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# Changes in respiratory symptoms during 48-week treatment with ARD-3150 (inhaled liposomal ciprofloxacin) in bronchiectasis: results from the ORBIT-3 and -4 studies

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ABSTRACT It is not known if inhaled antibiotics improve respiratory symptoms in patients with bronchiectasis. In the recent phase-3 ORBIT trials, 48 weeks' treatment with ARD-3150 (inhaled liposomal ciprofloxacin) did not significantly improve symptoms using the prespecified method of analysis comparing baseline symptoms to those after 48 weeks, when patients had been off treatment for 28 days. This method of analysis does not take account of possible improvements in symptoms while on active treatment.

A *post hoc* analysis of two identical randomised trials of ARD-3150 (ORBIT-3 and -4) administered 28 days on and 28 days off in patients with bronchiectasis and chronic *Pseudomonas aeruginosa* infection. The quality-of-life bronchiectasis respiratory symptom scale (QOL-B-RSS), which has a one-week recall period, was administered every 28 days. We examined whether respiratory symptoms improved during on-treatment periods and the relationship of changes in QOL-B-RSS to changes in bacterial load using a mixed-model repeated measures approach.

ARD-3150 treatment resulted in a significant improvement in respiratory symptoms during the on-treatment periods with concordant results between ORBIT-3 (estimate 1.4 points, SE 0.49; p=0.004) and ORBIT-4 (estimate 1.1 point, SE 0.41; p=0.006). The proportion of patients achieving a symptom improvement above the minimum clinically important difference was higher with ARD-3150 compared with placebo during on-treatment cycles (p=0.024). Changes in respiratory symptoms were correlated with changes in bacterial load in the treatment group (r=−0.89, p<0.0001). Individual estimates for decrements in the QOL-B RSS during exacerbation were −9.4 points (SE 0.91) in ORBIT-3 and −10.8 points (0.74) in ORBIT-4 (both p<0.0001).

Inhaled ARD-3150 resulted in significant improvements in respiratory symptoms during the on-treatment periods which were lost during off-treatment periods. These results supports the concept that reducing bacterial load can improve respiratory symptoms in patients with bronchiectasis.

## Introduction

The symptoms of bronchiectasis include daily cough, sputum production, breathlessness, chest pain and fatigue [1]. These symptoms combined with the impact of frequent exacerbations result in impairment of quality of life [2]. Symptoms and quality of life are most severely impaired in patients with chronic *Pseudomonas aeruginosa* infection [3, 4]. Patients with chronic *P. aeruginosa* infection had a 7.5-point higher score on the St George's Respiratory Questionnaire (SGRQ) in an analysis of European Registry data, even after adjustment for underlying severity of disease [4]. In a survey of more than 1000 patients with bronchiectasis, sputum production was rated as the most severe symptom, followed by exacerbations, fatigue, shortness of breath and cough [5]. Finding treatments that could reduce these symptoms as well as the frequency of exacerbations was rated as the key research priority [5].

There are currently no approved treatments to improve symptoms in bronchiectasis. Patients are advised to perform airway clearance, which can improve symptoms and quality of life [6]. Macrolides have been shown to reduce exacerbations but have not demonstrated a clinically meaningful effect on symptoms [7]. In bronchiectasis patients with chronic airway infection there is evidence that the symptom burden is correlated with the airway bacterial load [8, 9]. Higher airway bacterial counts promote neutrophil recruitment and release of inflammatory mediators that directly stimulate mucus production, plugging, bronchoconstriction and increase sputum volume and viscosity through release of inflammatory cell DNA [10, 11]. Thus effective antibiotic therapy would be expected to improve symptoms in bronchiectasis by decreasing airway bacterial load that leads to reduced inflammation.

Inhaled antibiotics are highly effective in reducing bacterial load in the respiratory tract but to date there is no consistent evidence that they can improve symptoms [12]. In a recent meta-analysis of 16 trials and 2597 patients, bacterial load was consistently reduced by all antibiotics tested, but there was no statistically significant improvement in the quality-of-life bronchiectasis questionnaire respiratory symptom score (QOL-B RSS) when the data were pooled [12]. Thus, the meta-analysis concluded that inhaled antibiotics reduce exacerbations but have no effect on quality of life or symptoms [12].

