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LETTER

Response to "Letter to the Editor Regarding a Multicenter Phase 2 Randomized Controlled Study on the Efficacy and Safety of Reparixin in the Treatment of Hospitalized Patients with COVID-19 Pneumonia"

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To the Editors,

We thank Ito et al. [1] for their comments on our article, "A multicenter phase 2 randomized controlled study on the efficacy and safety of reparixin in the treatment of hospitalized patients with COVID-19 pneumonia" [2]. They support the investigation of an oral novel CXCR1/2 inhibitor, reparixin, in patients with severe COVID-19 pneumonia. However, they suggest the definitions of rescue medication and intensive care unit (ICU) admission are unclear. We would like to take this opportunity to clarify these aspects of the study design.

The term rescue medications was defined in the manuscript and was based upon each physician's clinical judgement due to the study being conducted during the beginning of the COVID-19 pandemic. We are aware of the existence of bias from the open-label nature of the study, and this aspect was highlighted in the discussion of limitations in the manuscript. A placebo-controlled trial was not feasible at the time of study design as the sponsor was requested to have the investigators unblinded to the treatment the patients were receiving. For ethical reasons, the sponsor accepted this decision. As noted in the manuscript, while the use of rescue medications was necessary in a small number of cases, we acknowledge that their use may have reduced the significance of the difference in treatment response. The definition of ICU care was addressed in the manuscript as well. We clarify that the intent was to capture the need for ICU-level care due to worsening of respiratory status, and we confirm that only ICU admissions related to worsening of a patient's condition were collected and considered in the analyses.

The rates of each component of the composite primary endpoint were provided with the intent to show which component was more impacted by treatment with reparixin when compared with the standard of care. Further sensitivity analyses were planned and conducted to investigate the primary endpoint and its components. These analyses corroborated the results that the use of rescue medications was a component that supported the statistically significant difference observed between the treatment groups. Nonetheless, we consider it appropriate to maintain the original primary analysis in the manuscript as an ad hoc analysis of this nature designed after the release of the data is generally discouraged because of limited credibility according to CONSORT guidelines for randomized controlled trials [3].

A larger phase 3 clinical trial that addresses the limitations discussed in the manuscript and highlighted by Ito et al. [1] has been completed

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(NCT04878055) with results presented at the 2022 European Respiratory Society (ERS) International Congress [4]. Another phase 3 clinical trial is currently ongoing (NCT05254990) and aims to confirm the role of reparixin in limiting disease progression in adult patients with COVID-19 and other community-acquired pneumonia.

We thank the editors for the opportunity to share additional context and clarifications regarding the study limitations that were raised by Ito et al. [1].

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Author Contributions. FM drafted and edited the letter and approved the final version of the letter.

Disclosures. Flavio Mantelli, MD is an employee of Dompé Farmaceutici SpA.

Compliance with Ethics Guidelines. This letter is based on a previously conducted study and does not contain any study with human participants or animals performed by the author.

Data Availability. Data sharing is not applicable to this letter as no datasets were generated or analyzed during the current study.

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