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Synopsis

A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis

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Abstract

Background: Bronchiectasis is a long-term lung condition associated with bronchial dilatation, chronic inflammation and infection. Treatment is often empirical or extrapolated from other lung conditions, for example the use of inhaled therapies licensed for use in asthma or chronic obstructive pulmonary disease. Inhaled therapies, such as corticosteroids or long-acting bronchodilators (long-acting beta agonists or long-acting muscarinic antagonists), are commonly used in bronchiectasis despite scanty evidence on exacerbation reduction.

Objective: To assess whether:

1. dual bronchodilators (long-acting beta agonists/long-acting muscarinic antagonists) either as stand-alone therapy or in combination with inhaled corticosteroid are superior to placebo at reducing mean exacerbation rates over 12 months
2. dual bronchodilators (long-acting beta agonists/long-acting muscarinic antagonists) are non-inferior to triple therapy (inhaled corticosteroid/long-acting beta agonists/long-acting muscarinic antagonists) at reducing mean exacerbation rates over 12 months.

Design: Pragmatic, multicentre, placebo-controlled, three-arm, double-blinded, prospective, randomised controlled trial incorporating a 12-month internal pilot.

Target population: Six hundred adults with bronchiectasis and history of ≥ 2 exacerbations in any 12-month period within the preceding 2 years.

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Setting: United Kingdom National Health Service secondary care sites.
Interventions: Twelve months, one puff daily of either dual therapy [55 µg umeclidinium (long-acting muscarinic antagonists) and 22 µg vilanterol (long-acting beta agonists)], triple therapy [dual therapy plus 92 µg fluticasone furoate (inhaled corticosteroid)] or matched placebo dry powder inhalers, randomised in a 2 : 2 : 1 ratio, respectively.
Outcome measures: Primary: number of participants reported bronchiectasis exacerbations requiring treatment with antibiotics during the 12-month treatment period.
Primary economic: incremental cost per quality-adjusted life-year gained at 12 months.
Results: Recruitment rates did not follow projections due to the COVID-19 pandemic; 85 potentially eligible patients were screened, of whom 33 (39%) were randomised. Of the randomised participants, 30 (91%) completed follow-up at 12 months; 3 participants withdrew [1/14 (7%) dual therapy, 1/12 (8%) triple therapy and 1/7 (14%) placebo]. Five participants discontinued therapy during the trial [1/14 (7%) dual therapy, 2/12 (17%) triple therapy and 2/7 (29%) placebo].
Given the small sample size, the statistical and economic analyses are descriptive and exploratory. Exacerbation data were available for 32/33 (97%) of randomised participants (13 dual therapy, 12 triple therapy and 7 placebo). The median number of exacerbations during the follow-up (the primary outcome) was 1 (interquartile range 0–3) for dual therapy, 2 (1, 2.5) for triple therapy and 3 (2, 3) for placebo. No safety concerns were identified. Complete resource-use and quality-of-life data were available for 30/33 (91%) participants.
Conclusions: COVID-19 impacted delivery of the trial, affecting staff capacity, setting up of timelines, and ultimately, recruitment to the pilot. There was good retention and data completeness within the trial randomised participants. The trial is unable to provide evidence on the superiority or cost-effectiveness of dual or triple therapy to placebo at reducing mean exacerbation rates over 12 months or the non-inferiority of dual to triple therapy.
Future work and limitations: The main limitation of this work is the small sample size that prevents any firm conclusions to be made. However, the results do suggest that there is a signal of efficacy and that a larger trial is needed to provide valuable clinical evidence. These results underscore the importance of completing a large-scale trial of these therapies to help improve the understanding and best treatment for patients with bronchiectasis.
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Synopsis

Introduction and rationale

Bronchiectasis is a chronic lung condition, characterised by dilated airways or bronchi, leading to symptoms of breathlessness and chronic productive cough, with intermittent infective exacerbations. Bronchiectasis has various potential aetiologies, including immunodeficiency syndromes, chronic asthma, chronic obstructive pulmonary disease (COPD), ciliary dysfunction and post-infectious condition, yet studies have found that nearly half of cases are idiopathic.[3,4] Patients often have recurrent, costly hospital admissions, a poorer quality of life[5,6] and clinically significant fatigue.[7,8]

Bronchiectasis is associated with infective exacerbations leading to significant morbidity. Within the UK national audit data, the average exacerbation rate was approximately 3 per year, with an attendant increased risk of hospitalisation. Recent European data suggest a range of exacerbations depending on geography, but the average was 2 per year.[9] Hence, improved interventions in bronchiectasis are urgently required.