This conclusion may be confounded by the method of analysis used. Most studies were conducted using a 28-day on and 28-day off cyclical regimen designed to limit antibiotic resistance, by allowing antibiotic susceptible bacteria to recover during the off-periods [13, 14]. Most studies, including the ORBIT-3 and -4 trials of ARD-3150 (inhaled liposomal ciprofloxacin), evaluated symptoms at the end of the last off-treatment period [15]. As the QOL-B RSS has a recall period of only 1 week this method of analysis ignores changes in symptoms during the course of the study while on treatment and may therefore underestimate the effect of inhaled antibiotics on symptoms.

We hypothesised that improvements in symptoms during the ORBIT-3 and -4 studies of ARD-3150 would occur during "on-periods" when bacterial load is suppressed and that analysis of symptoms continuously through the study would demonstrate clinically meaningful impact of antibiotic treatment on respiratory symptoms.

## Methods

### The ORBIT-3 and -4 studies

A detailed description of the methodology of the ORBIT trials was previously published [15]. In brief, these were two replicate phase 3 randomised double-blind, placebo-controlled trials conducted between March 31, 2014, and August 19, 2015. Both studies enrolled patients from 16 countries worldwide. The inclusion criteria were adult patients aged 18 year or older with a clinical diagnosis of non-cystic fibrosis bronchiectasis confirmed by chest computed tomography (the protocol used the term non-cystic fibrosis bronchiectasis, for simplicity we use the term bronchiectasis throughout the rest of the manuscript). Patients had a history of at least two pulmonary exacerbations treated with antibiotics in the previous year and a forced expiratory volume in 1 s ($FEV_1$) of greater than or equal to 25% predicted [15]. Patients had chronic *P. aeruginosa* infection as documented on respiratory samples prior to the screening visit and were required to have at least one non-resistant *P. aeruginosa* isolate on a sputum sample taken at screening. Exclusion criteria included a pulmonary exacerbation during the 28 days prior to randomisation, a

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primary diagnosis of chronic obstructive pulmonary disease related to cigarette smoking of at least 10 pack-years, cystic fibrosis and active allergic bronchopulmonary aspergillosis or mycobacterial infection requiring treatment. Oral or inhaled antipseudomonal antibiotics were also not permitted. For full inclusion and exclusion criteria, readers are referred to the primary trial publication [15].

Patients were randomised 2:1 to receive either ARD-3150 or placebo (dilute liposomes in isotonic saline) for 48 weeks administered 28 days on and 28 days off. Randomisation was stratified by sex, smoking status and number of pulmonary exacerbations in the 12 months prior to randomisation. The primary outcome was time to first exacerbation with key secondary outcomes of frequency of exacerbations and change from baseline to 48 weeks in the QOL-B RSS [15].

### Post hoc *analysis of the quality-of-life respiratory symptom score*

The QOL-B questionnaire is a 37-item, patient-reported outcome measure developed for use in bronchiectasis trials [16]. The respiratory symptom domain has been extensively used to measure respiratory symptoms in bronchiectasis and has been shown to correlate with other measures of health status as well as being responsive to change in the context of exacerbations [9, 13, 14, 16, 17]. The questionnaire has a 7-day recall period. The QOL-B RSS was administered at the end of each on- and off-treatment period. In individuals who were experiencing a protocol defined exacerbation at the time of a scheduled visit this was recorded, allowing assessment of the changes in symptoms associated with an exacerbation. The pre-specified secondary endpoint in the trials was the difference between the baseline QOL-B RSS score and the score measured at the end of the final off-treatment cycle [15].

In a *post hoc* analysis, we modelled these repeated measurements of the QOL-B RSS to evaluate the impact of treatment on changes in symptoms during on-treatment cycles. Co-variates likely to impact on changes in symptoms were also evaluated including stable baseline macrolide use, occurrence of a pulmonary exacerbation, use of antibiotics for a respiratory cause that did not meet the criteria for a protocol defined exacerbation, sex, smoking and baseline exacerbation frequency. We also evaluated the relationship between *P. aeruginosa* colony forming units (cfu) per mL in sputum and changes in QOL-B RSS.

### Statistical analysis

We developed two statistical models to investigate the relationship between on- and off-treatment with ARD-3150 and presence of respiratory symptoms.

