INR	-	≤1.2	+0.3	>1.3
SGPT/ALT	U/L	0 - 2 ULN	+2 ULN	>3 ULN
SGOT/AST	U/L	0 - 2 ULN	+2 ULN	>3 ULN
Alkaline phosphatase	U/L	0 - 1.25 ULN	+0.5 ULN	PCA
Bilirubin	µmol/L	0 - 2 ULN	+0.5 ULN	>2 ULN
Serum creatinine	µmol/L	NR	+0.3 ULN	>2 ULN
Creatinine clearance	mL/sec	≥0.8333 mL/sec	-0.5 mL/sec	<0.8333 mL/sec
	mL/min	≥50 mL/min	-30 mL/min	<50 mL/min
Serum potassium	mmol/L	3.0 – 5.5 mmol/L	NAP	<3.0 or >5.5 mmol/L

NAP - Not Applicable
NR - Normal Range, which is used when no extended normal range is defined
ULN - Upper Limit Normal, using the laboratory normal range
[a] When two units are provided for an analyte, the first is the SI unit and the second is the Corresponding alternative unit in clinical use.
[b] Percent of absolute value for neutrophils and eosinophils

All laboratory data have been converted into SI units for the analysis.

Delta limits for variables in the differential blood count are given only in absolute units.

Clinically noteworthy abnormal laboratory values

Thirty-two (32) clinically noteworthy abnormal laboratory values (CNALVs) were observed in 27 (8.1%) subjects, 18 abnormal values in 14 (8.4%) subjects in the HMR 3647 5-d group; 14 abnormal values in 13 (7.8%) subjects in the HMR 3647 10-d group). Of the 32 CNALVs reported in this study, one in the HMR 3647 5-d group and six in the HMR 3647 10-d group were already abnormal at baseline, four in the HMR 3647 5-d group and six in the HMR 3647 10-d group were reported as medically relevant by the investigator, and three in the HMR 3647 5-d group and two in the HMR 3647 10-d group were reported as an adverse event by the investigator.

Of the 10 CNALVs reported as medically relevant by the investigator, four in the HMR 3647 5-d group and four in the HMR 3647 10-d group had returned to within the normal range at the last observation available; for the other two medically relevant CNALVs in the HMR 3647 10-d group, the investigator deemed that no further control was required. Of the CNALVs reported as adverse events, one in the HMR 3647 5-d group, and two in the HMR 3647 10-d group were considered as possibly related to the study medication by the investigator; all subjects recovered without sequelae.

The most common clinically noteworthy values in the HMR 3647 5-d group were decreased neutrophils (7 subjects) and decreased WBC (4 subjects) compared to increased potassium (4 subjects) and decreased neutrophils (3 subjects) in the HMR 3647 10-d group.

	Clinically noteworthy laboratory values					
	HMR 3647 5-d			HMR 3647 10-d		
	No. of subjects with:			No. of subjects with:		
Clinically noteworthy abnormal laboratory value	**CNALV**	**normal baseline value**	**missing baseline value**	**CNALV**	**normal baseline value**	**missing baseline value**
Hematology						
Leukocyte ↓	4	3	1	2	0	1
Neutrophil ↓	7	6	1	3	0	1
Eosinophil ↑	1	0	-	1	0	-
Hemoglobin ↓	1	1	-	0	-	-
Platelets ↓	0	-	-	1	-	-
PT INR ↑	2	1	1	2	1	-
Clinical chemistry						
AST (SGOT) ↑	1	1	-	0	-	-
ALT (SGPT) ↑	0	-	-	1	0	-
Potassium ↑	2	1	1	4	4	-
Total CNALVs	**18**			**14**		

Frequencies of clinically noteworthy abnormal laboratory values were similar between treatment groups for all variables. There were seven subjects in the HMR 3647 5-d group and three subjects in the HMR 3647 10-d group with a clinically noteworthy decrease in neutrophils. Fisher's exact test indicated that there were no significant differences between treatment groups in frequencies of clinically noteworthy abnormal laboratory values, including neutrophils (p=0.219).

The percentage of subjects with CNALVs for each selected analyte was calculated based on the number of subjects in the safety population. This population approximates the number of subjects who provided at least one sample for the period up to and including the last observation available on-therapy for these analytes. For coagulation-related analytes (i.e., prothrombin time, prothrombin time ratio and prothrombin INR), however, not all participating study centers performed the laboratory analysis for all three analytes. Therefore, the number of subjects who had samples for each of these analytes may not be a true reflection of the numbers in the safety population. In the text below, the number of subjects with a clinically noteworthy value for INR is stated relative to how many subjects had the analyte measured, rather than as a percentage of subjects in the safety population.

Decreased neutrophils: 7 (4.2%) subjects in the HMR 3647 5-d group and 3 (1.8%) subjects in the HMR 3647 10-d group had decreased neutrophils that were considered to be a CNALV (<1.5 G/L). None of these laboratory abnormalities led to discontinuation of the study medication. In the HMR 3647 5-d group, the lowest value reached on treatment was 0.8 G/L. Values had returned to normal in 4 subjects and for the remaining 3 subjects no further control was available.

In the HMR 3647 10-d group, two out of three subjects had values already low at pretherapy/entry. The lowest level reached on treatment was 1.0 G/L. Values had returned to normal in 2 subjects and for the remaining 1 subject no further control was considered necessary by the investigator.

Decreased leukocytes: 4 (2.4%) subjects in the HMR 3647 5-d group and 2 (1.2%) subjects in the HMR 3647 10-d group had decreased leukocytes that was considered to be a CNALV (□3.0 G/L). In the HMR 3647 10-d group, one subject already had decreased leukocyte value at pretherapy/entry. The lowest value reached on treatment was 2.2 G/L. None of the decreased leukocyte values led to discontinuation of study medication. Values had returned to normal in one subject and for the remaining subject no further control was considered necessary by the investigator.

Increased INR: 2 out of 53 subjects in the HMR 3647 5-d group and 2 out of 56 subjects in the HMR 3647 10-d group had an INR increase that was considered to be a CNALV (>1.3). Two subjects had values already increased at baseline. The maximum level reached was 2. Values had returned to normal in one subject and for the remaining three subjects no further control was considered necessary by the investigator.

ALT: one (0.6%) subject (701/015) in the HMR 3647 10-d group had an increase in ALT that was considered to be a CNALV (>3 ULN). This subject had an ALT value already above the normal range at pretherapy/entry (54 U/L). AST, alkaline phosphatase and bilirubin were within the normal range at pretherapy/entry. The ALT increased to 135 U/L (3 x ULN) and AST increased to 77 U/L (<3 ULN). The subject did not have other symptoms of liver abnormality, and there were no other known causes for the ALT increase. Increased ALT did not lead to discontinuation of study medication. ALT values decreased to 66 U/L after the end of study treatment. No further control was considered necessary by the investigator.

AST: 1 (0.6%) subject in the HMR 3647 5-d group (1101/001) had an increase in AST that was considered to be a CNALV (>3 ULN). The AST value was within the normal range at pretherapy/entry. ALT, alkaline phosphatase and bilirubin were within the normal range at pretherapy/entry. The AST peaked at 112 U/L (3 x ULN) with an ALT increase to 34 U/L from baseline value of 15 U/L. The subject did not have symptoms of liver abnormality, and there were no other known causes for the AST increase. Increased AST did not lead to discontinuation of study medication. AST decreased after the end of study treatment to 51 U/L and returned to within the normal range at study day 39.

Other safety data

Vital signs

There were no findings of clinical relevance in the vital signs data.

One subject in the HMR 3647 10-d group had an adverse event of hypotension as follows:

Subject 708/024, a 55-year-old female with a history of arterial hypertension enrolled in the study and was randomized to the HMR 3647 10-d group. At pretherapy/entry, the subject's blood pressure was 155/99 mmHg. On study day 2, the subject developed vertigo, asthenia and hypotension (BP: 128/83 mmHg). The investigator considered all three events to be of mild intensity

and possibly related to the study medication. The study medication was continued and all three events resolved on study day 4. The subject recovered without sequelae. At the last observation on study day 18, the subject's blood pressure was 131/84 mmHg.

ECGs

QTc findings were evaluated by a single cardiology expert.

Median QTc values during the study were as follows:

	Evolution of QTc during the study				
	Median QTc (msec)				
Treatment group	Pretherapy/ entry	On-therapy	Post-treatment	Median change pretherapy/entry to on-therapy [a]	Median change pretherapy/entry to post-treatment [a]
Bazett					
HMR 3647 5-d	403.6	403.5	400.2	3.1	–2.2
HMR 3647 10-d	400.3	402.6	399.4	1.7	–0.2
Fridericia					
HMR 3647 5-d	390.8	387.1	391.5	–0.9	0.6
HMR 3647 10-d	386.9	390.6	391.3	0.0	3.2

[a] The median of the per subject changes in QTc

Four subjects in the HMR 3647 5-d group and one subject in the HMR 3647 10-d group had QTc with Bazett or Fridericia formula >450 msec at pretherapy/entry. None of these subjects had an increase in QTc or symptoms of torsade de pointes during the study.

A clear increase in QTc (≥60 msec) was reported for one HMR 3647 5-d subject (405/005) and two HMR 3647 10-d subjects (406/009 and 602/002) using the Bazett formula. No subject in either group had a QTc increase of ≥60 msec using the Fridericia formula. There was no statistically significant difference between treatment groups in the number of subjects with PCs for QTc.

No subject in either treatment group had clinically noteworthy ECG findings. One subject in each treatment group had ECG findings reported as adverse events by the investigator as follows:

- Subject 708/021 in the HMR 3647 5-d group had two adverse events (QT interval prolonged and electrocardiogram abnormal) that started on study day 12. At post-treatment, the subject's QTc interval had increased from 386.8 msec at pretherapy/entry to 407.4 msec (Bazett formula). A similar pattern was observed for QTc interval calculated using the Fridericia formula. The investigator considered both adverse events to be of mild

intensity and possibly related to the study medication: both events resolved on study day 29 and the subject recovered without sequelae.

- Subject 708/033 in the HMR 3647 10-d group had an adverse event (QT interval prolonged) that started on study day 3. The subject's QTc interval increased from 411.4 msec at pretherapy/entry to 427.4 msec at the second ECG recorded on-therapy (day 10; Bazett formula). A similar pattern was observed for QTc interval calculated using the Fridericia formula. No post-treatment ECG data are available, but the adverse event resolved on study day 10 and the subject recovered without sequelae. The investigator considered the event to be of mild intensity and possibly related to the study medication.

For subjects 708/021 and 708/033, the cardiology expert did not confirm the local findings of the investigator. In both subjects, the maximal QTc increase was less than the 30 to 60 msec used to identify subjects with a predefined change of "slight QTc increase" and neither subject had a maximum QTc value of ≥500 msec which would have satisfied the clinically noteworthy criteria. The most common concomitant medications given were omeprazole (HMR 3647 5-d: 1; HMR 3647 10-d: 2) and amphotericin B (HMR 3647 5-d: 0; HMR 3647 10-d: 3). No clinically important ECG findings were reported for subjects who received concomitant medication with the potential for pharmacokinetic/pharmacodynamic interaction.

Applicant's Safety conclusions

The safety conclusions are as follows:

- HMR 3647 800 mg once daily, taken for either 5 or 10 days, was safe and well tolerated. The safety data in terms of adverse events, laboratory values, vital signs and ECG findings did not give any cause for concern.
- The adverse event profile of HMR 3647 observed in this study reflects the experience with antibiotics, especially macrolides in this patient population.
- Treatment emergent adverse events were most commonly reported in the digestive system in both treatment groups: 30/166 (18.1%) subjects in the HMR 3647 5-d group and 37/167 (22.2%) subjects in the HMR 3647 10-d group. Within the digestive system, diarrhea was the most common TEAE reported: (HMR 3647 5-d: 16 [9.6%] subjects; HMR 3647 10-d: 22 [13.2%] subjects).
- Most of the TEAEs experienced by subjects were mild or moderate in intensity. One TEAE (vomiting) reported by one subject in the HMR 3647 5-d group and 5 TEAEs (diarrhea, nausea, gastrointestinal pain, liver function test abnormal and rhinitis) reported by four subjects in the HMR 3647 10-d group were considered severe in intensity.

- The laboratory values, analysed as PCAs and CNALVs, did not show any obvious differences between treatment groups, in particular for transaminases.
- For QTc, the median change from pretherapy/entry and frequency of PCs were similar for both treatment groups. No subject in either treatment group had clinically noteworthy ECG findings.

