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SCIENTIFIC LETTER

LESSONS FROM THE ANTES B+ STUDY

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on behalf of the scientific committee of the ANTES

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To the Director,

About a year ago, *Archivos de Bronconeumologia* published the rationale, goals, design and methods of the ANTES B+ study (1), a pragmatic, prospective, randomized clinical trial whose primary objective was to investigate if treatment with inhaled triple therapy

(LABA-LAMA-ICS) improved clinical control (2) during 12 months follow-up *vs.* the GOLD recommended dual therapy (LABA-LAMA) in a specific subgroup of GOLD B patients that we named B+ (3). These B+ patients were characterized by having a CAT score >10 despite treatment with LABA-LAMA *and* having had a moderate exacerbation (treated with oral corticosteroids and/or antibiotics but not needing hospitalization) the year before *and* having more than 150 eosinophils / μL of circulating blood (1). These inclusion criteria were based on previous observations that showed that: *(1)* patients who remain symptomatic (CAT>10) despite treatment with LABA-LAMA are at higher risk of worse health outcomes (3); *(2)* GOLD B patients with 1 previous moderate exacerbation the year before had substantially higher hazard ratio of future exacerbation, all-cause hospitalization and respiratory hospitalization than those without them (4); and, *(3)* that higher level of circulating eosinophils identifies patients with a higher risk of future ECOPD, a better preventive response to inhaled corticosteroids (ICS), and reduced risk of ICS-related pneumonia (5). Indeed, this hypothesis was proposed before the Global Initiative for Chronic Obstructive Lung Disease (GOLD) suggested in the 2026 GOLD recommendations to consider one moderate exacerbation enough to move the patient to the GOLD E group (6). Finally, but importantly, this was going to be the first clinical trial with a composite outcome (clinical control) as the main endpoint. The concept of disease activity, disease stability and clinical control has also been highlighted in GOLD 2026 for the first time.

After obtaining all the necessary ethical approvals, recruitment of patients started in 2024. Unfortunately, one year later, despite having involved almost 40 recruiting centers around Spain, we had been able to randomize in the study only 48 patients. Given that the estimated sample size of the study was 1.028 patients (1), this rate of recruitment

would have required to prolong the study for several years, so it was agreed between the investigators and the sponsoring company to stop the trial.

In this scientific letter we first want to address our responsibility to inform the scientific community that the ANTES B+ study has been cancelled prematurely and the reasons for that but, also importantly, we would like to share some lessons learned from it because we think they may be useful for the design of future COPD trials. The first lesson is that double therapy works very well in alleviating symptoms in COPD because it was very difficult to find symptomatic patients on LABA-LAMA with CAT>10. In retrospect, this was probably a mistake on our side since GOLD recommends dual therapy in *naïve* B patients with CAT>10. Finding COPD patients who are highly symptomatic (CAT>10) but infrequent exacerbators while on dual therapy proved to be very difficult, which is actually an important clinical observation in itself. However, it should be noted that the majority of participating centers were tertiary hospitals, when it is possible that B+ patients may be more easily found in primary care. The second lesson learned relates to the difficulty in finding B patients with one moderate exacerbation the year before who were not already on triple therapy. A study by Vanfletern *et al* in the Swedish National Airway Registry reported the same observation in what they called B1 patients (same as B+ but excluding the requirement of CAT>10 while on double therapy) (4). This is an example that, sometimes, clinical practice does not follow the available scientific evidence. We think that it will be difficult to generate such scientific evidence in a formal prospective, randomized clinical trial but perhaps it may be possible to confirm this effect *in silico* in other available real-world databases. We hope to do so for the benefit of B+ patients. Finally, we regret that the ANTES B+ study had to be stopped prematurely for the reasons discussed above and could not, for

the first time, test a composite outcome (Clinical Control (2, 7)) as the main endpoint of the study (1), an approach that might have provided new and valuable insights into the level of disease stability achieved in these patients by triple therapy, as compared to dual treatment. We hope that this important question can be addressed in future trials.

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Artificial intelligence has not been used in this manuscript.

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