The first approach to estimate absolute changes in symptoms comparing ARD-3150 with placebo was a mixed model repeated measures (MMRM) model. Absolute QOL-B change from baseline was the dependent variable for the model and independent variables were as follows: treatment period, ARD-3150 treatment during an on-cycle, stable macrolide use at baseline, use of antipseudomonal antibiotics for a non-protocol-defined exacerbation, presence of a protocol-defined exacerbation during the time the questionnaire was administered, all two-way interactions of the above variables and the three stratification variables. A global test was performed to assess all two-way interactions in the model, with the exception of the treatment-period interaction. If this test was not statistically significant, the specified two-way interactions were eliminated from the model. If non-significant, two additional model tests were made: first it was determined if a "sawtooth" shape was present in the ARD-3150 and placebo independently, and then whether the minimum of the ARD-3150 sawtooth was not different from the minimum of the placebo sawtooth (or placebo regression line if no placebo sawtooth was observed).

The second statistical approach was designed to determine whether the proportion of patients experiencing a clinically significant improvement in symptoms was greater with ARD-3150 compared to placebo. We used a generalised estimating equations (GEE) model with a binary dependent variable indicating if the QOL-B absolute response was more than 8 points higher than the subject's baseline QOL-B value and the following independent covariates: treatment period, ARD-3150 treatment during an on-cycle, stable baseline macrolide treatment, occurrence of a pulmonary exacerbation during the time that the questionnaire was administered and antibiotic treatment for a non-protocol defined exacerbation. The minimum clinically important difference (MCID) for the QOL-B is considered to be greater than 8 points [16]. The odds that a patient would have an improvement above the MCID (greater than or equal to 8.5 points) at each study visit was modelled in GEE using a logistic-link function. The same stepwise progression for model development described in the MMRM model was again used in the GEE model.

The relationships between mean quality-of-life changes stratified by sex, stable macrolide use at baseline and prior number of exacerbations, and mean change in *P. aeruginosa* load expressed as cfu per g were calculated using the Spearman rank correlation statistic.

In all analyses, statistical significance was inferred at a p-value less than 0.05. Analyses are considered exploratory in view of their *post hoc* nature.

## Results

In ORBIT-3, 183 patients were randomised to ARD-3150 and 95 patients to placebo. In ORBIT-4, 206 patients were randomised to ARD-3150 and 98 patients to placebo. As previously reported there were no significant baseline imbalances in the groups in terms of age, sex, $FEV_1$ or baseline exacerbation history, but there was an imbalance in baseline macrolide use (23% *versus* 14% in ORBIT-3 comparing active *versus* placebo respectively and 17% *versus* 24% in ORBIT-4). The mean QOL-B RSS scores at baseline were 54.2 for ARD3150 and 53.6 for placebo in ORBIT-3 with the equivalent scores being 57.7 and 56.9 in ORBIT-4.

In the original pre-specified analysis, ARD-3150 did not result in improved respiratory symptoms. Change in QOL-B score from baseline to week 48 was −1.62 (95% CI −5.66–2.34; p=0.43) and −0.08 (95% CI −2.86–2.70; p=0.95), respectively, in ORBIT-3 and -4.

Figure 1 shows the mean QOL-B RSS scores in ORBIT-3 and -4 over the course of the study. Marked improvements in the QOL-B scores were observed over the first 28 days in both the active and placebo group with separation between groups subsequently appearing in both studies. The mean change from baseline was 3.7 and 4.0 points for the ARD3150 and placebo groups in ORBIT-3 and 7.85 and 4.4 points respectively in ORBIT-4.

The final MMRM model stepped down to a model containing the treatment-period interaction, the placebo-response curve having no sawtooth shape and being equivalent to the intercept value, and the ARD-3150 treated group having a sawtooth shape with a minimum equal to the intercept. Other significant independent variables were: stable baseline macrolide treatment, occurrence of a pulmonary exacerbation during the time that the questionnaire was administered and antibiotic treatment for a non-protocol defined exacerbation.

The changes in symptoms within the active treatment arm can be seen to follow a sawtooth pattern with improvements at the end of each on-treatment period (days 28, 84, 140, 196, 252, 308) and declines at the end of all but one of the off periods (the fifth off-treatment period in ORBIT-4). We, therefore, explored whether changes in the QOL-B scores followed changes in *P. aeruginosa* load.

