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Combination Therapy with a Long-Acting β-Agonist and a Leukotriene Antagonist in Moderate Asthma

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Statistical Methods:

The statistical analysis applied to the time-to-treatment failure and time-to-asthma exacerbation data is comparable to McNemar's test for paired binary data and was applied in an intent-to-treat manner (E1, E2). It was anticipated that the LTRA+LABA treatment would yield at least a 15% failure rate, whereas the ICS+LABA treatment would yield no more than a 5% failure rate.

Initially, formal stopping rules for interim efficacy analyses were not planned. The DSMB, however, decided that formal stopping rules for interim safety analyses should be incorporated into the trial. Therefore, five formal safety analyses were planned after approximately every 35 subjects completed the trial, via group sequential significance levels (0.0020, 0.0065, 0.0135, 0.0225, and 0.0349) that lie between the Pocock and O'Brien-Fleming significance levels (E3).

The longitudinal models constructed for the analysis of the secondary outcomes consisted of (1) an intercept and two slopes for each treatment regimen (the first slope for weeks 0-4 of the treatment period and the second slope for weeks 4-14 of the treatment period); (2) period and sequence effects; and (3) correlations for the repeated measurements within a subject. The objective of the longitudinal data analysis was to assess the difference in the changes between the end of the treatment period and the end of the run-in period for the two treatment regimens.

Due to the occurrence of treatment failures and the early termination of the trial by the DSMB, the mixed-effects linear models were nested with a pattern-mixture approach that characterized subjects as completers, withdrawals, early terminators due to study stoppage, or treatment failures (E4). Secondary outcome variables that were measured only at the beginning and end of each treatment period (e.g., methacholine PC_{20} and sputum-related variables) were analyzed via paired t-tests or Wilcoxon signed rank tests, after aligning differences for treatment sequence (i.e., the order in which treatment regimens were received) and period effects.

Reference List

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E4. Little, R. and D. Rubin. 2002. Statistical Analysis with Missing Data, Second Edition John Wiley & Sons, Inc, New York, NY.