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Overall Comments and Conclusions:

Based on the efficacy and safety data submitted from two studies, one controlled (study 3005) and the other uncontrolled (study 3002), the Medical Officer has the following comments:

- *Both the studies compared the 5-day treatment with 10-day telithromycin, and study 3005 had a control arm - Augmentin® (AMC). The clinical response at test-of-cure evaluation in the PPc population for Study 3005 was HMR 5-day: 110/146 (75.3%), HMR 10-day: 102/141 (72.3%), and AMC 10-day: 102/137 (74.5%). The clinical response at test-of-cure evaluation in the PPc population for Study 3002 was HMR 5-day: 112/123 (91.1%), and HMR 10-day: 121/133 (91.0%).* ***It is not clear why the clinical response rate is much higher in the uncontrolled study than in the controlled study.***
- *There was sparse bacteriological data collected from the controlled study 3005, but the uncontrolled study 3002 was set up as a bacteriologic study. The bacteriologic outcome was as follows for the two studies:*

	Study 3005		***Study 3002***	
	HMR 5-day	*HMR 10-day*	***HMR 5-day***	*HMR 10-day*
S. pneumoniae	***2/2***	*2/2*	***28/30***	*25/28*
H. influenzae	***2/2***	*3/3*	***14/14***	*11/13*
M. catarrhalis	***0***	*0*	***6/7***	*3/4*

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

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

The dosage and duration proposed is 800 mg (2 tablets) taken once daily for 5 days.

- *The Medical Officer concurs with the safety analysis performed by the applicant for this indication, but the way the ADRs were coded has to be verified by FDA, thus the overall safety data will be resubmitted and will be reviewed in detail by Dr. David Ross and Dr. Edward Cox. Please refer to their reviews.*

Medical Officer's Recommendations:

Given that acute bacterial sinusitis is treated empirically and based on the bacteriologic data submitted, it appears that the data are

insufficient (refer to Points to Consider document which states that in order to grant the acute sinusitis indication, you need at least 25 - S. pneumoniae, 25 - H. influenzae, and 15 - M. catarrhalis) to grant approval for acute sinusitis due to H. influenzae and M. catarrhalis.

In addition, the risk-benefit ratio of Ketek® can not be assessed at this time, since the updated safety data have not been completely reviewed.

/S/

Nasim Moledina, M.D.
Medical Officer, DAIDP
FDA

cc:
Orig NDA 21-144
HFD-340
HFD-520/DepDir/LGavrilovich
HFD-520/MO/NMoledina
HFD-520/MO/ADavidson
HFD-520/Pharm/TPeters
HFD-520/Micro/FMarsik
HFD-520/Chem/AYu
HFD-520/PM/JCintron
nm/12-19-2000;rev 12-21-2000.
rev 05-18-2001.

Concurrence Only:
HFD-520/Acting Div.Dir/JSoreth
HFD-520/ActingTL/JKorvick

MEDICAL OFFICER'S REVIEW OF NDA AMENDMENT 21,144

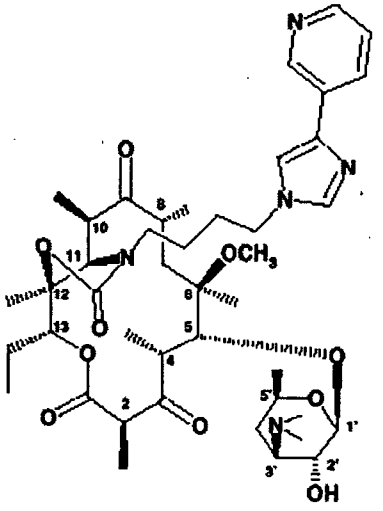
Acute Maxillary Sinusitis

Amendment Received:	February 28, 2001.
MOR Initiated:	March 27, 2001.
MOR Completed:	**May 08, 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

Background:

The applicant had originally submitted two studies, 3002 and 3005 in support for the indication of acute sinusitis. The Medical Officer's review of these two studies was completed on December 19, 2000.

This submission contains data from study 3011, which has been submitted on February 28, 2001, to support the claim for acute sinusitis caused by penicillin and erythromycin-resistant *Streptococcus pneumoniae.*

Medical Officer's Review:

The Medical Officer's review of this amendment will evaluate data collected from study 3011, and also summarize all three studies, give conclusions and recommendations.

STUDY 3011 SYNOPSIS

Title
A multinational, randomized, double-blinded, active-controlled study for evaluation of the efficacy and safety of oral HMR 3647 800 mg once a day for 5 days versus cefuroxime axetil 250 mg twice a day for 10 days in the treatment of acute maxillary sinusitis in adults.

Investigator(s), study site(s)
Multinational, multicenter study conducted at a total of 73 sites: Argentina (3 sites), France (6 sites), South Africa (9 sites) and United States (55 sites).

Phase 3

Indication
Acute maxillary sinusitis (AMS)

Objectives

Primary objective:
To demonstrate equivalence in clinical efficacy at posttherapy/test of cure (TOC) (days 17 to 21) and assess the safety of HMR 3647 800 mg given once daily for 5 days versus cefuroxime axetil 250 mg given twice daily for 10 days in the treatment of subjects with AMS.

Secondary objective:

To assess the bacteriological outcome at posttherapy/TOC (days 17 to 21) and to compare the clinical and bacteriological efficacy at the late posttherapy visit (days 31 to 36) of HMR 3647 800 mg given once daily for 5 days versus cefuroxime axetil 250 mg given twice daily for 10 days in the treatment of subjects with AMS. In addition, to assess the pharmacokinetic and

pharmacodynamic relationship of oral HMR 3647 relative to the clinical and bacteriological outcomes at the posttherapy/TOC visit in subjects with AMS.

Design

This was a multinational, prospective, multicenter, randomized (2 HMR 3647: 1 cefuroxime), double-blinded, active-controlled study.

There were five visits: a pretherapy/entry visit (day 1), an on-therapy visit (days 3 to 5), an end of therapy visit (days 11 to 13), a posttherapy/TOC visit (days 17 to 21), and a late posttherapy visit (days 31 to 36). The end-of-therapy and late posttherapy visits could have been a telephone contact/office interview unless lack of improvement, worsening of signs and symptoms, or reappearance of disease were noted during the telephone contact/office interview, or in the case of the late posttherapy visit, the subject missed the posttherapy/TOC visit. Study medication was first administered on day 1.

Population

Adult subjects, men and women aged 18 years or older with AMS diagnosed clinically and radiologically, who were willing to undergo sinus puncture (US sites) or sinus endoscopy (non-US sites) at the pretherapy/entry (day 1) visit. (An amendment revised the age requirement to allow subjects age 13 years or older at sites using sinus endoscopy to collect sinus aspirates). Approximately 340 subjects were to be enrolled, with the assumption that 75% of subjects would be clinically evaluable and 60% of subjects would be bacteriologically evaluable.

Treatments

HMR 3647 800 mg

Days 1 to 5: Capsules containing 400 mg HMR 3647 and matched capsules containing placebo. Two capsules containing HMR 3647 were taken in the morning and two capsules containing placebo were taken in the evening.

Days 6 to 10: Two matched placebo capsules given twice daily.

Cefuroxime axetil 250 mg

Days 1 to 10: Capsules containing 125-mg cefuroxime axetil (matched in appearance to look like the study medication capsules that contained HMR 3647 and placebo).

Two capsules containing cefuroxime were taken in the morning and two capsules containing cefuroxime were taken in the evening.

Medical Officer's Comments on Inclusion and Exclusion criteria:

Inclusion criteria

The inclusion criteria were similar to those in studies 3002 and 3005 with a few exceptions, which are as follows:

- *Radiographic criteria in studies 3002 and 3005 included patients with mucosal thickness of ≥ 6 mm, but in study 3011, the requirement for inclusion was ≥ 10mm thickness.*
- *Subjects were to have been enrolled before Gram stain or microbiological results were available.*

- *The radiological criteria may have been based on the investigator's assessment and then confirmed by a radiologist after enrollment.*

- *Non-US sites performed sinus endoscopy procedures to obtain specimens for culture. The procedure as described in the protocol is acceptable.*

Exclusion criteria

The criteria used for this study were similar to those used in both studies 3002 and 3005.

*The protocol outlined the **Description of Study Days, Methods of Data Collection, and Analysis of Efficacy and Safety Variables.** All of these criteria are acceptable and similar to the two previous studies submitted.*

APPLICANT'S RESULTS

Subjects were enrolled at 73 centers in 4 countries; however 7 centers (608, 610, 617, 627, 631, 635, 645, 651 and 660) enrolled but did not treat any subjects. Center 601 enrolled the most subjects (47 subjects) and centers 664, 677, and 735 enrolled the least (1 subject each). For the efficacy analysis, centers were pooled by geographic region to give 12 pooled centers.

Subject disposition

Disposition of subjects	**Total**
Number of subjects enrolled	593
Number of investigators (centers)	73
Number of investigators (centers) who randomized:	
less than 18 subjects randomized	71
18 or more subjects randomized	2
Number of investigator pools	12

Subject accounting

	HMR 3647	**Cefuroxime**	**Total**
Enrolled	-	-	**593 (100%)**
Randomized	260	125	**385 (100%)**
FDA censored sites*	8	3	**11 (2.9%)**
Treated	252	122	**374 (97.1%)**

*- These sites were also censored when data from study 3005 was reviewed.

Of the 593 subjects enrolled (gave informed consent), 385 subjects (64.9%) were randomized. The primary reason for enrolled subjects not being randomized was lack of sinus x-ray/CT scan evidence of disease.

Medical Officer's Comments:

Based on the FDA's recommendation, sites 607 and 726 were censored from all efficacy and safety analyses. The total number of subjects censored was 11 subjects (8 treated with HMR 3647 and 3 treated with cefuroxime). The 11 subjects from these 2 sites are excluded from the total number of subjects treated. This did not affect the overall analysis because these patients were excluded from all analysis.

Completion of study

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

	Study completion status					
Subjects with:	**HMR 3647**		**Cefuroxime**		**Total**	
Pretherapy/entry visit	252	(100%)	122	(100%)	**374**	**(100%)**
On-therapy visit	248	(98.4%)	119	(97.5%)	**367**	**(98.1%)**
End of therapy visit	238	(94.4%)	114	(93.4%)	**352**	**(94.1%)**
Posttherapy/TOC visit	236	(93.7%)	107	(87.7%)	**343**	**(91.7%)**
Late posttherapy visit	211	(83.7%)	93	(76.2%)	**304**	**(81.3%)**
Both posttherapy/TOC and late posttherapy visits	211	(83.7%)	93	(76.2%)	**304**	**(81.3%)**

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. This resulted in fewer subjects completing the late posttherapy visit.

Reasons for withdrawal from study

	Number of Subjects			
Reason for Withdrawal	**HMR 3647**		**Cefuroxime**	
Total subjects treated	252	(100%)	122	(100%)
Total subjects withdrawn from study [a]	37	(14.7%)	28	(23.0%)
New adverse event or worsening of an existing adverse event	6	(2.4%)	2	(1.6%)
Subject did not wish to continue in the study	2	(0.8%)	2	(1.6%)
Subject lost to follow-up	3	(1.2%)	2	(1.6%)
At the discretion of the Investigator	0	(0.0%)	1	(0.8%)
Treatment failure and /or new antibiotic started [b]	23	(9.1%)	14	(11.5%)
Sinus x-ray findings insufficient to meet inclusion criteria	2	(0.8%)	1	(0.8%)
Other reasons	1	(0.4%)	6	(4.9%)

[a] A subject could discontinue study medication but complete the study.
[b] Includes subjects who were treatment failures, had no clinical Improvement, had a deterioration of clinical condition, or who received a subsequent antimicrobial.

APPEARS THIS WAY
ON ORIGINAL

Discontinuation of study medication

A total of 23 subjects (HMR 3647: 12 and cefuroxime: 11) discontinued study medication before completion of the assigned treatment duration. The assigned treatment for study medication in both treatment groups consisted of 10 days. Subjects in the HMR 3647 group were to take 2 capsules containing HMR 3647 400 mg in the morning and 2 matched capsules containing placebo in the evening on days 1 to 5 followed by 2 matched placebo capsules in the morning and evening on days 6 to 10. Subjects in the cefuroxime group were to take 2 capsules containing cefuroxime axetil 125 mg in the morning and evening on days 1 to 10. Reasons for discontinuation of study medication were as follows.

Reasons for discontinuation of study medication

Reason for discontinuation of study medication	Number of subjects				
	HMR 3647		Cefuroxime		Total
Total subjects treated	252	(100%)	122	(100%)	**374 (100%)**
Total subjects discontinued study medication [a]	12	(4.8%)	11	(9.0%)	**23 (6.1%)**
Deterioration of clinical condition or delayed response	4	(1.6%)	0	(0.0%)	**4 (1.1%)**
New adverse event or worsening of an existing adverse event	5	(2.0%)	2	(1.6%)	**7 (1.9%)**
Pregnancy	0	(0.0%)	1	(0.8%)	**1 (0.3%)**
Subject did not wish to continue in the study	1	(0.4%)	2	(1.6%)	**3 (0.8%)**
Lost to follow-up	1	(0.4%)	1	(0.8%)	**2 (0.5%)**
Other reasons	1	(0.4%)	5	(4.1%)	**6 (1.6%)**

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

Number of subjects and the specific reasons for discontinuation of study medication due to "other" reason were as follows: *incorrect* dose of study medication - HMR 3657 one subject and cefuroxime 2 subjects; capsule broken so patient decided not to continue in study - cefuroxime one subject; laboratory abnormality - cefuroxime one subject and sinus x-ray/CT findings insufficient to meet inclusion criteria - cefuroxime one subject.

