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A treatment evaluator tool to monitor the real-world effectiveness of inhaled aztreonam lysine in cystic fibrosis

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Abstract

Background: Studies are required to evaluate real-world outcomes of inhaled aztreonam lysine in patients with cystic fibrosis (CF).

Methods: Our treatment-evaluator tool assessed the effectiveness of inhaled aztreonam in routine practice in 117 CF patients across four time periods (6–12 (P2) and 0–6 months (P1) pre-initiation, and 0–6 (T1) and 6–12 months (T2) post-initiation). Outcomes were: changes in %-predicted forced expiratory volume in 1 s (FEV1), body-mass index (BMI), hospitalisation days and intravenous antibiotic usage.

Results: Median FEV1% predicted for each 6-month period was 38.9%, 34.6%, 37.1% and 36.5%; median change was −0.6% (p < 0.001) between P2 and P1, increasing to +0.6% (p < 0.001) between P1 and T1. Annualised hospital bed-days was reduced (p = 0.05) post-initiation, as was intravenous antibiotics days (p = 0.001). BMI increased over 6 months post-initiation (p ≤ 0.001).

Conclusions: In patients with CF in routine practice, inhaled aztreonam lysine is associated with improved lung function and weight, and reduced hospitalisation and intravenous antibiotic use.

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Keywords: Aztreonam; Cystic fibrosis; Forced expiratory volume; Evaluation tool; Intravenous antibiotics

Abbreviations: BMI, body mass index; CF, cystic fibrosis; FEV1, forced expiratory volume in 1 s; IV, intravenous.

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1. Introduction

Patients with CF are highly susceptible to recurrent, and ultimately chronic, respiratory tract infections, principally with *Pseudomonas aeruginosa* (Pa), which result in progressive inflammation and irreversible airway damage [1,2]. This chronic infection leads to recurrent symptomatic exacerbations, which increase the rate of decline in lung function and are associated with increased risk of death and morbidity [3–8]. Inhaled antibiotics are an established therapeutic option for these patients although adherence and real-world effectiveness has been less than optimal in some studies [1,9,10].

Inhaled aztreonam lysine is a recent treatment option with a rapid delivery system shown in randomised controlled trials to improve forced expired volume in 1 s (FEV1) and reduce pulmonary exacerbations, compared with placebo in patients with CF [11,12]. The long-term safety and efficacy of inhaled aztreonam has been demonstrated [13]. In addition, the efficacy of inhaled aztreonam was demonstrated in an open-label active comparator study relative to the perceived current standard of care, nebulised tobramycin [14]. On the basis of these findings, inhaled aztreonam lysine is recommended for the treatment of chronic Pa lung infections in current CF management guidelines [1,9].

Although randomised controlled trials constitute the ‘gold standard’ evidence of treatment efficacy, they describe the efficacy of an intervention only under optimal conditions. They provide little information about the effectiveness of the treatment under real-world conditions, for example in patients with advanced pulmonary disease [15–17]. Adherence to treatment in CF clinical trials is not typical of that seen in routine practice [10] and trials have limited ability to demonstrate real cost-effectiveness or the value within a local health economy. As a consequence of narrowly defined selection criteria, patients enrolled in respiratory randomised trials represent fewer than 6% of patients encountered in routine practice [16,18].

Furthermore, there are a number of limitations associated with inhaled antibiotic therapy trials. The short duration and on/off courses of treatment may not be representative of regimens routinely used in the clinic. Equally there is a lack of evidence relating to the real-world effectiveness of any specific inhaled antibiotic in the context of combinations of inhaled antibiotics typically used in practice. Consequently, real-world studies of patients with CF are required to provide information that complements current clinical trial data.

To facilitate assessment of treatment impact on key outcome measures in patients with CF routinely managed in clinical practice, we developed a treatment evaluator tool to investigate the real-world effectiveness of inhaled aztreonam lysine.