There is no cure for bronchiectasis. Current treatment includes mucolytic drugs and regular physiotherapy, which are used to aid sputum clearance. Where symptoms dictate, long-term oral, inhaled or intravenous antibiotics are used for those patients with a history of recurrent exacerbations. Additional antibiotic courses are used to treat acute exacerbations. These are outlined in prevailing guidelines for the investigation, diagnosis and management of bronchiectasis, produced by the British Thoracic Society.[10]

National audits in the UK suggest that 40–80% of patients with bronchiectasis are on inhaled therapy despite limited evidence.[11,12] This varies by country, with a recent report

form Turkey noting 70% of patients with bronchiectasis on an inhaled corticosteroid (ICS).[10,13] Prior studies of ICS in bronchiectasis, mostly small in sample size and single-centre, have shown no clear benefit; hence, guidelines[10] do not recommended ICS for routine use in bronchiectasis. ICS, however, has been shown to have benefits in asthma[14] and in COPD.

Recent trials in COPD show that, the newer combination, dual bronchodilators using a long-acting beta agonist (LABA) combined with a long-acting muscarinic antagonist (LAMA) contained in a single inhaler are superior to existing therapies, such as salmeterol (a LABA developed 30 years ago) and tiotropium (a LAMA), in separate inhalers.[12] More recent studies have shown LABA/LAMA combinations are as good as or better than ICS/LABA combinations at reducing exacerbations when studied in selected COPD populations,[15] suggesting that ICS regimens might not be needed in all patients with COPD. However, ICS regimes clearly help in more severe COPD patients – a recent landmark study using the agents proposed herein showed a 25% reduction in exacerbations with ICS containing triple therapy (ICS/LAMA/LABA) versus LAMA/LABA dual bronchodilator therapy.[11] Using the inhaled drugs proposed herein in a moderate–severe COPD population has shown clear benefits: triple therapy with fluticasone furoate, umeclidinium and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone furoate–vilanterol (ICS/LABA) or umeclidinium–vilanterol (LAMA/LABA). Triple therapy in COPD also resulted in a lower rate of hospitalisation than LAMA/LABA.[11]

Newer bronchodilators and inhaled steroids have therefore emerged in COPD[12] that may prove effective in treating bronchiectasis. There are likely to be multifactorial mechanisms by which newer bronchodilators, such as LAMA and LABA, exert beneficial effects in COPD. These have been recently reviewed and extend beyond bronchodilation, with potentially important effects on mucus production, airway ciliary function, airway nerve desensitisation and reducing gas trapping.[13] Hence, newer bronchodilators may target mechanisms relevant to bronchiectasis.

Meta-analyses of studies in COPD have identified that ICS combined with long-acting bronchodilators, while significantly reducing COPD exacerbation rates, carries an increased risk of pneumonia;[12,14,16] this potential risk may be important in bronchiectasis, given the higher bacterial burden in bronchiectasis airways.

There is now increasing recognition of an eosinophilic responder element in COPD, where an increased response to inhaled steroids is noted.[15] Preliminary findings from a post hoc analysis of 82 patients treated with fluticasone indicate that bronchiectasis patients with neither asthma nor allergic bronchopulmonary aspergillosis nor COPD, but with high blood eosinophils, might respond to ICS treatment.[17] Those patients with COPD and peripheral eosinophil blood counts that are within, but towards the higher end of the normal range, for example 300 cells per µl (normal range is < 500 cells per µl or 0.5×10^9/l), may respond best to inhaled steroids. This potential responder phenotype in COPD can be simply assessed with peripheral blood eosinophil levels.[18] Prevailing guidelines for COPD now suggest careful assessment of patients with regard to the risk–benefit ratio of using inhaled steroids. Potential harms of inhaled steroids include risks of pneumonia and skin bruising.[15] Notably, data suggest that the inhaled steroids in bronchiectasis may be associated with an increased risk of non-tuberculous mycobacterial disease.[19]

Recent data from a European cohort suggested that bronchiectasis has an eosinophilic element seen in approximately 20% of patients.[20] This phenotype appears to be associated with shortened time to exacerbation after correcting for other risk factors.[20]

Database studies have also suggested a potential role for inhaled therapy in bronchiectasis,[21] but large high-quality randomised double-blind trials are lacking.