Major protocol violations

There were 78 subjects with major protocol violations in 356 subjects in the mITT population. These subjects were excluded from the PPc population. Of the 374 subjects treated, 18 were excluded from the mITT population due to lack of sinus x-ray/CT findings of the disease. The reasons for exclusion from the mITT and PPb populations, and the major protocol violations for PPc are summarized below.

Reasons for exclusion from mITT and PPb, and summary of major protocol violations for PPc

Reasons for exclusion and major protocol violations:	HMR 3647	Cefuroxime	TOTAL
Total treated	**252**	**122**	**374**
Total excluded from mITT analysis	**12**	**6**	**18**
Subjects without x-ray/CT findings consistent with AMS	12	6	18
Total subjects in mITT analysis	**240 (100%)**	**116 (100%)**	**356 (100%)**
Total excluded from PPc analysis	**51 (21.3%)**	**27 (23.2%)**	**78 (21.9%)**
Insufficient treatment duration	23	12	35
Wrong entry diagnosis	2	3	5
Missing appropriate posttreatment information (except failure)	18	8	26
Use of nonstudy systemic antimicrobial therapy between pretherapy/entry and posttherapy/TOC visits (except failure)	3	3	6
Treatment unblinded before posttherapy/TOC visit	1	0	1
Inability to determine treatment outcome at posttherapy/TOC	5	5	10
Without sinus x-ray/CT within 3 days of entry	2	2	4
Total subjects in PPc analysis	**189 (78.8%)**	**89 (76.7%)**	**278 (78.1%)**
Total excluded from PPb analysis	**89**	**40**	**129**
Without valid causative pathogen at pretherapy/entry	89	40	129
Total subjects in PPb analysis	**100**	**49**	**149**

Note: One subject may have had more than one reason for exclusion or major protocol violation.

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

Minor protocol violations

The following minor protocol violations were identified among the 278 subjects eligible for the primary analysis (PPc) population.

Summary of minor protocol violations – PPc population

Minor protocol violations:	HMR 3647	Cefuroxime	TOTAL
Total in PPc analysis	**189**	**89**	**278**
Posttherapy/TOC visit between days 22 and 24 inclusive (except failures)	18	10	28
Posttherapy/TOC visit on day 16	6	1	7
QTc >450 msec at pretherapy/entry	1	0	1
ALT or AST > 3 times upper limit	0	1	1
Total PPc subjects with minor violations	**25**	**12**	**37**

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

Administration of study medication

Dosage and duration

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

Treatment duration in the mITT population was as follows. 97.5% of patients in the HMR group took 5 days of the active medication, and 82.8% in the cefuroxime group took the medication for 10 days.

Duration of treatment for the mITT population

	Number of subjects (%)		
	HMR 3647		Cefuroxime
Duration of Treatment	Duration of study medication	Duration of *active* study medication [a]	Duration of study medication
Total subjects	240 (100%)	240 (100%)	116 (100%)
<2 days	0 (0.0%)	0 (0.0%)	0 (0.0%)
2 days	2 (0.8%)	2 (0.8%)	1 (0.9%)
3 days	0 (0.0%)	0 (0.0%)	3 (2.6%)
4 days	1 (0.4%)	1 (0.4%)	0 (0.0%)
5 days	3 (1.3%)	234 (97.5%)	2 (1.7%)
6 days	2 (0.8%)	-	2 (1.7%)
7 days	2 (0.8%)	-	0 (0.0%)
8 days	2 (0.8%)	-	0 (0.0%)
9 days	1 (0.4%)	-	1 (0.9%)
10 days	208 (86.7%)	-	96 (82.8%)
11 days	10 (4.2%)	-	8 (6.9%)
>11 days	6 (2.5%)	-	1 (0.9%)
Unknown	3 (1.3%)	3 (1.3%)	2 (1.7%)
Median (days)	10.0	5.0	10.0
Range (days)	2 – 26	2 – 5	2 – 16
Mean ± SD (days)	10.0 ± 1.9	5.0 ± 0.3	10.0 ± 2

[a] Based on comments in the case report form, there were 5 subjects (601/041, 601/045, 601/048, 612/004 and 622/001) who were Incorrectly instructed to take one capsule of study medication twice daily instead of two capsules twice daily. These subjects are included in the active dose duration of 5 days even though they took active study medication for more than 5 calendar days.

Medical Officer's Comments:

In the PPc population the treatment duration is shown in the table below. 98.9% of patients received 5 days of HMR therapy while 91% of cefuroxime patients received 10 days of therapy.

Duration of treatment for the PPc population

Duration of treatment	HMR 3647 Duration of study medication	Duration of *active* study Medication	Cefuroxime Duration of study medication
	Number of subjects (%)		
Total subjects	189 (100%)	189 (100%)	89 (100%)
2 days	1 (0.5%)	1 (0.5%)	0 (0.0%)
3 days	0 (0.0%)	0 (0.0%)	0 (0.0%)
4 days	1 (0.5%)	1 (0.5%)	0 (0.0%)
5 days	1 (0.5%)	187 (98.9%)	0 (0.0%)
6 days	2 (1.1%)	0 (0.0%)	1 (1.1%)
7 days	1 (0.5%)	0 (0.0%)	0 (0.0%)
8 days	1 (0.5%)	0 (0.0%)	0 (0.0%)
9 days	0 (0.0%)	0 (0.0%)	1 (1.1%)
10 days	175 (92.6%)	0 (0.0%)	81 (91.0%)
11 days	6 (3.2%)	0 (0.0%)	6 (6.7%)
>11 days	1 (0.5%)	0 (0.0%)	0 (0.0%)
Median (days)	10.0	5.0	10.0
Range (days)	2 – 12	2 – 5	6 – 11
Mean + SD (days)	9.9 ± 1.0	5.0 ± 0.2	10 ± 1

Demographics and baseline characteristics

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

Demographics and pretherapy/entry characteristics – mITT population

Characteristic	HMR 3647 240 (100%)	Cefuroxime 116 (100%)
Total treated		
Sex:		
Female N (%)	140 (58.3%)	68 (58.6%)
Male N (%)	100 (41.7%)	48 (41.4%)
Age (years):		
Median (range)	40.0 (14 – 84)	40.5 (15 – 81)
<65 years N (%)	221 (92.1%)	107 (92.2%)
13 - <18 years N (%)	4 (1.8%)	2 (1.9%)
18 - <65 years N (%)	217 (98.2%)	105 (98.1%)
≥65 years N (%)	19 (7.9%)	9 (7.8%)
BMI (kg/m^2):		
Mean ± SD	26.7 ± 5.5	25.9 ± 5.1
Weight (kg):		
Mean ± SD	77.0 ± 18.5	74.5 ± 17.1
Race:		
White N (%)	211 (87.9%)	98 (84.5%)
Black N (%)	18 (7.5%)	14 (12.1%)
Asian/Oriental N (%)	6 (2.5%)	3 (2.6%)
Multiracial N (%)	5 (2.1%)	1 (0.9%)
Smoking status:		

Smoker	68 (28.3%)	32 (27.6%)
Ex-smoker	30 (12.5%)	20 (17.2%)
Nonsmoker	142 (59.2%)	64 (55.2%)

Medical Officer's Comments:

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

Demographic and pretherapy/entry characteristics of the PPc, PPb, bmITT, and safety populations were similar.

Primary disease

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

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

	Number of subjects			
Characteristics/prognostic factors:	**HMR 3647**		**Cefuroxime**	
Total number of subjects	**240**	**(100%)**	**116**	**(100%)**
AMS episodes in the last year	94	(39.2%)	52	(44.8%)
Number of AMS episodes requiring antibiotic treatment in last 12 months:				
0	5	(5.3%)	5	(9.8%)
1-3	88	(93.6%)	45	(88.2%)
>3	1	(1.1%)	1	(2.0%)
History of asthma?	39	(16.3%)	16	(13.8%)
Episodes of allergic rhinitis in last 30 days?	64	(26.7%)	27	(23.3%)
Nasal septal deviation:	64	(26.7%)	37	(31.9%)
ENT related surgical history:	70	(29.2%)	27	(23.3%)
Duration of current episode:				
0 to 3 days	0	(0.0%)	0	(0.0%)
4 to 6 days	1	(0.4%)	2	(1.7%)
7-14 days	192	(80.0%)	98	(84.5%)
>15 days	47	(19.6%)	16	(13.8%)
Previous antibiotic therapy within 7 days prior to entry?	0	(0.0%)	0	(0.0%)
Investigator assessment of severity of current AMS episode:				
Mild	14	(5.8%)	2	(1.7%)
Moderate	173	(72.1%)	83	(71.6%)
Severe	53	(22.1%)	31	(26.7%)
Fever present	5	(2.1%)	2	(1.8%)
Sinus x-ray/CT scan findings:				
Air fluid level present	109	(45.4%)	53	(45.7%)
Total opacity present	85	(35.4%)	38	(32.8%)
Mucosal thickening ≥ 10 mm present	122	(50.8%)	61	(52.6%)
Unilateral sinusitis	147	(61.3%)	62	(53.4%)
Bilateral sinusitis	93	(38.8%)	54	(46.6%)
Sinus x-ray/CT scan severity:				
Air fluid level/total opacity with mucosal thickening ≥ 10 mm	56	(23.3%)	26	(22.4%)
Air fluid level/total opacity without mucosal thickening ≥ 10 mm	118	(49.2%)	55	(47.4%)
Mucosal thickening ≥ 10 mm only	66	(27.5%)	35	(30.2%)
Concomitant use of NSAIDs	17	(7.1%)	9	(7.8%)
Concomitant use of nasal steroids	38	(15.8%)	17	(14.7%)
Method of collection for microbiologic sample:				
Sinus puncture	138	(57.5%)	59	(50.9%)
Sinus endoscopy	102	(42.5%)	57	(49.1%)

The duration of the current AMS episode was at least seven days and less than 15 days for the majority of subjects in both treatment groups.

Medical Officer's Comments:

Among the subjects in the mITT population, only one subject in the HMR group had received a previous antimicrobial treatment in the 7 days before pretherapy/entry. Subject 661/005 received treatment with Orelox® (cefpodoxime) from 12 to 17 June 2000 and then started treatment with HMR 3647 on 23 June 2000 (exactly 7 days following treatment with cefpodoxime). This subject was included in the PPc and safety populations. The baseline characteristics and the nature of the primary disease in this patient were similar to the other patients in the group. With the exception of subject 661/005, there were no other subjects in the PPc, PPb or safety populations who received antimicrobial treatment in the 7 days before pretherapy/entry.

Concomitant illnesses

Relevant concomitant illnesses are included within the general risk factors for morbidity. The general risk factors for morbidity defined for this AMS study included chronic obstructive pulmonary disease, asthma, respiratory insufficiency, congestive heart failure, diabetes mellitus, alcoholism, renal disease, sickle cell disease, liver disease and coronary artery disease.

In the mITT population, 10 subjects (4.2%) in the HMR 3647 group and 4 subjects (3.4%) in the cefuroxime group had one general risk factor for morbidity. Only 1 subject (0.4%) in the HMR 3647 group and no subjects in the cefuroxime group had two or more risk factors for morbidity. The most common general risk factor in the mITT population was concurrent diabetes mellitus (HMR 3647 group: 7 subjects [2.9%] and cefuroxime group: 2 subjects [1.7%]).

Concomitant medication

Overall, 261 subjects in the mITT population (HMR 3647 group: 179 {74.6%} and cefuroxime group: 82 {70.7%}) received concomitant medication during treatment with study medication.

Concomitant non-antimicrobial medication

Overall, 261 subjects in the mITT population (HMR 3647 group: 179 subjects {74.6%} and cefuroxime group: 82 subjects {70.7%}) received concomitant medication during treatment with study medication. The most commonly prescribed concomitant nonantimicrobial medication class was nasal preparations, taken by 71 subjects (29.6%) in the HMR 3647 group and 39 subjects (33.6%) in the cefuroxime group. With the exception of corticosteroids for systemic use which were used in a higher percentage of subjects in the cefuroxime group 10.3% (12 subjects) than the HMR 3647 group 5.0% (12 subjects), the usage of concomitant medications which could affect sinusitis symptoms (i.e., analgesics, antiinflammatory products, antihistamines for systemic use, nasal preparations, and cough and cold preparations) was balanced between the two treatment groups. In the PPc population, there was one subject in the HMR 3647 group who received a concomitant medication, which was coded to "antibacterial for systemic use". Subject 620/001 received Ancef® (cephalexin, 1 gm IV for 1 dose) as prophylaxis for a nosebleed; this

subject was later determined a treatment failure and received a subsequent antimicrobial for sinusitis at that time.

