

APPENDIX A: BIostatistical Methods

Biostatistics Methods

The biostatistical approach was consistent across the Phase III studies. The same analysis population definitions and methods for determining non-inferiority were specified in the protocols and applied uniformly for all studies.

The analysis population definitions were as follows:

- mITT (modified intent to treat): All randomized subjects with a confirmed diagnosis of infection who received at least 1 dose of study medication. A confirmed diagnosis was defined by clinical signs and symptoms and X-ray findings as specified in the protocols.
- PPc (clinically evaluable per protocol): All mITT subjects except those with major protocol violations and/or indeterminate responses.
- bmITT (bacteriologically evaluable modified intent to treat): All mITT subjects with a pathogen at pretherapy/entry considered by the investigator to be responsible for the infection.
- PPb (bacteriologically evaluable per protocol): All PPc subjects with isolation of a causative pathogen from an adequate culture at pretherapy/entry.

Subjects were excluded from the PPc population if they had one or more major protocol violation or had indeterminate responses and were therefore included only in the mITT/bmITT analyses.

The major protocol violation criteria were as follows:

- Wrong entry diagnosis
- Signs and symptoms insufficient to meet clinical criteria
- Insufficient treatment duration – fewer than 5 consecutive days of treatment except if the subject was considered a failure during the first 5 days where 2 days of treatment were required; less than a 70% compliance rate overall unless the subject was considered a failure before the last dose
- Treatment unblinded before posttherapy/TOC
- Treatment discontinued after enrollment because of laboratory exclusion criteria at pretherapy/entry.

Indeterminate response criteria were as follows:

- Missing appropriate posttreatment information or inability to determine outcome at posttherapy/TOC: for subjects with a missing posttherapy/TOC assessment, clinical failure or unsatisfactory bacteriologic response before the planned assessment was carried forward to posttherapy/TOC
- If the late posttherapy assessment was missing, failure before the planned assessment was carried forward to late posttherapy

- In circumstances where it was not possible to give a binary cure or failure response, the clinical and bacteriologic responses were considered indeterminate and these subjects were excluded from the per-protocol analysis.

In the mITT and bmITT by-subject analyses, subjects with indeterminate response were classified as failures.

Efficacy analyses

The primary efficacy analysis was to determine a noninferiority margin between telithromycin and active comparators, using a 2-tailed 95% confidence interval approach (1992 FDA Points to Consider) for the clinical outcome at posttherapy/TOC in the PPc population. Estimates of cure rates with confidence intervals were prepared for the open-label studies.

The following analyses were secondary and supportive to the primary endpoint:

- Clinical outcome at posttherapy/TOC in the mITT population,
- Clinical outcome at late posttherapy in the PPc and mITT populations, and
- Bacteriologic outcome at posttherapy/TOC and late posttherapy in the PPb and bmITT populations.

The 2-sided 95% confidence interval was calculated as follows:

$$\text{lower bound} = (P_h - P_c) - 1.96 \times S - \frac{1}{2} \left(\frac{1}{N_h} + \frac{1}{N_c} \right)$$

$$\text{upper bound} = (P_h - P_c) + 1.96 \times S + \frac{1}{2} \left(\frac{1}{N_h} + \frac{1}{N_c} \right)$$

where S is the standard deviation for the treatment difference = $\sqrt{\frac{P_h(1-P_h)}{N_h} + \frac{P_c(1-P_c)}{N_c}}$, N_h and N_c are the numbers of subjects for telithromycin and comparator, respectively, and P_h and P_c are the observed response rates.

Non-inferiority margins were based on recommendations from *Points To Consider Clinical Development and Labeling of Anti-Infective Drug Products* (October 26, 1992) and interactions with the FDA during protocol development. The proposed noninferiority margins were 15% for indications with expected cure rates of 80% to 90%, and 10% for indications with expected cure rates above 90%. Since cure rates for CAP, AECB and AS were projected to be below 90% the studies were designed and sized based on a margin of 15%. In studies with 3 treatment groups (Studies A3005 and 4003), a closed comparison test was performed, comparing 10 days of telithromycin treatment with 10 days of comparator and 5 days of telithromycin with 10 days of comparator if noninferiority was demonstrated in the first comparison. The observed noninferiority margins were almost all below 10%.

