From the authors:

We thank P. Lebecque for his interest in our paper [1]. His comment as to whether measurement of cystic fibrosis transmembrane conductance regulator (CFTR) biomarkers are truly response measures relates to the recent paper by DURMOWICZ *et al.* [2] entitled ''Change in sweat chloride as a clinical end point in cystic fibrosis clinical trials: the ivacaftor experience''. These authors also point towards the uncertainty of using established measurements such as sweat chloride as a clinical end-point.

We are indeed in the early days of clinical use of CFTR modulators and much is to be learned about how improving CFTR biomarkers relates to clinical efficacy. In our further discussion, we will, as DURMOWICZ *et al.* [2] do, discuss only ivacaftor and lumacaftor monotherapy [3–5], since data on ataluren and on ivacaftor/lumacaftor combination therapy are only available as abstracts.

Let's start with a reasonable statement: if cystic fibrosis lung disease is secondary to CFTR dysfunction, then improving CFTR function must ameliorate cystic fibrosis lung disease. In the phase 2 study with ivacaftor [4], a dose response was observed: ivacaftor progressively improved CFTR function (measured in the sweat gland and on the nasal mucosa) and progressively improved lung function in patients with at least one G551D mutation. Sweat chloride and nasal potential difference (NPD) readout are, therefore, definitely responsive measures, as stated in our paper [1]. However, the discussion should be more focused on how close the correlation is between improving CFTR biomarker and improving lung function. Here we are not as disappointed as DURMOWICZ *et al.* [2]. The plots in figure 1 of their article indicate that nearly all subjects in the phase 3 trial with only one drug dose fall in the upper-left corner, *i.e.* show improvement in sweat chloride as well as improvement in forced expiratory volume in 1 s (FEV_1). That a strict dose–response relationship is not seen cross-sectionally in phase 3 studies is not so surprising. A dose escalation study in individual patients would provide more instructive data on how improving CFTR function can improve lung function or function in another target organ, since indeed the dose–effect relationship probably differs not only between subjects but also between different target organs. In cross-sectional phase 3 studies, many aspects that can be grouped under the general umbrella of ''physiological'', ''genetic'' and ''environmental'' play a role: baseline lung function, ''room for improvement'' in subjects with existing structural lung damage, presence of favourable or unfavourable genetic modifier genes, concurrent smoking or other environmental stressors, compliance with other cystic fibrosis lung treatments, drug absorption, *etc.* We should also not forget that even FEV_1 is only a surrogate outcome. In studies on efficacy of inhaled mucolytics and antibiotics, the improvement in FEV_1 does not parallel the improvement in clinical benefit as measured by the decrease in pulmonary exacerbations [6, 7]. In the ivacaftor phase 3 study, ivacaftor not only lowered sweat chloride and improved lung function, but also improved all clinical outcomes measured, giving fewer pulmonary exacerbations, better weight gain and improved quality-of-life score [3]. Thus, the robust improvement in sweat chloride seen in phase 2 trials really did concur with solid evidence of clinical benefit. Therefore, we await with great hope the long-term potential of ivacaftor. For lumacaftor monotherapy in patients homozygous for F508del, only phase 2 data are available [5]. A small dose-dependent effect was seen in sweat chloride, but not in NPD or FEV_1. The study was powered to detect changes in sweat chloride, but not to detect changes in NPD and FEV_1. Hence, let's not overconclude about efficacy from phase 2 data only.

As clinicians we certainly welcome more drugs that improve CFTR biomarker readout. Provided the drug reaches the different target organs and the latter are still amenable to improvement, a substantial improvement in CFTR function measured by an established CFTR biomarker should be paralleled by an improvement in or preservation of cystic fibrosis organ function. If not, we have to review the root cause of cystic fibrosis.

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CFTR biomarkers as surrogate end-points: improving CFTR function must ameliorate cystic fibrosis lung disease http://ow.ly/nv6Uh

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Allergic burden and the risk of venous thromboembolism

To the Editor:

We read with keen interest a recent article by MAJOOR *et al.* [1], who studied the relationship between asthma and venous thromboembolism (VTE). They provided evidence for the increased risk of VTE, specifically pulmonary embolism (PE), among asthmatics. In final regression models, after adjustment for potential confounders, MAJOOR *et al.* [1] found that body mass index was the sole independent predictor of deep vein thrombosis (DVT) risk, while only severe asthma and oral corticosteroid use independently predicted PE.

Mechanisms underlying the intriguing association of asthma with VTE remain unclear. However, several previous papers published by us and other investigators [2–5] showed that allergic diseases are associated with a number of prothrombotic alterations involving enhanced platelet activation, formation of dense fibrin clots that are relatively resistant to lysis, increased plasminogen activator inhibitor-1 levels or a disturbed protein C anticoagulant pathway. In a case–control study of subjects between 20 and 45 years old, we demonstrated that atopic diseases are more prevalent in patients with distal DVT, but not those with PE, and allergy to timothy grass pollen was over-represented in the VTE group [2]. Discrepancies in the patient characteristics and methodology between the current study [1] and ours [2] are likely to explain differences in the reported results.

The results by MAJOOR *et al.* [1] might also suggest that there are links between thrombosis and atopic sensitisation and/or allergic inflammation. Although less prevalent than in children, the atopic phenotype of asthma is common in adults, and $\geqslant$50% of adult asthmatics are positive for atopic sensitisation. The prevalence of other allergic diseases, such as atopic dermatitis and especially allergic rhinitis, which are quite common in the general adult population (about 2–10% and 20%, respectively), is increased in asthmatics in whom, when present, they further increase the allergic inflammation burden. One might speculate that the overall allergic inflammation burden could have also contributed to the increased risk of VTE which MAJOOR *et al.* [1] observed in severe asthma. Although they included atopy in the final regression models, showing lack of its effect, it would be interesting to evaluate VTE risk in the subgroups obtained by stratification of asthma based on accompanying allergic diseases and/or atopy, similar to those they had conducted according to asthma severity. It is also possible that the lack of any association of atopy in the regression analyses could have resulted from a rather limited number of VTE events (n=35) in the study by MAJOOR *et al.* [1].

Similarly, in this study, severe asthma showed the association with PE but not DVT and this observation might also be related to low numbers of PE (n=19) and DVT (n=16) events [1]. It cannot be excluded that DVT had been underestimated, which could have affected the results [1].

However, asthma has been independently reported to be associated with PE in a large retrospective primary care-based study by CAZZOLA *et al.* [6], although the DVT phenotype was not analysed in that study.