Concomitant antimicrobial medication

There were no subjects in the mITT population who received concomitant antimicrobial medication for AMS. In addition, there were no subjects in the PPc, PPb or safety populations who received concomitant antimicrobial medication for AMS.

APPLICANT'S RESULTS - EFFICACY

The primary efficacy variable was clinical outcome at posttherapy/TOC (days 16 to 24). The primary analysis population was the PPc population; the primary efficacy variable was also analyzed for the mITT population.

Medical Officer's Comments:
A random sample (about 30%) of patients was obtained, and detailed CRFs were reviewed to verify the clinical and bacteriologic outcome of these patients. In addition, all CRFs for investigator 629 – Dr. [redacted] were reviewed. It was reported to us by DSI that the technique used by Dr [redacted] to obtain specimens from sinus punctures was questionable, but we could still include his patients in the efficacy and safety analysis. There were no discrepancies found in the data reviewed, thus the applicant's analyses is acceptable.

Number of subjects included in analyses

The numbers of subjects included in each of the efficacy analyses are shown below.

Number of subjects evaluable at posttherapy/TOC visit

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

Applicant's clinical outcome - assessment at posttherapy/TOC visit in the PPc and PPb populations

The clinical outcome comparing HMR 3647 with cefuroxime at posttherapy/TOC in the PPc population is summarized in the table below.

Assessment	Applicant's Clinical outcome at posttherapy/TOC – PPc population 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

The clinical outcome comparing HMR 3647 with cefuroxime at posttherapy/TOC in the PPb population is summarized in the table below.

Assessment	Applicant's Clinical outcome at posttherapy/TOC – PPb population 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

Applicant's clinical outcome by isolated pretherapy/entry causative pathogen in the PPb population

The pathogens of importance in AMS are *S. pneumoniae, H. influenzae, H. parainfluenzae, M. catarrhalis* and *S. aureus*. The clinical outcome at the posttherapy/TOC visit for subjects with pathogens of importance in AMS isolated as a single pathogen at pretherapy/entry in the PPb population is shown in the table below.

Applicant's 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%)

The clinical outcome at the posttherapy/TOC visit for subjects with pathogens of importance in AMS isolated as a single or multiple pathogen at pretherapy/entry in the PPb population is shown in the table below.

Applicant's 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%)

Medical Officer's Comments:

I reviewed all the bacteriologic data submitted for this study from center 629, the investigator was Dr. — and the number of evaluable patients in the PPb population was 10. There were 7 in the HMR 3647 group and 3 in the cefuroxime group. The cure rate was 71% (5/7) in the HMR group versus 33% (1/3) in the cefuroxime group. There was only one penicillin-resistant S. pneumoniae isolated in the HMR group that was a cure. Since the data from Dr — site did not drastically change the overall outcome, his data was included in the overall analysis.

Applicant's clinical outcome - assessment at posttherapy/TOC in the mITT population

The mITT population was a secondary population that was used to support the efficacy analyses in the PPc population. The mITT population included all subjects with a confirmed diagnosis of AMS who received at least one capsule of study drug, excluding those subjects with a sinus x-ray/CT scan at pretherapy/entry that did not support a clinical diagnosis of bacterial sinusitis. The clinical outcome comparing HMR 3647 with cefuroxime at posttherapy/TOC in the mITT population is summarized in the table below.

Assessment	Applicant's Clinical outcome at posttherapy/TOC – mITT population Number of subjects (%) HMR 3647		Cefuroxime	Difference	95% CI [a]
N	240		11 6		
Cure	193	(80.4%)	84(72.4%)	8.0%	(-2.2; 18.2)
Returned to preinfection state	113		58		
Postinfectious stigmata [b]	80		26		
Failure	47	(19.6%)	32(27.6%)		
Failure	29		17		
Indeterminate	18		15		

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

The clinical response rates were 80.4% in the HMR 3647 group and 72.4% in the cefuroxime group, a difference between the groups of 8.0%. The 95% confidence interval of the difference was (-2.2%, 18.2%). The lower bound was greater than –15% and the upper bound was greater than zero, thereby providing further evidence that the two treatment regimens were equivalent. This result supports and reinforces the primary efficacy outcome in the PPc analysis.
The clinical cure rate at posttherapy/TOC was lower in the mITT population compared with the PPc population because indeterminate cases were classed as failure in the mITT analysis.

The reasons for indeterminate outcome in the 33 subjects (HMR 3647: 18 subjects and cefuroxime: 15 subjects) at posttherapy/TOC are summarized below.

Reasons for indeterminate classification in subjects at posttherapy/TOC – mITT population

Reason	HMR 3647 N	HMR 3647 Subject numbers	Cefuroxime N	Cefuroxime Subject numbers
	18		15	
No sinus x-ray/CT scan at posttherapy/TOC	4	600/001, 600/006, 654/002, 738/001	3	600/013, 675/010, 710/001
Insufficient treatment duration	4	601/048, 612/002, 612/004, 706/001	4	612/005, 613/001, 706/002, 756/001
Discontinued due to adverse event (not failure)	3	704/005, 712/005, 727/008	1	709/003
Lost to follow-up	3	733/002, 756/004, 661/004	2	671/002, 733/001
Subject did not wish to continue study (not failure)	2	671/005, 695/002	2	706/004, 733/010
Use of subsequent antimicrobial as treatment for new indication (not AMS failure)	2	650/003, 727/006	0	
Inability to determine clinical outcome at posttherapy/TOC	0		1	706/008
Study medication unblinded before posttherapy/TOC	0		1	664/001
Pregnancy	0		1	738/002

Applicant's bacteriological outcome by subject – assessment at posttherapy/TOC

The bacteriological outcome at the posttherapy/TOC visit in the PPb population was a secondary efficacy analysis in this study. The bmITT population was a secondary population that was used to support the efficacy analyses in the PPb population. The bmITT population included all mITT subjects with a bacteriological sample performed at pretherapy/entry and containing at least one pathogen that was considered by the investigator to be "responsible for infection."

The bacteriological outcome at the posttherapy/TOC visit for the PPb and bmITT populations is shown in the table below.

Applicant's Bacteriological outcome by subject at posttherapy/TOC – PPb and bmITT populations

	Number of subjects (%)					
Assessment	**HMR 3647**		**Cefuroxime**		**Difference**	**95% CI** *a*
PPb population						
N	100	(100.0%)	49	(100.0%)		
Satisfactory [b]	84	(84.0%)	39	(79.6%)	4.4%	[-10.4; 19.3]
Unsatisfactory [c]	16	(16.0%)	10	(20.4%)		
bmITT population						
N	126	(100.0%)	60	(100.0%)		
Satisfactory [b]	102	(81.0%)	44	(73.3%)	7.6%	[-6.7; 22.0]
Unsatisfactory [c]	24	(19.0%)	16	(26.7%)		
Indeterminate	8		6			

[a] Two-sided 95% confidence interval
[b] Includes eradication, presumed eradication, colonization.
c Includes reinfection, superinfection, recurrence, presumed persistence and persistence. For bmITT population unsatisfactory also includes indeterminate.

In the PPb population, the bacteriological outcome was satisfactory for 84 out of 100 subjects (84.0%) in the HMR 3647 group and 39 out of 49 subjects (79.6%) in the cefuroxime group. In comparison, the bacteriological outcome in the bmITT population was satisfactory for 102 out 126 subjects (81.0%) in the HMR 3647 group and 44 out of 60 subjects (73.3%) in the cefuroxime group. In the bmITT analysis, subjects with a bacteriological outcome of indeterminate were categorized as unsatisfactory. Of the 40 subjects (HMR 3647: 24 subjects and cefuroxime: 16 subjects) in the bmITT population with an unsatisfactory outcome, 14 subjects (HMR 3647: 8 subjects and cefuroxime: 6 subjects) had an indeterminate bacteriological outcome.

There were 26 subjects (HMR 3647: 16 subjects and cefuroxime: 10 subjects) in the PPb population with an unsatisfactory bacteriological outcome. In the HMR 3647 group, 13 of the 16 subjects had an outcome of presumed persistence and the remaining 3 subjects had an outcome of persistence. In the cefuroxime group, 9 of the 10 subjects had an outcome of presumed persistence and the remaining subject had an outcome of persistence.

Applicant's bacteriological outcome by pathogen – assessment at posttherapy/TOC

Eradication rates

The bacteriological eradication rates by-pathogen at posttherapy/TOC for all causative pathogens isolated at pretherapy/entry in the PPb and bmITT populations are summarized in the table below.

Applicant's **Eradication rates at posttherapy/TOC – PPb and bmITT populations**

	Eradication rate [b] (%)			
Pathogen [a]	**HMR 3647**		**Cefuroxime**	
PPb population				
Total	112/132	(84.8%)	50/61	(82.0%)
S. pneumoniae	26/29	(89.7%)	12/12	(100.0%)
H. influenzae	26/32	(81.3%)	12/14	(85.7%)
M. catarrhalis	7/7	(100.0%)	6/6	(100.0%)
S. aureus	12/12	(100.0%)	3/4	(75.0%)
H. parainfluenzae	3/6	(50.0%)	1/1	(100.0%)
Other [c]	33/39	(84.6%)	15/23	(65.2%)
bmITT population				
Total	139/159 [d]	(87.4%)	56/67 [d]	(83.6%)
S. pneumoniae	31/34	(91.2%)	15/15	(100.0%)
H. influenzae	34/40	(85.5%)	14/16	(87.5%)
M. catarrhalis	9/9	(100.0%)	6/6	(100.0%)
S. aureus	14/14	(100.0%)	3/4	(75.0%)
H. parainfluenzae	4/7	(57.1%)	1/1	(100.0%)
Other [c]	42/48	(87.5%)	16/24	(66.7%)

[a] Single and multiple pathogen infections
[b] Eradication includes both documented and presumed eradication
[c] "Other" includes pathogens with less than 6 isolates, for a complete list of pathogens included under "other" see the tables referenced in the paragraph above this table.
[d] Denominator was based on total evaluable, excluding indeterminate.

Applicant's Bacteriological outcome at late posttherapy – PPb population

	Number of subjects (%)			
Assessment	**HMR 3647**	**Cefuroxime**	**Difference**	**95% CI**
N	92	46		
Satisfactory	73 (79.3%)	34 (73.9%)	5.4%	[-11.3; 22.2]
Unsatisfactory[a]	19 (20.7%)	12 (26.1%)		

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

The bacteriological outcome rates at late posttherapy are comparable between the HMR 3647 group and the cefuroxime groups in the PPb population.

In the PPb population, there were a total of 11 subjects (HMR 3647: 8 subjects and cefuroxime: 3 subjects) who were included in PPb population at posttherapy/TOC but not at the late posttherapy visit. The reasons for exclusion at late posttherapy for these subjects was as follows: bacteriological outcome was satisfactory but the late posttherapy visit was out of the time window specified (HMR 3647: 7 subjects and cefuroxime: 3 subjects); bacteriological outcome at late posttherapy was indeterminate (HMR 3647: 1 subject and cefuroxime: no subjects). Thus, there were a total of 138 subjects (HMR 3647: 92 subjects and cefuroxime: 46 subjects) evaluable for bacteriological response at the late posttherapy visit.

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

Applicant's Bacteriological outcome at late posttherapy – bmITT population

	Number of subjects (%)				
Assessment	**HMR 3647**		**Cefuroxime**	**Difference**	**95% CI**
N	126		60		
Satisfactory	98	(77.8%)	41 (68.3%)	9.4%	[-5.6; 24.5]
Unsatisfactory[a]	28	(22.2%)	19 (31.7%)		
Indeterminate	9		6		

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

S. pneumoniae *isolates (single + mixed infection)*

In the bmITT population, there were a total of 49 subjects with *S. pneumoniae* from single or mixed pathogen infections isolated at pretherapy/entry that were confirmed by CMI (Clinical Microbiology Institute) and had MIC testing completed. Of the 49 subjects, 35 subjects were in the HMR 3647 group and 14 subjects were in the cefuroxime group. Of the 35 subjects in the HMR 3647 group, 18 subjects (51.4%) had a *S. pneumoniae* isolate that was resistant to penicillin G or erythromycin A or both. Of the 14 subjects in the cefuroxime group, 7 subjects (50.0%) had a *S. pneumoniae* isolate that was resistant to penicillin G or erythromycin A or both.