In the ARD-3150 treatment group there was an association between change in QOL-B RSS and the change in cfu per g which was not evident in the placebo group. The QOL-B score improved during the on treatment periods and declined during off-treatment periods in parallel with decreases and increases in the *P. aeruginosa* load (figure 2). The correlation between change in cfu and change in QOL values was −0.89 (95% CI −0.76–0.95; p<0.0001), for the pooled data, −0.92 (95% CI 0.71–0.98; p<0.0001) for ORBIT-3 and −0.89 (95% CI 0.65–0.97; p=0.0002) for ORBIT-4. The corresponding correlation in the placebo group were 0.05 (p=0.8) for the pooled data.

### Analysis of repeated measures of respiratory symptoms using the QOL-B RSS

Analysis of repeated measures found a statistically significant effect of treatment with ARD-3150 on QOL-B RSS score at the visits at the end of the on-treatment periods. The results of the model for the pooled ORBIT-3 and -4 studies are shown in table 1. Significant effects on QOL-B RSS were observed for ARD-3150 treatment, protocol-defined exacerbations and use of anti-pseudomonal antibiotics that did not meet the criteria for a protocol defined exacerbation. Stable macrolide use at baseline was also associated with worse symptoms.

Results were concordant between ORBIT-3 where the estimated effect (±SE) of treatment was an improvement of 1.4±0.49 points (p=0.004) and ORBIT-4 where the estimate was an improvement of 1.1 ±0.41 points (p=0.006).
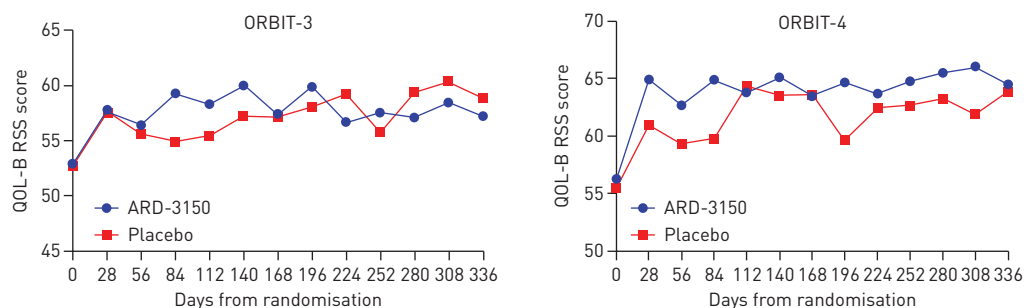


FIGURE 1 Mean quality-of-life bronchiectasis respiratory symptom scale (QOL-B RSS) scores in the active and placebo groups during the ORBIT-3 and ORBIT-4 studies.

TABLE 1 Mixed model for repeated measures for the pooled ORBIT-3 and -4 studies

| Variable | Model results | | |
| --- | --- | --- | --- |
| | Estimate | Standard error | p-value |
| On-treatment cycle for ARD3150 | 1.29 | 0.32 | <0.001 |
| Protocol-defined pulmonary exacerbation at time of questionnaire | −10.16 | 0.57 | <0.001 |
| Anti-pseudomonal antibiotic use for respiratory event not meeting the criteria for a pulmonary exacerbation | −4.15 | 0.73 | <0.001 |
| Macrolide treatment at baseline (yes *versus* no) | −4.53 | 1.71 | 0.009 |
| Sex (male *versus* female) | 2.39 | 1.47 | 0.10 |
| Pulmonary exacerbation category in the previous year (4+ *versus* 2–3) | −2.44 | 1.68 | 0.15 |
| Smoking stratum (smoker *versus* non-smoker) | −0.04 | 7.32 | 1.00 |

Individual estimates for decrements in the QOL-B RSS during an exacerbation were −9.4±0.91 points in ORBIT-3 and −10.8±0.74 points in ORBIT-4 (both p<0.0001).

Controlling for the absence during the trial of: a pulmonary exacerbation; any treatment with macrolides; and the absence of treatment with anti-pseudomonal antibiotics for a non-protocol defined exacerbation, this model reduced to a flat response curve for subjects treated with placebo and as a sawtooth shaped curve for subjects treated with ARD-3150. The minimum of the modelled sawtooth touched the placebo response line just before the beginning of the active cycle and the maximum of the modelled sawtooth was 1.0 to 1.5 units higher than the minimum (figure 3).

