

Longitudinal Assessment of Air Conduction Audiograms in a Phase III Clinical Trial for Prevention of Sporadic Colorectal Adenomas

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Adenomatous polyps are precursors to colorectal cancer. An independent Data and Safety Monitoring Board (DSMB) recommended early termination in favor of efficacy for a randomized placebo controlled, double-blind clinical trial of difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas. For detailed safety assessment regarding potential hearing loss, the DSMB requested that a sophisticated statistical approach be developed for analysis of air conduction audiograms performed at baseline, after 18 months and 36 months of therapy, and six months after stopping therapy. Initially, an arbitrary threshold criteria of at least 15 dB hearing loss from baseline in 2 or more consecutive frequencies across the entire range tested was applied. By this criteria, unadjusted log-binomial regression showed that of 259 participants, there were 25 of 136 (18.4%) in the DFMO plus sulindac group and 12 of 123 (9.8%) in the placebo group with hearing loss (relative risk, 1.88; 95% interval, 0.99 to 3.59). Because pure tone thresholds are measured at increasing frequency levels (Hz) in both ears for each subject and hearing loss develops with age, more detailed analyses were required to consider the correlation between values across frequencies for individual subjects, hearing thresholds measured in left and right ears, age adjustment, and differences between off-treatment and baseline values. Kaplan-Meier estimates showed that treatment groups were similar with regard to time between randomization until performance of the outcome audiogram. Subject-specific lowess-smoothed profiles of pure tone thresholds illustrated comparable hearing changes over time for treatment groups. Generalized estimating equations were applied with subjects as clusters and pure tone threshold measured at the end of the therapy as the outcome variable. On average, there was less than 2 dB difference in pure tone threshold for the two treatment groups, below the limits of accuracy for audiogram testing (± 5 dB). For assessment of toxicity in clinical trials, appropriate statistical methods are necessary for analysis of longitudinal data to estimate and compare the degree of difference between treatment groups.