In the PPb population, there were a total of 38 subjects with *S. pneumoniae* from single or mixed pathogen infections isolated at pretherapy/entry that were confirmed by CMI and had MIC testing completed. Of the 38 subjects, 27 subjects were in the HMR 3647 group and 11 subjects were in the cefuroxime group. Of the 27 subjects in the HMR 3647 group, 14 subjects (51.9%) had a *S. pneumoniae* isolate that was resistant to penicillin G or erythromycin A or both. Of the 11 subjects in the cefuroxime group, 6 subjects (54.5%) had a *S. pneumoniae* isolate that was resistant to penicillin G or erythromycin A or both.

There were 5 subjects with *S. pneumoniae* resistant to penicillin G and/or erythromycin A that were excluded from the PPb population. Four of the 5 subjects were in the HMR 3647 group and the remaining subject was in the cefuroxime group. Subjects may have been excluded for more than one reason. The reasons for exclusion were as follows for the 4 subjects in the HMR 3647 group: insufficient treatment duration – 1 subject, insufficient treatment duration and addition of subsequent antimicrobial – 1 subject, no sinus x-ray within 3 days of entry – 1 subject, posttherapy/TOC visit was after day 24 – 1 subject. The reason for exclusion for the one subject in the cefuroxime group was as follows: missing x-ray at posttherapy/TOC – 1 subject.

The outcome for those 5 subjects with *S. pneumoniae* resistant to penicillin G and/or erythromycin A that were excluded from the PPb population were as follows: in the HMR 3647 group the clinical and bacteriological outcomes for 3 of the 4 subjects were cure and presumed eradication, the remaining subject was assessed with clinical and bacteriological outcomes of indeterminate; in the cefuroxime group the one subject was assessed with clinical and bacteriological outcomes of indeterminate.

The number of subjects with *S. pneumoniae* isolates resistant to penicillin G or erythromycin A or both in the bmITT and PPb populations are presented in the table below.

Number of subjects with *S. pneumoniae* isolates (single + mixed pathogens) resistant to penicillin G or erythromycin A or both - bmITT and PPb populations

Population Treatment Group	Total *S. pneumoniae* [a]	Resistant *S. pneumoniae* [a]	Pen -R [b]	Ery-R [b]	Both Pen-R and Ery-R
bmITT Total	49	25	16	22	13
HMR 3647	35	18	11	16	9
Cefuroxime	14	7	5	6	4
PPb Total	38	20	13	17	10
HMR 3647	27	14	9	12	7
Cefuroxime	11	6	4	5	3

[a] Total *S. pneumoniae* includes all strains isolated at pretherapy/entry confirmed by CMI with MIC data.
[b] Pen-R = penicillin G resistant (MIC ≥2.0 µg/mL); Ery-R = erythromycin A-resistant (MIC ≥1.0 µg/mL)

S. pneumoniae *isolates (single + mixed infection) bacteriological and clinical outcome in evaluable subjects*

The bacteriological eradication and clinical cure rate at posttherapy/TOC in evaluable subjects with *S. pneumoniae* isolates (single + mixed pathogens) are provided in the table below for the bmITT population.

Bacteriological eradication and clinical cure rates at posttherapy/TOC for evaluable subjects with *S. pneumoniae* isolates (single + mixed pathogens) – bmITT 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]	32	29 (90.6%)	13	13 (100%)	32	28	(87.5%)	13	13	(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.

In the bmITT population, 28 of the 32 evaluable subjects with *S. pneumoniae* isolates in the HMR 3647 group had a clinical outcome of cure and had a bacteriological outcome of presumed eradication at the posttherapy/TOC visit. One additional subject (735/001) had a clinical outcome of failure and bacteriological outcomes of documented eradication for *S. pneumoniae* and documented persistence for *H. influenzae*, based on the results of a second sinus puncture. The remaining 3 subjects (604/007, 626/007 and 659/018) had a clinical outcome of failure and a bacteriological outcome of presumed persistence for *S. pneumoniae*.

S. pneumoniae isolates (single + mixed infection) resistant to penicillin G or erythromycin A or both

The bacteriological eradication and clinical cure rates at posttherapy/TOC in subjects with *S. pneumoniae* isolates (single + mixed pathogens) resistant to penicillin G or erythromycin A or both are provided in the table below for the PPb population.

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	n	(%)
Total *S. pneumoniae* [b]	27[d]	24 (88.9%)	11	11 (100%)	27[d]	23	(85.2%)	11	11	(100%)
Total Pen-R or Ery-R [c]	14	12 (85.7%)	6	6 (100%)	14	12	(85.7%)	6	6	(100%)
Pen-R	9	7 (77.8%)	4	4 (100%)	9	7	(77.8%)	4	4	(100%)
Ery-R	12	10 (83.3%)	5	5 (100%)	12	10	(83.3%)	5	5	(100%)
Both Pen-R and Ery-R	7	5 (71.4%)	3	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 ≥ 1.0 µg/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.

In the PPb population, 12 of the 14 subjects in the HMR 3647 group with a *S. pneumoniae* isolate resistant to penicillin G and/or erythromycin A had a clinical outcome of cure and a bacteriological outcome of presumed eradication. Two subjects (604/007 and 659/018) had a clinical outcome of failure and a bacteriological outcome of presumed persistence for *S. pneumoniae*. Both of these subjects had a single *S. pneumoniae* isolate that was sensitive to HMR 3647 and resistant to penicillin G and erythromycin A. Subject 604/007 showed improvement in facial maxillary pain symptoms but still had mild to moderate purulent symptoms of nasal and postnasal discharge on day 13. The sinus x-ray for this subject showed improvement with resolution of mucosal thickening. This subject was given subsequent antimicrobial therapy with amoxicillin + clavulanic acid and had a sinusitis outcome of cure. Subject 659/018 showed resolution of facial/maxillary pain symptoms and improvement in purulent symptoms (from moderate to mild) as well as improvement in mucosal thickening shown by sinus x-ray at posttherapy/TOC. This subject was given subsequent antimicrobial therapy with gatifloxacin and had a sinusitis outcome of failure. Therefore, the assessment of this subject as a failure from the HMR 3647 treatment is questionable. There was an improvement in both symptoms (only mild symptoms remaining) and sinus x-ray following treatment with HMR 3647 and a subsequent course of treatment with a quinolone antimicrobial also resulted in failure. However, a stringent approach was taken and the investigator's assessment of clinical failure was kept.
In the PPb population, all 6 subjects in the cefuroxime group with a *S. pneumoniae* isolate resistant to penicillin G and/or erythromycin A had a clinical outcome of cure and a bacteriological outcome of presumed eradication.

In the bmITT population, 15 of the 18 subjects in the HMR 3647 group with a *S. pneumoniae* isolate resistant to penicillin G and/or erythromycin A had a clinical outcome of cure and a bacteriological outcome of presumed eradication. Two subjects (604/007 and 659/018) had a clinical outcome of failure and a bacteriological outcome of presumed persistence for *S. pneumoniae*. One subject (706/001) had clinical and bacteriological outcomes of indeterminate.

In the bmITT population, 6 of the 7 subjects in the cefuroxime group with a *S. pneumoniae* isolate resistant to penicillin G and/or erythromycin A had a clinical outcome of cure and a

bacteriological outcome of presumed eradication. The remaining subject had clinical and bacteriological outcomes of indeterminate due to missing post-treatment data (i.e., no sinus x-ray at posttherapy/TOC).

S. pneumoniae isolates (single pathogen) resistant to penicillin G or erythromycin A or both

The wording "single pathogen" used in the following tables displaying *S. pneumoniae* resistant to penicillin G and/or erythromycin A indicates that no other causative pathogen was isolated in that subject.

In the bmITT population, there were a total of 31 subjects with *S. pneumoniae* from single pathogen infections isolated at pretherapy/entry that were confirmed by CMI and had MIC testing completed. Of the 31 subjects, 22 subjects were in the HMR 3647 group and 9 subjects were in the cefuroxime group. Of the 22 subjects in the HMR 3647 group, 14 subjects (63.6%) had a single *S. pneumoniae* isolate that was resistant to penicillin G or erythromycin A or both. Of the 9 subjects in the cefuroxime group, 4 subjects (44.4%) had a *S. pneumoniae* isolate that was resistant to penicillin G or erythromycin A or both.

In the PPb population, there were a total of 24 subjects with *S. pneumoniae* from single pathogen infections isolated at pretherapy/entry that were confirmed by CMI and had MIC testing completed. Of the 24 subjects, 17 subjects were in the HMR 3647 group and 7 subjects were in the cefuroxime group. Of the 17 subjects in the HMR 3647 group, 12 subjects (70.6%) had a single *S. pneumoniae* isolate that was resistant to penicillin G or erythromycin A or both. Of the 7 subjects in the cefuroxime group, 3 subjects (42.9%) had a *S. pneumoniae* isolate that was resistant to penicillin G or erythromycin A or both.

The bacteriological eradication and clinical cure rate at posttherapy/TOC in subjects with single pathogen *S. pneumoniae* isolates resistant to penicillin G or erythromycin A or both are provided in the table below for the PPb population.

Applicant's 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).

In the PPb population, 10 of the 12 subjects in the HMR 3647 group with single *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A had a clinical outcome of cure and a bacteriological outcome of presumed eradication. Two subjects (604/007 and 659/018) had a clinical outcome of failure and a bacteriological outcome of presumed persistence for *S. pneumoniae*.

In the PPb population, the 3 subjects in the cefuroxime group with a *S. pneumoniae* isolate resistant to penicillin G and/or erythromycin A all had a clinical outcome of cure and a bacteriological outcome of presumed eradication.

In the HMR 3647 group, there were a total of 16 subjects with a *S. pneumoniae* isolate that was resistant to erythromycin A. These resistant isolates were genotyped to determine the mechanism of resistance to erythromycin A. Eight of the 16 subjects with a *S. pneumoniae* isolate that was resistant to erythromycin A had an isolate with a resistance genotype of mefE (all 8 subjects were from study sites in the US) and the remaining 8 subjects had an isolate with a resistance genotype of ermB (one subject was from a study site in the US, 2 subjects were from study sites in France and 5 subjects were from study sites in South Africa).

In the cefuroxime group, 6 of the 7 subjects with a *S. pneumoniae* isolate resistant to penicillin G and/or erythromycin A had a clinical outcome of cure and bacteriological outcome of presumed eradication. The remaining subject had clinical and bacteriological outcome of indeterminate. Five of those 6 subjects who were a clinical cure and bacteriological presumed eradication had a *S. pneumoniae* isolate with resistant MIC values for cefuroxime. Three of those 6 subjects had a mixed infection with either *M. catarrhalis* or *H. influenzae* isolates with sensitive MIC values for cefuroxime. In 4 of the 6 subjects the bacteriological sample was obtained via sinus endoscopy and for the remaining 2 subjects the bacteriological sample was obtained via sinus puncture. The cefuroxime tissue concentrations achieved for these 5 subjects with *S. pneumoniae* resistant to cefuroxime may have been high enough to provide a clinical cure and/or the sensitivity to cefuroxime for the additional pathogens in 3 of the subjects contributed to improvement of clinical and radiological symptoms.

Among the 6 subjects in the cefuroxime group with a *S. pneumoniae* isolate that was resistant to erythromycin A, one subject had an isolate with a resistance genotype of mefE (this subject was from a study site in the US) and the remaining 5 subjects had an isolate with a resistance gentotype of ermB (3 subjects were from study sites in France and 2 subjects were from study sites in South Africa).

In the HMR 3647 group, for 7 of the 8 subjects that had a *S. pneumoniae* with intermediate resistance to penicillin G the clinical outcome was cure and the bacteriological outcome was presumed eradication. The remaining subject had clinical and bacteriological outcomes of indeterminate.

In the cefuroxime group, for both subjects that had a *S. pneumoniae* with intermediate resistance to penicillin G the clinical outcome was cure and the bacteriological outcome was presumed eradication.

Applicant's Efficacy analysis of special subject groups

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

- Demographic characteristics: sex, age (<65 years, ≥65 years), race (white, black, Asian/Oriental, and multiracial), smoking status (smoker, ex-smoker, nonsmoker).
- General risk factors for morbidity: none, one, more than one.

- Characteristics of current infection and AMS-specific prognostic factors: number of AMS episodes that required antibiotic treatment in last 12 months (0, 1 to 3 or >3); history of asthma (yes/no); episodes of allergic rhinitis in the last 30 days (yes/no); nasal septal deviation (yes = mild/moderate/severe, no = absent); ENT-related surgical history (yes/no); duration of current AMS episode (7 to 14, ≥15 days to <28days); investigator's assessment of intensity (mild/moderate/ severe); fever (yes/no); sinus x-ray/CT findings (air fluid level, total opacity, mucosal thickening ≥10 mm, unilateral or bilateral AMS, sinus x-ray/CT severity, concomitant use of NSAIDS, concomitant use of nasal steroids, method of collection for microbiologic sample (sinus puncture or sinus endoscopy).

Applicant's clinical outcome in subjects with special demographic factors of special interest is shown in the table below.