### Analysis of clinically significant improvement in symptoms

The GEE model using the binary MCID variable (improvement greater than or equal to 8.5 points as a clinically important improvement in symptoms) was used to describe clinically significant changes in the QOL-B RSS [16]. The final shape of the response curve had an analogous treatment-period shape to the model described in the MMRM model. In the GEE for the pooled ORBIT-3 and -4 studies (figure 4), ARD-3150 on treatment cycles were associated with a statistically significant increase in the probability of experiencing a clinically meaningful improvement in QOL-B RSS (estimate −0.11, 95% CI −0.02 to −0.21; p=0.024). The presence of a protocol defined pulmonary exacerbations and antibiotic use for respiratory events not meeting the criteria for a pulmonary exacerbation were also associated with statistically significant worsening of symptoms above the MCID (p<0.001 for both). This again shows that, at the end of on-treatment cycles, there was a small but significant increase in patients reporting clinically significant improvements in symptoms. Full model results are displayed in supplementary table S1.

Since we observed an improvement in respiratory symptoms, we investigated the extent to which this could be balanced by a worsening in the treatment burden domain of the QOL-B due to treatment exposure. Changes in the treatment burden domain are shown in supplementary figure S1. This showed in both ORBIT 3 and 4 an increase in treatment burden from baseline to the first on-treatment visit that then remained relatively stable throughout the study.
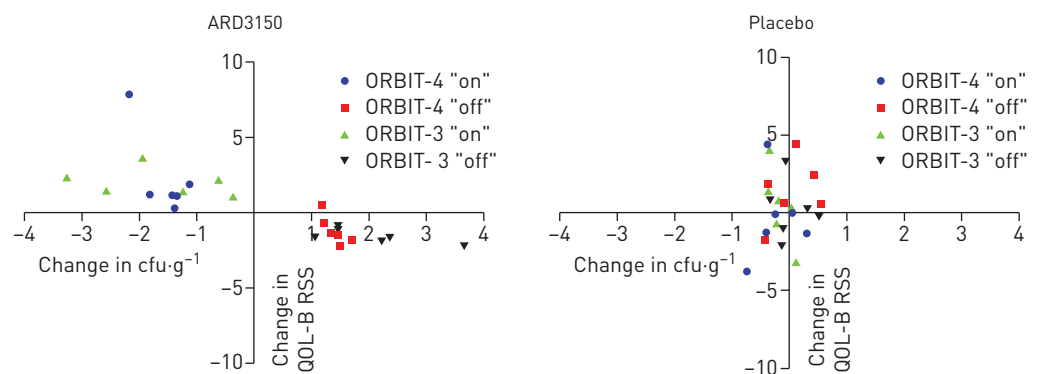


FIGURE 2 Relationship between changes in colony forming units (cfu) per g and quality-of-life bronchiectasis respiratory symptom scale (QOL-B RSS) in the active treatment and placebo group. A positive change in QOL-B RSS represents an improvement.

FIGURE 3 Results of the mixed model repeated measures for the pooled ORBIT-3 and -4 studies. The maximum has been allowed to vary according to the observed mean at each treatment cycle for the ARD-3150-treated group, and the placebo response rate has been set to the grand mean for the placebo-treated subjects. QOL-B RSS: quality-of-life bronchiectasis respiratory symptom scale.
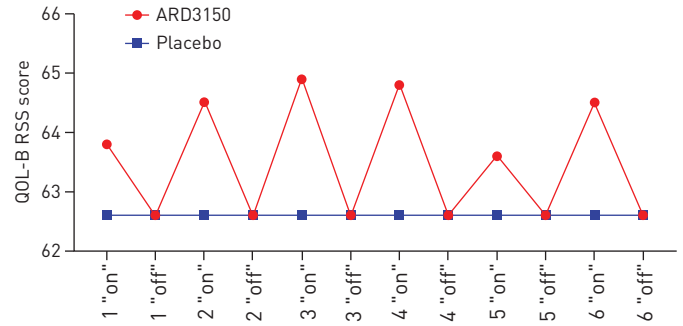
## Discussion