2. Materials and methods

2.1. Development of the treatment evaluator tool

The project was conducted over 24 months from January 2012 to January 2014. The treatment evaluator tool was developed through consensus by an independent Steering Committee with representatives from nine large cystic fibrosis centres (>100 patients attending service) in Ireland and the UK. Initial meetings of the Steering Committee were held between January 2012 and December 2012 to agree and define patient- and treatment-related information that could be easily recorded during routine clinical care and would inform real-world treatment outcomes [Table 1]. Genotype classification was determined according to previous methods [19].

An online, user-friendly interface was developed to facilitate entry of the agreed data. The treatment evaluator tool assigned a unique study identity number so as to anonymise the data. Only the Site Investigator was aware of the actual patient identity. FEV1% predicted was calculated from absolute measurements [20].

2.2. Patient selection

The decision to initiate inhaled aztreonam lysine, and/or discontinue another inhaled antibiotic, was taken by the specialist CF physician responsible for individual patient care, based on a clinical need for therapy. Current clinical guidelines recommend the use of inhaled aztreonam lysine in patients with chronic Pa lung infections. Patients were seen in routine clinical practice at one of the nine large adult CF centres participating in the study. The only entry criteria were attending a participating CF centre, being 18 years or older at the time of initial data extraction, and having commenced inhaled aztreonam lysine therapy. The treatment evaluator tool was completed retrospectively on all

Table 1
Patient- and treatment-related data collected in the treatment evaluator tool.

<table>
<thead>
<tr>
<th>Baseline patient-related data</th>
<th>Treatment-related data</th>
<th>On-going patient-related data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Baseline key nebulised therapy</td>
<td>FEV1 (L)</td>
</tr>
<tr>
<td>Date of birth</td>
<td>Treatment changes</td>
<td>Height (cm)</td>
</tr>
<tr>
<td>Age</td>
<td>IV antibiotic use (at home and in hospital)</td>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Age at diagnosis of CF</td>
<td>Start and stop date of any treatment changes</td>
<td>Exacerbations requiring IV antibiotics</td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td>Number of hospital bed days</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic mutations present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past medical history (including diabetes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; CF, cystic fibrosis; FEV1, forced expiratory volume in 1 s; IV, intravenous.
patients at the participating CF centres who commenced inhaled aztreonam lysine during the data abstraction period.

2.3. Evaluation of outcomes

Participating centres collected baseline data into the treatment evaluator tool at the visit when inhaled aztreonam lysine was initiated (time 0), with retrospective data for these patients for the previous 12 months derived from patient medical notes (including out-patient and in-patient FEV1 values). Monitoring data were collected into the treatment evaluator tool during follow-up at 6 months post-initiation of inhaled aztreonam lysine and at 12 months, or at last available follow-up if the patient had less than 12 months of data at the end of abstraction. The duration of treatment recorded by the tool was determined by the difference between inhaled aztreonam lysine start date and the last FEV1 measurement recorded in the treatment evaluator tool. Spirometry was recorded in keeping with clinical schedules and therefore was not timed around “on” or “off” months of inhaled therapy. For analysis, observations were combined into consecutive 6-month periods, relative to when the patient initiated inhaled aztreonam lysine therapy: P2 (6–12 months pre-initiation), P1 (0–6 months pre-initiation), T1 (0–6 months post-initiation) and T2 (6–12 months post-initiation). For patients with less than 12 months of follow-up after initiation of inhaled aztreonam lysine therapy, event rates were annualised to a 12-month event rate to allow for comparison with the time period pre-initiation of therapy. Participating centres had access to data from their own patients and to aggregated data from all centres.

The primary study endpoint was the change in FEV1% predicted in the 6 months immediately before and after initiation of inhaled aztreonam lysine therapy (P1 to T1) relative to the change in the two consecutive 6-month periods pre-aztreonam (P2 to P1). As each patient had a variable number of FEV1 assessments, the mean FEV1 for each patient within each of the 6 month time periods was calculated.

