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Reply letter to Adeli and Jazi – "Intravenous N-acetylcysteine in respiratory disease with abnormal mucus secretion"

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Dear Editor,

We thank Dr. Adeli and Dr. Jazi for their appreciation of our study and their comments[1]. Some of the data they identified as missing in the paper were indeed omitted for brevity, but additional details on the study can be found in the results by accessing the clinicaltrial.gov website (NCT03843541)[2].

As they pointed out, the intravenous (IV) formulation of N-acetylcysteine (NAC) may be preferred to the more common oral formulation in specific circumstances, such as in hospitalized patients. The primary objective of this study was to demonstrate, in a large, well-designed, placebo-controlled trial, the mucolytic efficacy and safety of that NAC formulation, including an active-control arm (i.e., IV ambroxol)[3]. The study was not designed to compare intravenous NAC formulation with the oral formulation.

As reported in the Patients and Methods section and Table II, the study population included hospitalized patients with various respiratory conditions (e.g., chronic obstructive pulmonary disease (COPD), acute or chronic bronchitis, bronchiectasis), all characterized by abnormal mucus secretion (defined by sputum viscosity score ≥2, and expectoration difficult score ≥2, in a 4-point scale), who could benefit from mucolytic treatment. Of the 15 participants in the NAC group who prematurely discontinued the study, 3 subjects discontinued before any drug dose was administered due to concern about participating in a clinical trial (subjects were randomized but not treated; the number of withdrawals in Figure 1 presents a mistake and will be corrected accordingly through an erratum). Regarding the other 12 participants in the NAC group, apart from adverse events (n=5), other reasons for discontinuation were related to withdrawal due to feeling better (n=3), withdrawal due to unwillingness to continue (n=2), technical issues (n=1), transfer to another medical center (n=1). No study participant discontinued due to COVID-19. No differences in the incidence of treatment-emergent adverse events among the treatment groups were observed.

Overall, 22 (6.7%) subjects experienced at least one treatment-emergent adverse event related to study medication [11 (10.2%) and 11 (10.0%) subjects in the NAC and ambroxol groups, respectively; none in

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the placebo group]. Ten (3%) subjects experienced treatment adverse events leading to study discontinuation [5 (4.6%), 2 (1.8%), and 3 (2.7%) subjects in the NAC, ambroxol, and placebo groups, respectively]. Among these, 3 (0.9%) subjects experienced serious adverse events, none considered related to the study medication: 1 (0.9%) subject in the NAC group experienced worsening of pre-existing heart failure (leading to death), 1 (0.9%) subject in the ambroxol hydrochloride group experienced coronary arteriosclerosis, and 1 (0.9%) subject in the placebo group with congenital cerebrovascular anomaly.

Safety findings from this trial confirm the good tolerability profile of IV NAC reported from the previous small literature, and no new safety concerns were identified (no drug-related side effects were observed or reported in any of the published studies listed in Table V, apart from one case of bronchospasm that led to discontinuation in the study by Gunella et al[4]). Some rare cases of hypersensitivity reactions have been reported in the literature for both NAC and ambroxol intravenous administration; no anaphylactic reactions have been observed in our study[5,6]. We trust that this response will assist the authors in addressing any remaining questions from previous comments, and we extend our gratitude once more to the authors for their keen interest in our research.

Conflict of Interest

WT, DZ, FW, JFX, JPY, ZPD, XBC, JMQ were investigators of this study. AP received fees or honoraria from Chiesi, Astrazaneca, GSK, Menarini, MSD, Mundipharma, Novartis, Sanofi, Zambon, IQVIA, Avillon, Elpen, Edmon Pharma.

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