48 weeks' treatment with inhaled ARD-3150 resulted in clinically and statistically significant improvements in respiratory symptoms assessed using the QOL-B RSS compared with placebo when taking into account the dynamic changes in symptoms that occur over time and particularly the effects of treatment during the on-treatment periods. Importantly, although the average change in the symptom score was less than the MCID, a significantly greater proportion of patients experienced clinically significant improvements in symptoms with ARD-3150 compared with placebo. The original conclusions of the ORBIT-3 and -4 studies were that there was no significant effect of treatment [15]. This reflects the pre-specified secondary endpoints which was the difference between the baseline and the end of trial values for the QOL-B RSS. As can be seen in figure 1, the difference at the single point in time at the end of the trial when patients had been off treatment for 28 days did not reflect the variable symptoms experienced by patients during the full 48 weeks. Bronchiectasis is a long-term condition and, therefore, in retrospect evaluating symptoms at a single point in time while off treatment, using a tool with a 7-day recall period, clearly did not accurately reflect long term variation in symptoms.

A recent meta-analysis concluded that inhaled antibiotics do not significantly improve respiratory symptoms [12]. This is reflected in international guidelines for bronchiectasis where inhaled antibiotics are recommended to prevent exacerbations in patients with *P. aeruginosa* and at least three exacerbations per year and are not recommended for treatment of symptoms [18]. Our analysis, however, demonstrates that inhaled antibiotics can be shown to improve respiratory symptoms if appropriate methods of analysis are employed. There are likely to be patients where such treatment may be indicated to improve symptoms in addition to reducing exacerbations. This is consistent with some individual studies where symptom benefits have been observed [19].

The key conclusions of this study are: first, that evaluation of symptoms in bronchiectasis trials should consider the use of MMRM to demonstrate the dynamics of symptom changes over time. This increases statistical power to demonstrate effects and is more reflective of the reality of a long-term chronic condition. Secondly, there is a clear relationship between reductions in bacterial load and changes in respiratory symptoms in the ORBIT-3 and -4 studies in patients receiving ARD-3150. This adds to the emerging evidence that bacterial load measured as colony forming units per gram in sputum is a key biomarker in bronchiectasis [8, 9, 20]. Patients with higher bacterial loads have higher levels of airway inflammation measured through neutrophil elastase activity and cytokines/chemokines, such as interleukin (IL)-1β and CXCL8 [9, 20, 21]. Higher bacterial load predicts a higher frequency of exacerbations and hospital admissions during follow-up and most importantly a recent re-analysis of the AIR-BX trials of inhaled aztreonam suggested that bacterial load predicted response to inhaled antibiotics in terms of respiratory symptoms [8, 9]. Limitations of the study by SIBILA et al. [9] include that the AIR-BX studies



FIGURE 4 Results of the GEE model for the pooled ORBIT-3 and -4 studies. The maximum has been allowed to vary according to the observed mean at each treatment cycle for the ARD-3150-treated group, and the placebo response rate has been set to the average response rate for the placebo-treated subjects. QOL-B RSS: quality-of-life bronchiectasis respiratory symptom scale.
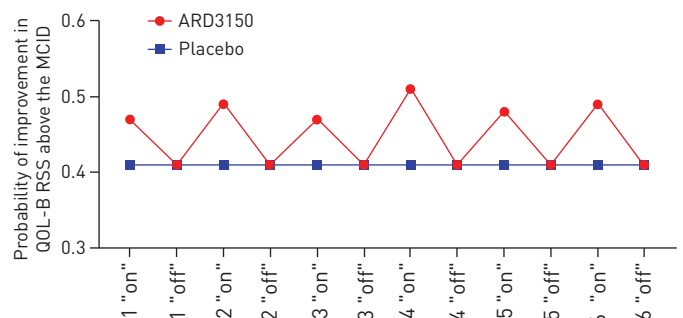
enrolled patients with a mixture of different pathogens and patients without baseline pathogens, and that follow-up in the study was limited to just two cycles of antibiotics [9, 17]. The present analysis of the ORBIT-3 and -4 studies therefore provides more robust evidence of the relationship between cfu reductions and symptomatic improvements by demonstrating a correlation between these two variables across 6 cycles over 48 weeks in 2 replicate trials. The consistency of this signal across multiple inhaled antibiotic studies strengthens the value of bacterial load as a surrogate endpoint and "treatable trait" [22, 23].