Secondary outcomes were change in hospital bed days per year, change in IV antibiotics days per year (both total and categorised by location; home or hospital) and change in body mass index (BMI) (kg/m2).

2.4. Statistical considerations

As the majority of the study data had a skewed distribution they are summarised using medians and intra-quartile ranges. Due to different practice patterns at different sites, the number of patients with a specific measurement in a given 6-month period varied; we therefore present data (a) restricting the analysis to the number of patients with data available at relevant time periods (b) using all available patient data at each timepoint. The former approach results in a smaller sample size but ensures that any differences are not simply the result of different patients contributing data at different time points. In either case statistical significance was measured using the Wilcoxon Signed Rank test, with a type I error rate of ≤0.05. Analysis was conducted using PASW Statistics version 18.

2.5. Ethical approval and funding

As its purpose is to facilitate a service evaluation of treatment outcomes as used in current clinical practice, and as the study involved no direct patient contact and no study-mandated investigations, the National Research Ethics Service and appropriate local bodies confirmed that individual ethical approval was not required for the development of the treatment evaluator tool and its subsequent use [21]. Funding for tool development and its use to evaluate outcomes in patients treated with inhaled aztreonam lysine was provided by Gilead Sciences UK & Ireland Ltd., which had no access to the data. Data management was performed by SolverMinds Pharma Ltd., Milton Keynes, UK. Data analysis was undertaken by a researcher who was completely independent of the funder and of the clinical research group and who had not otherwise been involved in the data collection. The Steering Committee had full independent editorial control over the resulting study manuscript.

3. Results

3.1. Patient characteristics

Data on 117 patients were available for analysis. The median (interquartile range) duration of follow-up was 37.6 weeks (22.6–47.9). Table 2 summarises baseline characteristics, which demonstrate a relatively severe clinical phenotype prior to the initiation of inhaled aztreonam lysine (median FEV1 36.1% predicted). The majority of patients were receiving inhaled anti-pseudomonal treatment prior to initiation of inhaled aztreonam lysine, with approximately equal proportions treated with colistin mono-therapy (24%), tobramycin mono-therapy (20%) or a combination of the two treatments (24%). The vast majority of patients were prescribed inhaled aztreonam on an alternate month basis (19 subjects in conjunction with alternate month nebulised colistin, 36 with nebulised alternate month tobramycin, 20 with alternate month inhaled tobramycin); 6 subjects were prescribed inhaled aztreonam on a continuous basis. A total of 74% had

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients</th>
<th>Males, n (%)</th>
<th>Age, median years (IQR)</th>
<th>Age at diagnosis &lt;3 years, n (%)</th>
<th>BMI kg/m², median (range)</th>
<th>Diabetes, n (%)</th>
<th>Baseline FEV1% predicted, median (IQR)</th>
<th>Baseline inhaled antibiotic therapy, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>117</td>
<td>57 (49%)</td>
<td>32.0 (25.7, 37.0)</td>
<td>90 (76.9%)</td>
<td>21 (9–30)</td>
<td>46 (39.3%)</td>
<td>36.1 (27.5, 45.3)</td>
<td>- Colistin monotherapy 27 (24%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Tobramycin monotherapy 23 (20%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Colistin/tobramycin 27 (24%)</td>
</tr>
<tr>
<td>Genotype, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Class I–III mutation</td>
<td>87 (74%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Class IV–VI mutation</td>
<td>5 (4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Unknown/unclassified</td>
<td>25 (21%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; IQR, interquartile range.
Class I–III mutations, of which 7 had a Class III mutation. Five patients had G551D mutations; two of whom had completed their one-year follow-up prior to the introduction of ivacaftor. The remainder could have potentially commenced ivacaftor during the study follow-up period but this data was not recorded in the dataset.

