From the authors:

We would like to thank C. Méhats and colleagues for their comments regarding our paper on phosphodiesterase (PDE)4 inhibition in hyperoxia-induced bronchopulmonary dysplasia (BPD) [1]. In our article, we stated that inhibition of PDE4 with cilomilast leads to an improved alveolarisation in hyperoxia-induced lung injury in mice [1]. C. Méhats and colleagues raised concerns about our study design and the obtained results. We would like to respond to the issues in question.

The first point of criticism addresses differences regarding the therapeutic impact of the PDE4 inhibitor cilomilast in our study of mice, as compared to rolipram in the study of MÉHATS *et al.* [2], which was conducted on rats. MÉHATS *et al.* [2] demonstrated that treatment of hyperoxia-exposed rats with 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$ rolipram prolonged the survival of the treated rats significantly but could not improve alveolarisation. Further doses of rolipram slowed the growth of the treated hyperoxic and normoxic rat pups compared to the untreated hyperoxic group. In contrast, DE VISSER *et al.* [3] reported improved histopathology in terms of thinning of septa and a reduction of inflammation and oedema after PDE4 inhibition with rolipram and piclamilast. Interestingly, DE VISSER *et al.* [3] did not note adverse effects on the body weight with a dose of 125 $\mu g \cdot kg^{-1} \cdot day^{-1}$ rolipram and were able to prolong the median survival by 3 days. In our study, mice were used instead of rats. In addition, the animals in our study were exposed to lower oxygen concentrations (85% O_2) as compared to those used in the study of MÉHATS *et al.* [2] (95% O_2). Extremely high levels of O_2 are known to induce oedema formation, inflammation, and high mortality in rats, thus mimicking acute lung injury rather than an arrest in lung alveolarisation. Slightly lower O_2 levels as used in our study, however, appear to be better suited to the investigation of BPD-like events, as characterised by increased medial wall thickness and thinning of septa. In addition, no side-effects on food intake were observed in the animals treated with cilomilast. On the contrary, the treated hyperoxic mice even showed a slight improvement in body weight as opposed to hyperoxic controls. Of course, the issue of nutrition is important in this regard, as described in studies from MASSARO *et al.* [4], who showed that proper feeding has a direct impact on murine alveolar regeneration.

C. Méhats and colleagues claim that the conclusion of our study regarding a potential impact of cilomilast for the treatment of BPD is overstated. They refer to the minor degree of changes in the histopathological parameters and a lack of biological effects that can be related to these changes. It is possible that C. Méhats and colleagues have misinterpreted figure 9 of our paper [1], which clearly shows that dynamic compliance is significantly reduced in hyperoxic mice (as compared to controls). This proves that treatment with cilomilast significantly and expediently restores this functional parameter (with compliance values even slightly above control levels).

Another point of criticism refers to the morphometric methodology used in our study. The customised Leica Q Win analysing software (Leica Microsystems GmbH, Wetzlar, Germany) can be regarded as a reliable tool for accurate quantification of alveolar structures in an investigator-independent manner [5–8]. When establishing this methodology in our laboratory, of course, validations were undertaken by comparison to standard techniques, revealing a high accuracy of the automatised technique. In addition, inter-observer variability is avoided by this software-based method as opposed to the standard point-counting method.

Finally, it has to be kept in mind that compounds like rolipram belong to the first generation of PDE4 inhibitors and their clinical utility is limited by several side-effects, including nausea, emesis and gastric acid secretion. In contrast, the second generation of PDE4 inhibitors offer an improved side-effect profile and cilomilast is already approved for treatment of chronic obstructive pulmonary disease.

In conclusion, we think that based on the above listed facts, it is appropriate to say that cilomilast has potential beneficial effects in bronchopulmonary dysplasia.

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STATEMENT OF INTEREST

None declared.

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