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LETTER

Superiority of tiotropium plus olodaterol in comparison with salmeterol plus fluticasone

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Dear editor

We read with interest the article entitled "The lung function profile of once-daily tiotropium and olodaterol via Respimat® is superior to that of twice-daily salmeterol and fluticasone propionate via Accuhaler® (ENERGITO® study)" by Beeh et al.[1] We would appreciate hearing from the authors on the three points as follows. First, the authors described inclusion criteria in the text and showed exclusion criteria in Table S1. However, we could not clearly understand how the authors excluded patients with bronchial asthma. We wondered whether there were a few patients with bronchial asthma included in this study, despite the study showing a superiority of tiotropium plus olodaterol in comparison with salmeterol plus fluticasone. Second, the authors showed that 59 of 288 patients were not randomized due to screening failure. We wondered whether a randomized error in such a large number of patients was unusual in a Phase III study and how the authors evaluated this. Third, as this study was a four-treatment, complete crossover study, the authors divided patients into four groups. We would appreciate hearing from the authors on what the effect of sequence had on the four treatments. Was there any effect of sequence on the results in this study? Please let us know how we should statistically evaluate its effect on the results.

Disclosure

The authors report no conflicts of interest in this communication.

Reference

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Dear editor

We read with great interest the letter from Tamura and Satoh and would like to provide answers to their queries. The first question related to our method of excluding patients with bronchial asthma. We can clarify that, in addition to the exclusion criteria documented in Table S1, a history of asthma was defined in the protocol as a specific exclusion criterion. Furthermore, for patients with allergic rhinitis, atopy, or a total blood eosinophil count of $\geq 600/mm^3$, source documentation was required to verify that the patient did not have asthma. Therefore, we consider it unlikely that any patients with bronchial asthma were included in the study.

Regarding the question on the number of patients who failed to be randomized in the study following enrollment, 59 out of 288 patients (~20%) were screened but not randomized to treatment in the study. These 59 individuals did not meet the inclusion and/or exclusion criteria and were, therefore, not randomized and did not receive any treatment. This proportion of patients is in line with – and, in fact, smaller than – several large Phase III studies, such as ILLUMINATE, where 37% of patients screened were not randomized,[1] SHINE, where 41% of patients were not randomized to treatment,[2] and SPARK, where 42% of patients were screening failures.[3]

The third question related to the method of randomization to treatment groups and whether the sequence of treatments affected the outcome. Patients were randomized to one of four possible treatment sequences via a computer program. The order of the administration of each treatment was not expected to affect the outcome since each treatment was followed by a 21-day washout period and a Williams design was selected, such that each treatment occurred only once within each sequence and once within each period.

Disclosure

The institution where KMB is employed has received compensation for organizing or participating in advisory boards for Almirall Hermal, Cytos, Chiesi, Boehringer Ingelheim, AstraZeneca, Mundipharma, Novartis, and Revotar Biopharmaceuticals, and for participation in scientific meetings or courses supported by various pharmaceutical companies (Almirall Hermal, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, and Takeda) in the past 3 years. KMB's institution has also received consulting fees from Ablynx, Apellis Pharmaceuticals, Chiesi, and Cytos. The institution has received compensation for the design, performance, or participation in single or multicenter clinical trials in the past 3 years from several companies, including Almirall, Boehringer Ingelheim, Cytos, GSK, Mundipharma, Novartis, Pfizer, Revotar Biopharmaceuticals, Sterna AG, and TEVA. ED reports consultancy fees from Actelion, Boehringer, AstraZeneca, and Cipla, advisory board fees for Chiesi, AstraZeneca, and CSL Behring, and speaker fees for GlaxoSmithKline and Boehringer. LG and AH are employees of Boehringer Ingelheim. JES, DZ, and LB report no conflicts of interest in this communication.

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