### 3.2. Lung function

One hundred and eight patients had FEV1 data for each of the three initial 6-month periods, P2, P1 and T1. Lung function was actively deteriorating in the year prior to therapy, with the median FEV1% predicted falling significantly from 39.6% in P2 to 36.2% in P1 (p < 0.001), but it significantly improved post-initiation of inhaled aztreonam lysine to 38.0% in T1 (p = 0.04), [Table 3]. The median within-patient change in FEV1% predicted between P2 and P1 was −2.0% (−4.6%, +0.6%) with 77 patients showing a deterioration in their FEV1. The median within-patient change between periods immediately before (P1) and immediately after (T1) treatment was +0.6% (−2.0, +3.8) with only 43 patients manifesting an ongoing deterioration in their FEV1 following initiation of therapy. The deterioration in within-patient change in FEV1% predicted was significantly less following initiation of inhaled aztreonam than prior to its introduction, (p < 0.001) [Fig. 1A].

Fig. 1B shows FEV1% predicted across the four time periods using all available measurements. In those patients with available data, FEV1% deteriorated prior to the initiation of treatment (P2 vs. P1; p < 0.001) but significantly improved in the 6 months post-initiation (T1 vs. P1; p = 0.03). The median FEV1 value remained higher in T2 than P1, but this was non-significant.

Similar trends for the change in FEV1% predicted were evident when analysis was restricted to the 78 patients who had complete data in all four periods [Table 3].

![Fig. 1A](image1.png)

**Table 3**

Distribution of FEV1% predicted by 6-month time period for patients with available data in each of the three initial 6-month periods, in all four 6-month periods and using all available data.

<table>
<thead>
<tr>
<th>Time period</th>
<th>6–12 months pre- (P2)</th>
<th>0–6 months pre- (P1)</th>
<th>0–6 months post- (T1)</th>
<th>6–12 months post- (T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete FEV1% predicted data in each of first three time periods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>108</td>
<td>108</td>
<td>108</td>
<td>n/a</td>
</tr>
<tr>
<td>Median</td>
<td>39.6</td>
<td>36.2</td>
<td>38.0</td>
<td>n/a</td>
</tr>
<tr>
<td>p-Value (vs. P1) *</td>
<td>p &lt; 0.001</td>
<td>Reference</td>
<td>p = 0.04</td>
<td>n/a</td>
</tr>
<tr>
<td>Complete FEV1% predicted data in all four time periods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>78</td>
<td>78</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Median</td>
<td>38.9</td>
<td>34.6</td>
<td>37.1</td>
<td>36.5</td>
</tr>
<tr>
<td>p-Value (vs. P1) *</td>
<td>p &lt; 0.001</td>
<td>Reference</td>
<td>p = 0.03</td>
<td>p = 0.48</td>
</tr>
<tr>
<td>All available data FEV1% predicted in all four periods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>110</td>
<td>116</td>
<td>115</td>
<td>83</td>
</tr>
<tr>
<td>Median</td>
<td>39.6</td>
<td>36.1</td>
<td>37.3</td>
<td>36.6</td>
</tr>
<tr>
<td>p-Value (vs. P1) *</td>
<td>p &lt; 0.001</td>
<td>Reference</td>
<td>p = 0.03</td>
<td>p = 0.43</td>
</tr>
</tbody>
</table>

* p values calculated using Wilcoxon Signed Rank test for difference relative to P1 (0–6 months pre-initiation).

Fig. 1. Boxplots showing median within-patient change (solid line), interquartile range (box) and outlying (circle) and extreme outlying (asterisks) values for: (A) FEV1% predicted between 6 and 12 months (P2) and 0–6 months pre- (P1) initiation of inhaled aztreonam lysine therapy (on left) and between 0 and 6 months pre- (P1) and 0–6 months post- (T1) initiation of therapy (on right); (B) FEV1% predicted in all patients across the four time periods. p-Values calculated using Wilcoxon Signed Rank tests.
3.3. Clinical effectiveness and exacerbation outcomes

The median number of annualised hospital bed-days per patient decreased by 16% from 15.0 to 12.6 days following initiation of inhaled aztreonam lysine therapy (p = 0.05) [Table 4]. The median number of days of intravenous antibiotic treatment reduced by 26.8% from 56.0 to 41.0 days (p = 0.001) and significant reductions were seen for both intravenous antibiotics administered in-hospital, (33% reduction; p = 0.05), and at home (30% reduction; p = 0.01) [Table 4].