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

		Clinical outcome Number of subjects (%)				
		HMR 3647			Cefuroxime	
Subgroup	**N**	**Cure**	**Failure**	**N**	**Cure**	**Failure**
All Subjects:	189	161 (85.2%)	28 (14.8%)	89	73 (82.0%)	16 (18.0%)
Sex:						
Male	78	67 (85.9%)	11 (14.1%)	39	31 (79.5%)	8 (20.5%)
Female	111	94 (84.7%)	17 (15.3%)	50	42 (84.0%)	8 (16.0%)
Age:						
<65 years	175	149 (85.1%)	26 (14.9%)	81	67 (82.7%)	14 (17.3%)
13 - <18 yrs	4	3 (75.0%)	1 (25.0%)	2	1 (50.0%)	1 (50.0%)
18 - <65 yrs	171	146 (85.4%)	25 (14.6%)	79	66 (83.5%)	13 (16.5%)
≥65 years	14	12 (85.7%)	2 (14.3%)	8	6 (75.0%)	2 (25.0%)
Race:						
Black	13	10 (76.9%)	3 (23.1%)	10	7 (70.0%)	3 (30.0%)
White	167	144 (86.2%)	23 (13.8%)	76	64 (84.2%)	12 (15.8%)
Multiracial	5	5 (100.0%)	0 (0.0%)	1	1 (100.0%)	0 (0.0%)
Asian/Oriental	4	2 (50.0%)	2 (50.0%)	2	1 (50.0%)	1 (50.0%)
Smoking status:						
Never smoked	119	105 (88.2%)	14 (11.8%)	50	43 (86.0%)	7 (14.0%)
Smoker	46	39 (84.8%)	7 (15.2%)	21	17 (81.0%)	4 (19.0%)
Ex-smoker	24	17 (70.8%)	7 (29.2%)	18	13 (72.2%)	5 (27.8%)

The general risk factors for morbidity defined for this AMS study included chronic obstructive pulmonary disease, asthma, respiratory insufficiency, congestive heart failure, diabetes mellitus, alcoholism, renal disease, sickle cell disease, liver disease and coronary artery disease. Clinical outcome at posttherapy/TOC in subjects with general risk factors for morbidity is shown in the table below.

Clinical outcome in subjects with general risk factors for morbidity - PPc population at posttherapy/TOC

		Clinical outcome Number of subjects (%)				
		HMR 3647			Cefuroxime	
Number of risk factors	**N**	**Cure**	**Failure**	**N**	**Cure**	**Failure**
All subjects	189	161 (85.2%)	28 (14.8%)	89	73 (82.0%)	16 (18.0%)
No risk factors	181	154 (85.1%)	27 (14.9%)	86	71 (82.6%)	15 (17.4%)
At least 1 risk factor	8	7 (87.5%)	1 (12.5%)	3	2 (66.7%)	1 (33.3%)
More than 1 risk factor	0	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)

Clinical outcome in subjects according to prognostic factors specific for AMS is shown in the table below.

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

		Clinical outcome number of subjects (%) HMR 3647			Cefuroxime	
Subgroup	**N**	**Cure**	**Failure**	**N**	**Cure**	**Failure**
Total treated	189	161 (85.2%)	28 (14.8%)	89	73 (82.0%)	16 (18.0%)
AMS episodes in the last year	74	60 (81.1%)	14 (18.9%)	41	33 (80.5%)	8 (19.5%)
AMS episodes requiring antimicrobial treatment in the last 12 months						
0	4	3 (75.0%)	1 (25.0%)	2	2 (100.0%)	0 (0.0%)
1-3	70	57 (81.4%)	13 (18.6%)	38	30 (78.9%)	8 (21.1%)
> 3	0	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)
History of asthma	30	23 (76.7%)	7 (23.3%)	14	9 (64.3%)	5 (35.7%)
Episodes of allergic rhinitis in last 30 Days	52	45 (86.5%)	7 (13.5%)	24	15 (62.5%)	9 (37.5%)
Nasal septal deviation	49	42 (85.7%)	7 (14.3%)	29	20 (69.0%)	9 (31.0%)
ENT related surgical history	57	52 (91.2%)	5 (8.8%)	23	20 (87.0%)	3 (13.0%)
Concomitant use of NSAID	15	12 (80.0%)	3 (20.0%)	7	5 (71.4%)	2 (28.6%)
Duration of current AMS episode:						
7-14 days	153	133 (86.9%)	20 (13.1%)	75	65 (86.7%)	10 (13.3%)
>15 and <28 days	36	28 (77.8%)	8 (22.2%)	14	8 (57.1%)	6 (42.9%)
Investigator assessment of intensity of current AMS episode:						
Mild	9	9 (100.0%)	0 (0.0%)	1	1 (100.0%)	0 (0.0%)
Moderate	143	121 (84.6%)	22 (15.4%)	64	52 (81.3%)	12 (18.8%)
Severe	37	31 (83.8%)	6 (16.2%)	24	20 (83.3%)	4 (16.7%)
Fever present	5	4 (80.0%)	1 (20.0%)	2	2 (100.0%)	0 (0.0%)
Sinus x-ray/CT scan findings:						
Air fluid level present	81	70 (86.4%)	11 (13.6%)	43	35 (81.4%)	8 (18.6%)
Total opacity present	67	60 (89.6%)	7 (10.4%)	27	22 (81.5%)	5 (18.5%)
Mucosal thickening ≥10mm	89	73 (82.0%)	16 (18.0%)	45	31 (68.9%)	14 (31.1%)
Unilateral	116	95 (81.9%)	21 (18.1%)	49	41 (83.7%)	8 (16.3%)
Bilateral	73	66 (90.4%)	7 (9.6%)	40	32 (80.0%)	8 (20.0%)
Sinus x-ray/CT scan severity						
Air fluid level/total opacity with mucosal thickening ≥ 10 mm	34	29 (85.3%)	5 (14.7%)	19	10 (52.6%)	9 (47.4%)
Air fluid level/total opacity without mucosal thickening ≥ 10 mm	100	88 (88.0%)	12 (12.0%)	44	42 (95.5%)	2 (4.5%)
Mucosal thickening ≥ 10 mm only	55	44 (80.0%)	11 (20.0%)	26	21 (80.8%)	5 (19.2%)
Concomitant use of NSAID	15	12 (80.0%)	3 (20.0%)	7	5 (71.4%)	2 (28.6%)
Concomitant use of nasal steroid	33	26 (78.8%)	7 (21.2%)	16	12 (75.0%)	4 (25.0%)
Method of collection for microbiologic sample:						
Sinus puncture	108	88 (81.5%)	20 (18.5%)	43	31 (72.1%)	12 (27.9%)
Sinus endoscopy	81	73 (90.1%)	8 (9.9%)	46	42 (91.3%)	4 (8.7%)

The clinical outcome for the HMR 3647 group in all subgroups analyzed was similar to the clinical outcome seen for cefuroxime in the overall PPc population.

Applicant's Efficacy conclusions

The efficacy conclusions are as follows:

- The primary efficacy analysis of clinical outcome at posttherapy/TOC for the PPc population demonstrated equivalence between HMR 3647 800 mg given once daily for 5 days and cefuroxime axetil 250 mg given twice a day for 10 days when used to treat AMS in adult subjects. The clinical cure rate at posttherapy/TOC was 85.2% (161/189 subjects) for the HMR 3647 group and 82.0% (73/89 subjects) for the cefuroxime group (95% CI -7.1;13.4). The results of the analyses for the mITT population supported the results of the primary efficacy analyses with a clinical cure rate of 80.4% (193/240 subjects) in the HMR 3647 group and 72.4% (84/116 subjects) in the cefuroxime group.

- The results of the secondary analyses of clinical outcome at late posttherapy were comparable between treatment groups and support the results of the primary analysis. The clinical cure rate at late posttherapy was 79.9% (139/174 subjects) for the HMR 3647 group and 78.0% (64/82 subjects) for the cefuroxime group.
- The results of the secondary analyses of bacteriological outcome for the PPb population at the posttherapy/TOC visit demonstrated bacteriological efficacy with a satisfactory outcome in 84.0% of subjects (84/100 subjects) for the HMR 3647 group and in 79.6% of subjects (39/49 subjects) for the cefuroxime group. The results of the analyses for the bmITT population supported the results of the secondary efficacy analysis with bacteriological outcome of satisfactory in 81.0% of subjects (102/126 subjects) for the HMR 3647 group and in 73.3% of subjects (44/60 subjects) for the cefuroxime group.
- The results of the secondary analyses of bacteriological outcome at late posttherapy were comparable between treatment groups and support the results of the analyses for bacteriological outcome at posttherapy/TOC. The bacteriological outcome was satisfactory at late posttherapy for 79.3% of subjects (73/92 subjects) in the HMR 3647 group and for 73.9% of subjects (34/46 subjects) in the cefuroxime group.
- The eradication rates by pathogen at posttherapy/TOC for pathogens of importance in AMS isolated at pretherapy/entry in the PPb population were as follows:

– *S. pneumoniae*: HMR 3647 89.7% (26/29) and cefuroxime 100.0% (12/12).
– *H. influenzae*: HMR 3647 81.3% (26/32) and cefuroxime 85.7% (12/14).
– *M. catarrhalis*: HMR 3647 100.0% (7/7) and cefuroxime 100.0% (6/6).
– *S. aureus*: HMR 3647 100.0% (12/12) and cefuroxime 75.0% (3/4).

- Based on central reference microbiology laboratory testing, there were a total of 20 subjects in the PPb population with a *S. pneumoniae* isolate (single + multiple pathogens) that was resistant to penicillin G, erythromycin A or both (HMR 3647: 14 subjects and cefuroxime: 6 subjects).

– Among the 14 subjects in the HMR 3647 group, 9 subjects had *S. pneumoniae* resistant to penicillin G, 12 subjects had *S. pneumoniae* resistant to erythromycin A and 7 subjects had *S. pneumoniae* resistant to both penicillin G and erythromycin A.

– Among the 6 subjects in the cefuroxime group, 4 subjects had *S pneumoniae* resistant to penicillin G, 5 subjects had *S. pneumoniae* resistant to erythromycin A and 3 subjects had *S. pneumoniae* resistant to both penicillin G and erythromycin A.

– The bacteriological eradication and clinical cure rates for resistant *S. pneumoniae* isolates was 85.7% (12/14) for the HMR 3647 group and 100.0% (6/6) for the cefuroxime group.

- The bacteriological eradication and clinical cure rates for *S. pneumoniae* isolates resistant to penicillin G was 77.8% (7/9) for the HMR 3647 group and 100% (4/4) for the cefuroxime group.
- The bacteriological eradication and clinical cure rates for *S. pneumoniae* isolates resistant to erythromycin A was 83.3% (10/12) for the HMR 3647 group and 100% (5/5 for the cefuroxime group.

Medical Officer's Comments:

The Medical Officer concurs with the applicant's conclusions pertaining to the clinical and bacteriologic outcomes. The applicant has included S. aureus as one of the causative pathogens of acute sinusitis. The Medical Officer does not agree with that conclusion. Most the patients that have S. aureus isolated from their sinuses suffer

from chronic sinusitis. All of the patients in this study had mixed infection where S. aureus was one of the organisms isolated. Thus, S. aureus is not considered as a pathogen of importance for this indication.

APPEARS THIS WAY
ON ORIGINAL

APPLICANT'S RESULTS - SAFETY

Extent of exposure

A total of 374 subjects received at least one capsule of study medication: 252 subjects in the HMR 3647 group and 122 in the cefuroxime group. Of the subjects treated, 1 in the cefuroxime group (Subject 733/001) received study treatment but did not undergo postbaseline safety assessments. This subject was lost to follow-up and was not evaluable for safety. The total number of safety evaluable subjects was therefore 373 (252 HMR 3647 and 121 cefuroxime).

Treatment duration was calculated from the first to last day of study medication, inclusive. In the safety population, the mean calculated treatment duration was 10.0 days for both the HMR 3647 and cefuroxime groups (including the 5-day placebo period for HMR 3647). The mean duration of active treatment in the HMR 3647 group was 5.0 days.

In the HMR 3647 group, the duration of active treatment was 5 days in 246 (97.6%) subjects, and fewer than 5 days in 3 subjects. In the cefuroxime group, the duration of treatment was 10 days in 101 (83.5%) subjects, fewer than 10 days in 10 subjects, and 11 or more days in 9 subjects. In the safety population, the cumulative number of days of active treatment, derived from the median number of doses of active treatment, was 5.0 days in the HMR 3647 group and 10.0 days in the cefuroxime group.

Adverse events

This section presents adverse events (whether treatment emergent or not), followed by a detailed presentation of treatment-emergent adverse events (TEAEs). The term *all adverse events* or *all TEAEs* refers to events irrespective of their relationship to study medication.

