

## CORRESPONDENCE

## Response to: 'Lumacaftor/ivacaftor for patients homozygous for Phe508del-CFTR: should we curb our enthusiasm?' by Jones and Barry

The commentary on ivacaftor for patients homozygous for Phe508del-CFTR (c.1521\_1523delCTT; formerly F508del) 'Should we curb our enthusiasm?' by Jones and Barry makes a number of important points regarding the potential impact of ivacaftor/lumacaftor combination in cystic fibrosis (CF).<sup>1</sup> However, the view taken by the authors is rather pessimistic regarding the scientific and clinical impact of combination therapy for people with CF. The TRAFFIC and TRANSPORT studies were designed to test the efficacy and safety of this combination in line with regulatory requirements from the Federal Drugs Administration and European Medicines Agency (EMA). The phase III pivotal programme, as noted in the commentary, met its primary end point of improvement in FEV<sub>1</sub>, with significant changes in secondary end points in the pooled analyses of frequency of exacerbations and quality of life.<sup>2</sup> The reduction in exacerbations (39%) and hospitalisations (61%) are clinically important outcomes as frequent exacerbations are associated with accelerated decline in lung function and worse survival.<sup>3,4</sup> In a study recently published using registry data from patients with the Gly551Asp mutation treated with ivacaftor in the clinic, there is continued benefit in attenuation of the rate of decline in lung function.<sup>5</sup> This suggests that the benefits of restoration of cystic fibrosis transmembrane conductance regulator (CFTR) function go beyond initial improvement in FEV<sub>1</sub> alone.

The scientific underpinning of combination therapy is that lumacaftor has a correcting effect on mutant Phe508del-CFTR, increasing its processing to the cell membrane and ivacaftor, then potentiating the mutant protein. These effects have been clearly demonstrated in cell culture.<sup>6</sup> The translation of these *in vitro* discoveries to the positive clinical effect of lumacaftor/ivacaftor combination therapy is a significant landmark in CF treatment as it demonstrates this approach is scientifically valid. Lumacaftor may not ultimately be the most effective drug to improve

processing of CFTR, but demonstration of *in vitro* correction and potentiation with the associated clinical benefit is a strong encouragement to pursue therapies targeted at CFTR correction. The first drug developed in a new class rarely is the most potent, and there are a number of academic and commercial programmes studying potentially more efficacious correctors.<sup>7</sup> Nonetheless, this proof of principle of clinical benefit from a corrector/potentiator combination is a very significant development in CF treatment.

It is correctly noted in the commentary that the effect size of FEV<sub>1</sub> at 3% is modest. However, the implication that the improvement was related to suboptimal conventional treatment particularly with regard to azithromycin is incorrect. The patients recruited to TRAFFIC and TRANSPORT studies were on optimal therapy. The percentage of patients treated with inhaled antibiotics or inhaled therapies and azithromycin are in line with US and European registry data. For example, in the 2013 UK CF registry, 57% of patients aged >16 years received azithromycin compared with 61% in the patients recruited to TRAFFIC and TRANSPORT.<sup>8</sup> The effect of combination therapy was in addition to optimal therapies and still demonstrated beneficial spirometric, exacerbation, quality of life and nutritional effects.

The authors also encourage us that combination therapy should not represent a 'holy grail' for homozygous Phe508del patients. It is unclear why the authors would evoke this historic metaphor, but restoration of normal CFTR function in CF is therapeutically the primary goal of research in this disease. Further correctors and potentiators and molecular approaches such as gene therapy and gene editing are being tested to provide alternative and potentially more efficacious approaches to correction of the basic defect in CF. However, the demonstration that combination therapy with lumacaftor and ivacaftor improves important end points such as FEV<sub>1</sub> and pulmonary exacerbations should not be understated. The development of precision therapies based on an understanding of the underlying biology in CF is the best opportunity to deliver effective treatments that are transformative in people with CF and change the natural history of this disease by improving the length and quality of life.<sup>9</sup> Progress in this context should be applauded and encouraged.

The authors also raised the important and difficult issues around reimbursement for drugs developed in rare diseases,

particularly for CF. However, the cost of treatment should not impact the interpretation of data. Combination therapy with lumacaftor/ivacaftor has now been approved by the US Food and Drug Administration for use in the USA where it is already being prescribed. The price of \$259 000 annually for treatment in the USA is very expensive. Other countries, particularly in Europe, will undertake a Health Technology Assessment to determine whether the benefit for patients is sufficient to justify its cost. Final pricing will then be negotiated in each country. This is an appropriate approach for a new therapy. Affordability is an important issue, and the clinical trial results will inform assessments of cost effectiveness but should not influence the interpretation of clinically relevant outcomes. It is of note that in some other chronic lung diseases, such as idiopathic pulmonary fibrosis, drugs such as pirfenidone and nintedanib maintain stability or reduce rate of decline of primary outcome measures such as FEV<sub>1</sub> and FVC, rather than improve them compared with placebo.<sup>10,11</sup> These treatments are also important advances and have been approved by licensing authorities but show less benefit compared with combination therapy in CF. Similarly, in Duchenne muscular dystrophy, conditional approval has been granted by the EMA to PTC 124 (Ataluren) for showing a slowing of decline, but no improvement in the six-minute walk test, a key functional end point in this disease.<sup>12</sup> In contrast, lumacaftor/ivacaftor significantly improved lung function and reduced pulmonary exacerbations.<sup>2</sup>

Pharmaceutical companies and health-care commissioners (payers) must find ways to deliver sustainable funding arrangements that recognise the costs of developing new therapies in rare diseases and also make treatment accessible to all in the world who will benefit from innovative therapies. More efficacious CFTR modulators may also become available in due course, but effective therapies such as lumacaftor/ivacaftor should not be denied to patients who will benefit.

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