3.4. Body mass index

Median (interquartile range) BMI was stable in the year prior to initiation of therapy: 20.9 kg/m² (19.1, 23.1) in P2 and 20.8 kg/m² (19.1, 23.2) in P1 (p = 0.47). The median BMI increased significantly to 21.4 kg/m² (19.4, 23.4) in the 6 months following initiation of inhaled aztreonam lysine (T1 vs. P1; p < 0.001), [Fig. 2]. BMI in T2 remained significantly higher than in P1 at 21.6 kg/m² (19.2, 23.5) (T2 vs. P1; p = 0.01). There were similar significant findings when the analysis was restricted to the 77 patients with complete BMI data at all 4 time points, median BMI at P2, P1, T1 and T2 of 20.9, 21.0, 21.5 and 21.6 kg/m² respectively, with T1 being significantly higher than P1 (p =0.003).

4. Conclusions

This was the first real-world multicentre study of the use of inhaled aztreonam lysine in clinical practice. Patients evaluated in the analysis were identified from routine practice at clinics in the UK and Ireland. The study demonstrates that the ‘real-world’ cohort receiving the therapy had a more severe clinical phenotype than those documented in clinical trials (a median FEV1 of 36.1% predicted compared with between 52.2% and 56.7% in clinical trials) [11–14]. In this real-world population, the introduction of inhaled aztreonam lysine was associated with significant improvements in lung function and gain in weight, and a significant reduction in hospitalisations and intravenous antibiotic use, compared to the previous year. These findings are consistent with the results of the clinical trials conducted for inhaled aztreonam lysine in selected patient populations [11,12,14].

The patients included in the evaluation were actively deteriorating, as shown by the decline in FEV1% predicted and low BMI prior to therapy, despite the majority of patients receiving treatment with colistin and/or tobramycin as mono- or dual therapy. The introduction of inhaled aztreonam lysine in these patients is consistent with management guidelines [1,9]. The improved outcomes associated with the introduction of inhaled aztreonam lysine also raise the question of the potential value if the therapy had been used earlier, but the current study does not address this issue.

This study demonstrated a significant reduction in exacerbation rates which is critical to improving CF outcomes, given that the number of exacerbations for patients with CF is a significant predictor of decline in FEV1 [3,5,6] and FEV1 often does not return to baseline levels after an exacerbation [8]. In our evaluation, we used hospital bed-days and intravenous antibiotic use as real-world surrogate measures of exacerbation rate. The observed reduction in these measures associated with the introduction of inhaled aztreonam lysine is an important finding with potential benefits for patients, their families and society; at a fiscal level, these reductions would result in substantial savings in hospital and community based costs.

Low body weight in CF is a common problem, and is associated with poor clinical outcomes in CF [22–24]. Addressing this issue is critical to both acute and chronic care. In our study, patients showed a median weight gain of 2 kg in the 6 months following introduction of inhaled aztreonam lysine. Although this gain is modest, it reversed the decline in weight seen in previous

### Table 4

<table>
<thead>
<tr>
<th>Measure</th>
<th>Exacerbation outcomes (median days per patient per year)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before inhaled aztreonam lysine</td>
<td>After inhaled aztreonam lysine</td>
</tr>
<tr>
<td>Hospital bed-days</td>
<td>15.0 (3.5, 45.5)</td>
<td>12.6 (0.0, 43.0)</td>
</tr>
<tr>
<td>Total IV antibiotic days</td>
<td>56.0 (28.0, 93.5)</td>
<td>41.0 (16.5, 73.5)</td>
</tr>
<tr>
<td>In-hospital antibiotic treatment days</td>
<td>19.5 (5.3, 42)</td>
<td>13.0 (0.0, 42.7)</td>
</tr>
<tr>
<td>At-home IV antibiotic treatment days</td>
<td>24.0 (0.0, 55.3)</td>
<td>16.8 (0.0, 41.3)</td>
</tr>
</tbody>
</table>

IV, intravenous.