Adverse events are summarized by body system for all adverse events and for possibly related adverse events. Serious adverse events are presented by seriousness criterion and timing of the event (pretreatment, on-treatment, or posttreatment). All and possibly related serious adverse events are also presented by body system and coded term.

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

All adverse events

A total of 144 subjects experienced one or more adverse events in this study: 100 (39.7%) in the HMR 3647 group and 44 (36.4%) in the cefuroxime group. Of these, 23 HMR 3647 and 8 cefuroxime subjects experienced one or more adverse events that were not treatment emergent. Most non–treatment-emergent events occurred during the posttreatment period, and the most common of these events were headache and upper respiratory tract infection.

Adverse events and TEAEs were comparable with respect to overall incidence and incidence by coded term.

All treatment-emergent adverse events

A total of 129 subjects experienced one or more TEAEs irrespective of relationship to study medication: 91 (36.1%) HMR 3647 subjects and 38 (31.4%) cefuroxime subjects. All TEAEs by body system are presented below.

All TEAEs by body system

	Number of subjects (%)			
Body system	**HMR 3647**		**CXM**	
Total safety population	252	(100%)	121	(100%)
Total with TEAEs	91	(36.1%)	38	(31.4%)
Digestive system	58	(23.0%)	22	(18.2%)
Nervous system	23	(9.1%)	8	(6.6%)
Body as a whole	16	(6.3%)	4	(3.3%)
Respiratory system	13	(5.2%)	3	(2.5%)
Special senses	8	(3.2%)	4	(3.3%)
Urogenital system	8	(3.2%)	3	(2.5%)
Skin and appendages	5	(2.0%)	3	(2.5%)
Hemic and lymphatic system	3	(1.2%)	2	(1.7%)
Metabolic and nutritional Disorders	3	(1.2%)	1	(0.8%)
Musculoskeletal system	3	(1.2%)	1	(0.8%)
Cardiovascular system	1	(0.4%)	3	(2.5%)

The most common TEAEs (those reported in 2% or more of subjects in either treatment group), irrespective of relationship to study medication, are presented by coded term in the table below.

All TEAEs in ≥2% of all subjects in either treatment group

	Number of subjects (%)			
Adverse event	**HMR 3647**			**CXM**
Total safety population	252	(100%)	121	(100%)
Total with TEAEs	91	(36.1%)	38	(31.4%)
Diarrhea	19	(7.5%)	6	(5.0%)
Nausea	18	(7.1%)	5	(4.1%)
Headache	7	(2.8%)	4	(3.3%)
Dizziness	7	(2.8%)	2	(1.7%)
Vomiting	6	(2.4%)	3	(2.5%)
Dyspepsia	5	(2.0%)	1	(0.8%)

Intensity of TEAEs

Most TEAEs were mild (in 24.2% of HMR 3647 and 23.1% of cefuroxime subjects) or moderate (in 17.1% HMR 3647 and 11.6% cefuroxime subjects) in intensity. A total of 11 (4.4%) HMR 3647 and 4 (3.3%) cefuroxime subjects experienced one or more severe TEAEs. Severe TEAEs are summarized below.

- Severe TEAEs in the HMR 3647 group were headache (in 3 subjects); and vomiting, dizziness, hemorrhoids, asthenia, accidental injury, moniliasis, epistaxis, conjunctivitis, urolith (probable urolithiasis), and herpes zoster (each in 1 subject). Study medication was permanently

discontinued in 2 HMR 3647 subjects due to the following severe TEAEs: herpes zoster and vomiting. The occurrence of accidental injury was categorized as a nonrelated serious TEAE .

- Severe TEAEs in the cefuroxime group were nausea, headache, vertigo, dyspnea, bronchitis, pneumonia, and vasodilation (each in 1 subject). Study medication was permanently discontinued in 2 cefuroxime subjects due to the following severe TEAEs: dyspnea, and nausea and headache. Dyspnea, bronchitis, and pneumonia (all of which occurred in the same cefuroxime subject) were categorized as serious TEAEs, of which dyspnea was considered to be treatment related.

Diarrhea, nausea, and vomiting

The body system most commonly affected by TEAEs was the digestive system. The most common digestive system TEAEs were diarrhea, nausea, and vomiting, which are summarized below.

Overview of all diarrhea, nausea, and vomiting TEAEs

	Number of subjects (%)			
	HMR 3647		**CXM**	
Total safety population	252	(100%)	121	(100%)
Total with digestive TEAEs	58	(23.0%)	22	(18.2%)
Total with diarrhea	19	(7.5%)	6	(5.0%)
Intensity: Mild	14	(5.6%)	3	(2.5%)
Moderate	5	(2.0%)	3	(2.5%)
Severe	0	(0.0%)	0	(0.0%)
Serious TEAE	0	(0.0%)	0	(0.0%)
Led to discontinuation	0	(0.0%)	0	(0.0%)
Total with nausea	18	(7.1%)	5	(4.1%)
Intensity: Mild	10	(4.0%)	4	(3.3%)
Moderate	8	(3.2%)	0	(0.0%)
Severe	0	(0.0%)	1	(0.8%)
Serious TEAE	0	(0.0%)	0	(0.0%)
Led to discontinuation	0	(0.0%)	1	(0.8%)
Total with vomiting	6	(2.4%)	3	(2.5%)
Intensity: Mild	1	(0.4%)	0	(0.0%)
Moderate	4	(1.6%)	3	(2.5%)
Severe	1	(0.4%)	0	(0.0%)
Serious TEAE	0	(0.0%)	0	(0.0%)
Led to discontinuation	1	(0.4%)	1	(0.8%)

Dizziness and headache

A total of 23 (9.1%) HMR 3647 subjects and 8 (6.6%) cefuroxime subjects reported TEAEs of the nervous system. The most common nervous system TEAEs were dizziness and headache, which are summarized below.

Overview of all dizziness and headache TEAEs

	Number of subjects (%)			
	HMR 3647			
			CXM	
Total safety population	252	(100%)	121	(100%)
Total with nervous system TEAEs	23	(9.1%)	8	(6.6%)
Total with dizziness	7	(2.8%)	2	(1.7%)
Intensity: Mild	5	(2.0%)	1	(0.8%)
Moderate	1	(0.4%)	1	(0.8%)
Severe	1	(0.4%)	0	(0.0%)
Serious TEAE	0	(0.0%)	0	(0.0%)
Led to discontinuation	0	(0.0%)	0	(0.0%)
Total with headache	7	(2.8%)	4	(3.3%)
Intensity: Mild	4	(1.6%)	3	(2.5%)
Moderate	0	(0.0%)	0	(0.0%)
Severe	3	(1.2%)	1	(0.8%)
Serious TEAE	0	(0.0%)	0	(0.0%)
Led to discontinuation	0	(0.0%)	1	(0.8%)

One HMR 3647 subject experienced severe dizziness, and 3 HMR 3647 subjects experienced severe headache. None of the occurrences of dizziness or headaohe were categorized as serious or led to discontinuation of study medication..

Treatment-emergent adverse events possibly related to study medication

Approximately half of all reported TEAEs were considered by the investigator to be possibly related to study medication. Such TEAEs occurred in 56 (22.2%) HMR 3647 subjects and 20 (16.5%) cefuroxime subjects. Possibly related TEAEs are summarized by body system below.

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%)

The digestive system was most commonly affected by TEAEs. The most common possibly related TEAEs (those reported in 2% or more of subjects in either treatment group) are presented by coded term in the table below.

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%)

The most common possibly related TEAEs were nausea and diarrhea. Diarrhea was considered to be possibly related to study medication in 15/19 HMR 3647 and 6/6 cefuroxime subjects who experienced this event, and nausea was considered to be possibly related to study medication in 17/18 HMR 3647 and 5/5 cefuroxime subjects.

Serious adverse events (including those leading to death)

Only 1 subject in each treatment group experienced one or more serious TEAEs (1 event in HMR 3647 and 3 events in cefuroxime). These serious TEAEs are summarized by seriousness criterion below.

All serious TEAEs by seriousness criterion

	Number of subjects (%)			
Criterion for serious TEAE	**HMR 3647**			**CXM**
Total subjects in safety population	252	(100%)	121	(100%)
Total with serious TEAEs	1	(0.4%)	1	(0.8%)
Death	0	(0.0%)	0	(0.0%)
Life threatening	0	(0.0%)	0	(0.0%)
Required or prolonged hospitalization	1	(0.4%)	1	(0.8%)
Permanently or significantly disabling	0	(0.0%)	0	(0.0%)
Occurred with overdose	0	(0.0%)	0	(0.0%)
Involved cancer	0	(0.0%)	0	(0.0%)
Congenital abnormality	0	(0.0%)	0	(0.0%)
Medically important	0	(0.0%)	0	(0.0%)
Required medical intervention	0	(0.0%)	0	(0.0%)

All serious TEAEs in this study met the criterion of requiring or prolonging hospitalization and are shown by coded term below.

All serious TEAEs

Adverse event coded term	Number of subjects (%) HMR 3647			CXM
Total subjects in safety population	252	(100%)	121	(100%)
Total with serious TEAEs	1	(0.4%)	1	(0.8%)
Accidental injury	1	(0.4%)	0	(0.0%)
Bronchitis	0	(0.0%)	1	(0.8%)
Dyspnea	0	(0.0%)	1	(0.8%)
Pneumonia	0	(0.0%)	1	(0.8%)

HMR 3647 Subject 661/001 experienced accidental injury (traumatic amputation of the right thumb and index finger in a lawn-mower accident). Cefuroxime Subject 652/004 experienced severe dyspnea, pneumonia, and bronchitis.

Deaths

There were no deaths in this study.

Other significant adverse events

Adverse events were classified as *other significant events* if they met one or more of the following criteria: the event led to discontinuation of study medication, interruption of therapy, required dosage reduction or treatment with a counteractive medication, or was a laboratory abnormality reported as an adverse event. These events are presented by criterion and are summarized below.

All other significant TEAEs by adverse event criterion

Criterion for other significant TEAE	Number of subjects (%) HMR 3647			CXM
Total subjects in safety population	252	(100%)	121	(100%)
Total with other significant TEAEs	40	(15.9%)	12	(9.9%)
Adverse event				
Discontinuation of study medication	5	(2.0%)	2	(1.7%)
Therapy interrupted	0	(0.0%)	0	(0.0%)
Dosage reduced	0	(0.0%)	0	(0.0%)
Treated with counteractive medication	36	(14.3%)	11	(9.1%)
Medically important lab abnormality	4	(1.6%)	0	(0.0%)

Treatment-emergent adverse events leading to discontinuation

Study medication was permanently discontinued due to TEAEs in 5 (2.0%) HMR 3647 and 2 (1.7%) cefuroxime subjects, summarized below.

All TEAEs leading to discontinuation of study medication

	Number of subjects (%)			
Adverse event coded term	**HMR 3647**			**CXM**
Total subjects in safety population	252	(100%)	121	(100%)
Total with TEAEs leading to discontinuation of study medication	5	(2.0%)	2	(1.7%)
Vomiting	1	(0.4%)	1	(0.8%)
Cystitis	1	(0.4%)	0	(0.0%)
Herpes zoster	1	(0.4%)	0	(0.0%)
Liver function test abnormal	1	(0.4%)	0	(0.0%)
Somnolence	1	(0.4%)	0	(0.0%)
Dyspnea	0	(0.0%)	1	(0.8%)
Headache	0	(0.0%)	1	(0.8%)
Nausea	0	(0.0%)	1	(0.8%)

Laboratory adverse events

TEAEs were reported as medically important laboratory values in 4 (1.6%) HMR 3647 subjects and no cefuroxime subject. The coded terms for these medically important TEAEs were SGPT/ALT increased, creatine phosphokinase increased, thrombocytosis, and LFT abnormal. These findings are summarized below.

Subjects with medically important TEAE laboratory abnormalities

Treatment/ Subject number HMR 3647	**Coded term**	**Relationship to study med.**	**Intensity**	**Serious TEAE**
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 629/008 (a 67-year old man) experienced a mild TEAE of increased creatine phosphokinase (CPK) on day 4. The subject presented in the emergency room with left flank pain, but no angina, shortness of breath, or chest discomfort. The CK-MB was 4.1 U/L (normal range=0.0 to 2.5 U/L), and tronponin I was measured as 15 ng/mL (within the normal range). The results of a stress test suggested no cardiac involvement. The subject was not admitted to the hospital and recovered without sequelae. Increased CPK was not considered to be related to study medication but rather to an underlying/concomitant illness: the subject had a history of nephrolithiasis.

Other TEAEs in this subject were urolith (presenting with hematuria, urinary burning sensation, and pain in the left flank, left abdominal side, and back) and headache, and the subject also experienced a clinically noteworthy abnormal laboratory value for low creatinine clearance.

- 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.

Other TEAEs in this subject were vomiting, back pain, and arthralgia.

