



# Trying to find a cure for cystic fibrosis: CFTR biomarkers as outcomes

To the Editor:

In a recent issue of the *European Respiratory Journal*, DE BOECK *et al.* [1] provided a systematic review of the clinimetric properties of cystic fibrosis transmembrane conductance regulator (CFTR) biomarkers, giving supporting evidence for promoting these biomarkers as surrogate end-points. The authors are to be congratulated not only for having collected exhaustive data about CFTR biomarkers and attempted to clarify their role but also for having led tremendous efforts towards standardisation of these techniques over recent years. They concluded that available data demonstrate reliability, validity and responsiveness of nasal potential difference (NPD), as well as validity and responsiveness of sweat chloride levels. However, one may wonder whether these conclusions are in agreement with the results of the last randomised clinical trials involving the three most promising small molecules in the context of searching for a CFTR mutation-specific treatment. A phase 3 randomised clinical trial evaluating the effects of ataluren has been recently completed [2]. The study involved 238 patients carrying at least one class I CFTR mutation who were randomised to receive ataluren or placebo for 48 weeks. From a pragmatic point of view, statistically significant benefit in terms of forced expiratory volume in 1 s (FEV<sub>1</sub>) was restricted to patients who were not using inhaled tobramycin, and the magnitude of the benefit was comparable to that reported with inhaled tobramycin [3]. The pulmonary exacerbation rate was 23% lower in favour of ataluren. In keeping with a previous study, sweat chloride levels were unchanged. In contrast to the three much smaller previous studies, epithelial chloride secretion as assessed by NPD did not improve. This raises several possibilities. If ataluren is an effective drug, the validity of NPD and sweat chloride as CFTR biomarkers may be questioned; if ineffective, the reliability of NPD may be doubted. Furthermore, in patients homozygous for the F508del mutation, lumacaftor alone [4, 5] or in combination with ivacaftor [5] induced similar, modest (<10 mmol·L<sup>-1</sup>) but significant decreases in sweat chloride. However, improvement of FEV<sub>1</sub> was only observed when combining the drugs. Again, this challenges the above conclusions, casting doubt on the validity of the biomarkers and raising the possibility that FEV<sub>1</sub> improvement in these studies might be unrelated to ion transport correction.



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CFTR biomarkers as surrogate end-points: recent trials cast doubt on validity of NPD and sweat chloride measurements <http://ow.ly/nuTOD>

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## References

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- 5 Boyle MP, Bell S, Konstan M, *et al.* The investigational CFTR-corrector, VX-809 (lumacaftor) co-administered with the oral potentiator ivacaftor improved CFTR and lung function in F508del homozygous patients: phase II study results. *Pediatr Pulmonol* 2012; 47: Suppl. 35, 315.