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months, which may be clinically important in patients with a severe phenotype awaiting lung transplantation.

In the study reported here, the treatment evaluator tool was used to evaluate outcomes following the introduction of inhaled aztreonam lysine but it has potential value in assessing the impact of a wide range of treatments in the real-world setting. Although another study on ‘real-world’ effectiveness of inhaled tobramycin has been reported recently [25], it provided data from only one centre. The ability to aggregate data from a number of centres is a useful feature of our tool.

The tool has the potential to provide information about the clinical effectiveness of a therapy/intervention in a variety of practice settings, and on the impact of therapy on diverse clinical, economic and patient-related outcomes. Analysis and comparison of different mono- and combined inhaled antibiotic therapies in a ‘real-world’ setting is possible, although the current study lacks sufficient numbers to answer this question. This is of particular importance given that the recent Aztreonam for Inhalation Solution Continuous Alternating Therapy (CAT) for Cystic Fibrosis study failed to achieve its required recruitment due, in part, to the prevalence of CAT regimens in standard patient care [26].

This study has some limitations. As an observational study of routine clinical practice, there was no comparator group, so conclusions cannot be drawn about the cause of changes seen, only that there was an association with the treatment initiated. Data used for comparison before the introduction of the therapy was obtained retrospectively. Inevitably with a real-world study using a very mixed patient population, inter-patient variability may make statistical significance difficult to reach, even for clinically meaningful changes. As with any observational study, there is the potential for bias arising from patient selection. Additionally as measurements were obtained as part of routine clinical practice across different sites, not all patients had available measurements at all timepoints. We therefore adopted two complementary analytical strategies: (1) restricting the sample to those that had an available measurement from the period of interest and (2) using all available data points in all periods. In our analysis both strategies revealed reassuringly similar findings. Adherence to treatment is a critical aspect of CF care [10] but the tool and study were not designed to address this. Finally, the tool was not configured to record the use of inhaled antibiotics outside of those recommended by the ECFC guidelines, prior to the initiation of inhaled aztreonam.

The treatment evaluator tool has provided valuable insights into outcomes in patients with CF in a real-world setting, demonstrating that the introduction of inhaled aztreonam lysine was associated with significant improvement in lung function and gain in weight, and a significant reduction in hospitalisations and intravenous antibiotic use, compared to the previous year [27].

Acknowledgements

All authors took part in consensus discussions leading to development of the treatment evaluator tool. BJP, DGD, CG, CSH, AMJ, EFM, DGP, IK and DB identified patients for inclusion in the study and collected relevant data into the treatment evaluator tool. JAE understood the statistical methods employed and conducted the analyses. All authors reviewed the data and understood the analyses. BJP developed the first presentation of data from which the manuscript outline was developed. All authors critically reviewed the outline and subsequent manuscript, and agree that it accurately and fairly describes the methods, results and conclusions. The authors would like to thank the clinical teams in all participating CF units who inputted the relevant data to the online tool. This work was supported by Gilead Sciences UK & Ireland Ltd. Gilead had no influence over the data or scientific content of this manuscript. The authors also thank Sarah Bryant and Gillian Wain of iS Health for editorial support, which was funded by Gilead Sciences UK & Ireland Ltd., and Vaneet Nayar and Rak Patel of SVMPharma for data management, which was funded by Gilead Sciences UK and Ireland Ltd.

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