- HMR 3647 Subject 712/006 (a 20-year old woman) experienced a TEAE of increased thrombocytes with onset on day 4. Platelet counts for this subject were as follows: day 1=391 G/L, day 4=472 G/L, day 18=337 G/L. The value on day 4 was above the upper limit of the normal range (140 to 400 G/L). This event was mild in intensity and considered to be possibly related to study medication, but was not categorized as serious. Other TEAEs in this subject were stomatitis (dry mouth, ageusia, hypoesthesia of the oral cavity) and infection (impetigo in the nasal area).
- HMR 3647 Subject 727/008 (a 40-year old woman) experienced a TEAE coded abnormal LFT. This subject also experienced clinically noteworthy abnormal laboratory values for increased SGPT/ALT and SGOT/AST, but no other adverse events.

Overall incidence of CNALVs (Clinically Noteworthy Abnormal Lab Values)

A total of 38 CNALVs were reported in 35 (13.9%) HMR 3647 subjects, and 19 CNALVs in 17 (14.0%) cefuroxime subjects. Other than abnormally low creatinine clearance, there were few CNALVs in either treatment group; 26 (10.3%) HMR 3647 and 14 (11.6%) cefuroxime subjects experienced one or more CNALV for creatinine clearance. CNALVs are summarized in the table below.

Clinically noteworthy abnormal laboratory values (CNALVs)

		No. of subjects (%)			
		HMR 3647		CXM	
Total safety population		**252 (100%)**		**121 (100%)**	
CNALV (abnormal value)	**n**	**(%)**	**(NR at P)**	**n (%)**	**(NR at P)**
Hematology					
Prothrombin time	1	(0.4)	(1)	0(0.0)	(0)
Leukocytes (WBC) (<3 G/L)	2	(0.8)	(1)	0(0.0)	(0)
Absolute neutrophils (<1.5 G/L)	4	(1.6)	(3)	0(0.0)	(0)
Absolute eosinophils (>1 G/L)	3	(1.2)	(2)	0(0.0)	(0)
Clinical chemistry					
AST/SGOT (>3 x ULN)	1	(0.4)	(0)	1(0.8)	(0)
ALT/SGPT (>3 x ULN)	1	(0.4)	(0)	3(2.5)	(1)
Total bilirubin (>2 x ULN)	0	(0.0)	(0)	1(0.8)	(0)
Creatinine clearance (<0.833 mL/s)	26	(10.3)	(8)	14(11. 6(4)[a]	
Total CNALVs	**38**			**19**	
Total (%) subjects with CNALVs	**35**	**35 (13.9%)**		**17 (14.0%)**	

N (%) = number (percent) of subjects with CNALV.
NR at P = number of subjects with CNALV within the extended normal range at pretherapy/entry.
Note: CNALV for each laboratory analyte was included once only per subject, even if the value was clinically noteworthy at more than one timepoint.
[a]Day -6 data for Subject 682/002.

Due to the high incidence of abnormalities in creatinine clearance, this analyte is discussed below. Although elevations in AST/SGOT and ALT/SGPT occurred in few subjects, these variables are also summarized in order to provide a comprehensive discussion of potential liver function abnormalities.

Low creatinine clearance

As shown above, 26 (10.3%) HMR 3647 subjects and 14 (11.6%) cefuroxime subjects experienced CNALVs for creatinine clearance. For 18 HMR 3647 and 10 cefuroxime subjects with CNALVs in this variable, the pretherapy/entry value was also below the lower limit of the extended normal range.

The lower limit of the normal range and the CNALV criterion for creatinine clearance were both <0.8333 mL/s. The mean change in creatinine clearance from pretherapy/entry to last observation available on therapy was –0.3mL/s in the HMR 3647 group and 0.02mL/s in the cefuroxime group. The lowest value in HMR 3647 subjects being 0.53 mL/s and that in cefuroxime subjects being 0.49 mL/s. The maximum change from pretherapy/entry to any postbaseline assessment was 0.45 mL/s in HMR 3647 subjects and 0.24 mL/s in cefuroxime subjects.

Few of the noteworthy values in creatinine clearance resolved by final visit. Of the 26 HMR 3647 subjects with a CNALV for creatinine clearance, 10 subjects had a later assessment (at a visit after the CNALV was reported) for this variable, either on therapy or posttherapy. For 3/10 of these subjects, the value resolved by the final assessment. Of the 14 cefuroxime subjects with

a CNALV for creatinine clearance, the value resolved in only 1 of the 8 subjects who underwent a final assessment. None of the laboratory values resulted in discontinuation of study medication.

A total of 8/26 HMR 3647 and 5/14 cefuroxime subjects with CNALVs in creatinine clearance experienced one or more TEAE. Of these, only cefuroxime Subject 652/004 experienced serious TEAEs: dyspnea, bronchitis, and pneumonia. This subject also experienced constipation and arrhythmia. In all other subjects, few TEAEs were severe; none was both severe and related to study medication, and none was associated with cardiac abnormalities or suggestive of a notable trend.

Liver function tests

There were few CNALVs for liver function tests: 1 HMR 3647 and 3 cefuroxime subjects experienced abnormal elevations in ALT/SGPT and/or AST/SGOT, and a further cefuroxime subject experienced an abnormal elevation in total serum bilirubin.

One HMR 3647 subject experienced CNALVs in both ALT/SGPT and AST/SGOT, and LFT abnormal was reported as a medically important TEAE in this subject. This subject is described below.

- Subject 727/008 (a 40-year old woman) had ALT/SGPT and AST/SGOT values above the extended normal range of 2 x ULN at the pretherapy/entry and day 6 assessments. Liver function tests in this subject are summarized below.

Liver function tests in HMR 3647 Subject 727/008

Variable	Normal range	CNALV criterion	Value	
			Day 1	Day 6
SGOT/AST	9–34 U/L	>3 x ULN	261 U/L (h)	393 U/L (c)
SGPT/ALT	6–34 U/L	>3 x ULN	84 U/L (h)	122 U/L (c)
Alkaline phosphatase	31–110 U/L	Increase 50 U/L	109 U/L	118 U/L
Total bilirubin	3–21 µmol/L	>2 x ULN	9 µmol/L	10 µmol/L

(h): pretherapy/entry value above the extended normal range.
(c): meets criterion for CNALV.

Other hepatic markers for this subject were within the extended normal ranges (1.25 x ULN for alkaline phosphatase and 2 x ULN for total bilirubin). No posttherapy liver function test results were reported. The investigator did not consider the medically important TEAE in Subject 727/008 to be related to study medication, but medication was withdrawn as a result.

Four cefuroxime subjects experienced CNALVs in one or more liver function test. These findings are summarized below.

CNALVs for liver function tests: cefuroxime subjects

Subject	Variable	CNALV criterion	Pretherapy/entry value	Lab. values
613/001	SGPT/ALT	>3 x ULN	136 U/L (h)	Day 3: 145 U/L (c) Day 6: 121 U/L (c)
682/025	SGOT/AST	>3 x ULN	122 U/L (h)	Day 3: 125 U/L (c)
	SGPT/ALT	>3 x ULN	207 U/L (h)	Day 3: 211 U/L (c)
712/002	Total bilirubin	>2 x ULN	32 µmol/L	Day 4: 38 µmol/L Day 11: 46 µmol/L (c) Day 18: 46 µmol/L
733/008	SGPT/ALT	>3 x ULN	24 U/L	Day 3: 40 U/L Day 13: 141 U/L (c)

(h): pretherapy/entry value above the extended normal range limit of >2 x ULN.
(c): CNALV.

ECGs

Patients were to undergo 12-lead ECGs at the pretherapy/entry visit and the on-therapy visit if the subject met one or more of the following criteria: the subject received specified concomitant medications, and/or the subject had a concomitant relevant risk factor for chronic obstructive pulmonary disease, respiratory insufficiency, congestive heart failure, hepatic or renal disease. Repeat ECGs were to be performed if a serious adverse event occurred.

Paired ECG data (pretherapy/entry and 1 or more postbaseline assessment) were available for only 1 HMR 3647 and no cefuroxime subjects in this study. HMR 3647 Subject 709/001 underwent ECG recordings at visits 1, 3, and 4 because she received concomitant aminophylline. The subject did not experience any adverse events in the study.

According to the protocol requirements, 4 other HMR 3647 and no cefuroxime subjects should have undergone pre- and postbaseline ECG recordings, but did not. These subjects were: Subject 618/004 (concomitant coumadin), Subject 682/027 (concomitant flecainide acetate), Subject 704/002 (concomitant theophylline), and Subject 650/003 (COPD). Of these, only Subject 650/003 reported an adverse event during the study: a bone neoplasm (left ethmoid osteoma). Subject 618/004 was entered into the study in error as coumadin usage was a protocol exclusion.

Adverse events categorized as *other clinically important TEAEs*, with a potential for association with QTc prolongation, occurred in cefuroxime Subjects 648/004 and 652/004. Neither of the subjects with such TEAEs fulfilled the protocol criteria for postbaseline ECG assessments, and therefore QTc values are unavailable for these subjects.

Applicant's Safety conclusions

The safety conclusions are as follows:

- HMR 3647, administered at a dosage of 800 mg once daily for 5 days, was safe and well tolerated, and comparable with the active comparator cefuroxime. Safety data, including adverse events, clinical laboratory values, and vital signs, revealed no serious safety concerns for HMR 3647.
- Treatment-emergent adverse events were most commonly reported for the digestive system (in 23.0% of HMR 3647 and 18.2% of cefuroxime subjects). Diarrhea (in 7.5% HMR 3647 and 5.0% cefuroxime subjects) and nausea (in 7.1% HMR 3647 and 4.1% cefuroxime) were the most common events in both treatment groups. All nausea and diarrhea TEAEs in HMR 3647 subjects were mild or moderate in intensity, and none was severe, resulted in discontinuation, or was categorized as serious.
- Most TEAEs were mild or moderate in intensity. Severe TEAEs occurred in 11 (4.4%) HMR 3647 and 4 (3.3%) cefuroxime subjects.
- There were no deaths in this study. One subject in each treatment group experienced one or more serious TEAE: accidental injury in HMR 3647, and dyspnea, bronchitis, and pneumonia in cefuroxime. Severe dyspnea in the cefuroxime subject was the only serious TEAE considered to be related to study medication.
- Treatment with study medication was discontinued in 5 (2.0%) HMR 3647 and 2 (1.7%) cefuroxime subjects. Of these, vomiting and somnolence (each in 1 HMR 3647 subject) and dyspnea, headache, nausea, and vomiting (in 2 cefuroxime subjects) were considered by the investigator to be related to study medication.
- There were few noteworthy laboratory findings in this study. Only 1 HMR 3647 and 4 cefuroxime subjects experienced clinically noteworthy abnormal laboratory values in one or more liver function test. The results of predefined change and clinically noteworthy abnormal laboratory assessments demonstrated that all findings, including those for liver function tests, were comparable between HMR 3647 and cefuroxime, and infrequent.
- Changes from pretherapy/entry in vital signs were very small and comparable between treatments.

Medical officer's Comments:

The data from study 3011 was submitted to the agency for review to basically increase the experience of Ketek for PRSP (penicillin-resistant S. pneumoniae) and erythromycin-resistant S. pneumoniae (ERSP) in acute sinusitis. As is evident from the clinical and bacteriologic analysis, the number of PRSP isolated in the per-protocol population was small – 8. At the test-of –cure visit, six of those (75%) were cures. In the PPb population, the number of ERSP isolated was 10. At the test of cure visit, 8 of those (80%) were cures.

This Medical Officer concurs with the applicant's conclusions regarding safety in this particular study. It should be noted that there were about 2.8% (7/252) in the HMR group that reported dizziness compared to none in the cefuroxime group. Specific criteria were described in the protocol to follow serial ECGs in this study, thus paired ECGs were available in only one HMR patient and none in the cefuroxime group. This patient did not experience any adverse events in this study.

The data from this study and the other two studies will be combined, and the final conclusions and recommendations will be made to determine whether Ketek has any additional benefit over the drugs already being marketed for this indication.

MEDICAL OFFICER'S 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

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.

MEDICAL OFFICER'S CONCLUSIONS:

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.

APPEARS THIS WAY
ON ORIGINAL

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.

/S/

Nasim Moledina, M.D.
Medical Officer, DAIDP
FDA

cc:
Orig NDA 21-144
HFD-340
HFD-520/DepDir/LGavrilovich
HFD-520/MO/NMoledina
HFD-520/MO/ADavidson
HFD-520/Pharm/TPeters
HFD-520/Micro/FMarsik
HFD-520/Chem/AYu
HFD-520/PM/JCintron
nm/12-19-2000;rev12-21-2000.
rev 05-18-2001; 06-08-01.

Concurrence Only:
HFD-520/Acting Div.Dir/JSoreth
HFD-520/ActingTL/JKorvick