A third key conclusion of this work is that the intermittent administration of antibiotics using 28-day on and 28-day off regimens results in improvements in symptoms during the on-period but a relapse in symptoms during the off-period when bacterial loads increase back to baseline levels. This phenomenon is well recognised in cystic fibrosis where many patients have taken to administering a second antibiotic during the off periods to avoid this rebound in bacterial load and consequent worsening of health status [24]. There has been an active debate for many years over whether continuous or intermittent administration of inhaled antibiotics is the optimal approach [25]. The intermittent approach using 28 day or 14 day cycles has been used because of a belief that removing antibiotic selection pressure for a period would allow regrowth of the antibiotic sensitive bacterial flora and therefore limit the emergence of resistance [13, 14]. There are no head-to-head studies of intermittent *versus* continuous antibiotic administration [25]. Our results nevertheless suggest that continuous administration of ARD-3150 and perhaps other inhaled antibiotics may be more beneficial in terms of maintaining symptom improvements because continuous bacterial suppression appears to be required to continuously lower symptom burden. Such an approach would need to be weighed against the theoretical risk of greater resistance emergence and the increased cost and treatment burden. It is recognised that the QOL-B RSS measures symptoms in isolation and that quality of life is also influenced by other factors including potentially being negatively impacted by the need to take regular treatment.

It should be noted that the differences we observed in the ORBIT-3 and -4 studies between ARD-3150 and placebo were small, with average differences between active and placebo groups of only 1–2 points in the QOL-B RSS, a level below the MCID [16]. Only a proportion of patients would therefore be likely to gain a clinically meaningful change in symptoms. Nevertheless, the MCID for QOL-B is not well established and individual patients should be allowed to decide if their changes in symptoms are clinically meaningful. One reason that this difference was small is the large placebo effect we observed. As illustrated in figure 1, randomisation to placebo was associated with a mean 4.4 and 4.0 point improvement in the QOL-B RSS between baseline and day 28, an effect which never returned to baseline during the trial. Further research is needed to understand placebo effects in the context of bronchiectasis randomised trials. Several large studies have now observed large placebo effects in terms of quality-of-life improvements or reductions in exacerbation frequency from a past history of more than 2 exacerbations to mean exacerbation frequencies of less than 1 during a 1 year observation period [13, 14, 26, 27]. It is well documented that patients may change their behaviour during a trial, becoming more adherent to other therapies or changing their lifestyles in a way that promotes improved health status. Other explanations for the observed behaviour are possible.

Our study also demonstrates the important impact that pulmonary exacerbations have on patients quality of life. Pulmonary exacerbations meeting the protocol definition were associated with a decrement in symptoms of approximately 10 points. Previous work suggests that the symptoms of exacerbations last for several weeks and that approximately 20% of patients do not return to their usual health status by 1 month post event [28]. The changes observed in this study were somewhat lower than the 14-point decrement observed in 60 patients in the AIR-BX studies used to validate the QOL-B. The difference may be due to the much larger sample size in our study or differences in the study population [16]. Our post-hoc analyses show that the treatment with ARD-3150 improves QOL-B RSS independent of occurrence of PEs as well as by reducing the number of these events.

The lessons learnt from ORBIT-3 and -4 will inform the next generation of clinical trials in bronchiectasis. However, this study also important limitations. The analyses are *post hoc* and hence the findings should be considered exploratory and p-values interpreted with caution. The QOL-B RSS was the only health status measure included in the ORBIT-3 and -4 studies. Other studies such as the RESPIRE trials documented different results between the QOL-B which has a 1-week recall period and the St Georges Respiratory Questionnaire which has a longer recall period and different questions [13, 14]. Future studies are required to identify the optimal symptom tool in bronchiectasis. Our study was not designed to look at the question of which individual patients had the best overall symptom response as this is a separate research question and should be addressed in future research.

In summary, ARD-3150 resulted in a small but significant improvement in respiratory symptoms over 48 weeks. Future randomised trials should use the repeated measures approach used in this study to

account for changes across the full duration of the trial. Symptoms change in line with changes in bacterial load during on-treatment periods confirming bacterial load as a key biomarker of inhaled antibiotic response in bronchiectasis.

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