Methods

The main study protocol was approved by the Northeast – Newcastle and North Tyneside 2 Research Ethics Committee (reference: 21/NE/0020) and has been published elsewhere.[1]

Objectives

The primary objectives of the Dual Bronchodilators in Bronchiectasis Study (DIBS) trial were to test the two hypotheses in adults with bronchiectasis:

- Dual therapy (LABA/LAMA), either as a stand-alone therapy or used in combination with ICS therapy (triple therapy: ICS/LABA/LAMA), is superior to placebo at reducing the number of protocol-defined bronchiectasis exacerbations (per participant) during the 12-month treatment period requiring treatment with antibiotics.
- Dual therapy is non-inferior to triple therapy at reducing the number of protocol-defined bronchiectasis exacerbations (per participant) during the 12-month treatment period requiring treatment with antibiotics.

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The primary economic objective was to compare the cost-effectiveness over the 12-month treatment period measured in terms of incremental cost per quality-adjusted life-year (QALY) gained.

Secondary objectives were to compare the effects of dual therapy and triple therapy and placebo on hospital admissions with a primary diagnosis of exacerbation of bronchiectasis, time to first exacerbation of bronchiectasis, emergency hospital admissions, adverse events (AEs), cessation of treatment, disease related health status, health-related quality of life, breathlessness, lung function, mortality, incremental cost per exacerbation avoided, costs to the NHS, Personal Social Services (PSS) and patients and incremental cost per QALY gained over a lifetime horizon and rates of radiologically confirmed pneumonia. Exploratory objectives included exploring the relationship between exacerbations and quality of life with baseline eosinophil levels and baseline Bronchiectasis Severity Index (BSI). In addition, subgroup analyses of suspected aetiology comparing idiopathic and post-infectious conditions to all other aetiologies for exacerbations and quality of life were also included.

Trial design

The DIBS was a pragmatic multicentre, placebo-controlled, three-arm, double-blind, parallel-group, prospective, randomised controlled trial, incorporating a 12-month internal pilot and 12-month follow-up.

Internal pilot

Originally, the pilot was 6 months; however, it was agreed with the funder to extend the pilot to 12 months after the first site was activated. It was included to monitor the recruitment and retention at each site, investigate the processes at each site and identify good practice that could be shared.

The plan was to open 25 sites as soon as possible in a staggered way with approximately 15 sites open by the end of the pilot phase, with a planned minimum collective period of 78 recruitment months. During the pilot, we aimed to recruit 98–125 trial participants (equating to an average recruitment of 1.25–1.6 participants per site per month) over a 12-month period.

The progression criteria to proceed from the internal pilot to the main trial were as follows:

- average recruitment ≥ 1.6 participants/month/site activated – continue to main trial and open additional sites (up to 25 sites total)
- average recruitment ≥ 1.25 participants/month/site activated – continue to main trial and open additional sites (up to 25 sites total) plus provide an improvement plan after identifying barriers to recruitment through discussion with sites, Trial Management Group (TMG), Trial Steering Committee (TSC) and Independent Data Monitoring and Ethics Committee (IDMEC) as required
- average recruitment < 1.25 participants/month/site activated – seek further guidance from funder.

Setting

This was a multicentre trial, conducted at 13 UK NHS secondary care sites with experience in conducting bronchiectasis studies. Basic bronchiectasis care was already established at these sites in accordance with national guidelines.

Participants were identified in both primary and secondary care settings by clinical research teams, with recruitment and delivery of the trial taking place at secondary care sites. Further details of the identification and consent process are published.[1]

Participants

In brief, participants were deemed eligible if they were of age ≥ 18 years, had historical records of bronchiectasis confirmed by computed tomography (CT) scan or equivalent (e.g. bronchogram) and had two or more exacerbations in any 12-month period in the preceding 24 months. Key exclusion criteria included predominant COPD or asthma diagnosis in the opinion of recruiting investigator or any indication to remain on ICS (e.g. asthma, COPD, allergic bronchopulmonary aspergillosis and inflammatory bowel disease) or known intolerance to any of the trial drugs or their ingredients. See *Appendix 1* for full details. *Appendix 1*, *Box 1* details the changes to eligibility criteria during the trial.

Interventions

Dual therapy (long-acting muscarinic antagonist/long-acting beta agonist)

Once daily dose of 55 µg umeclidinium (LAMA) and 22 µg vilanterol (LABA): Anoro™ Ellipta dry powder inhaler. AQ1

Triple therapy (inhaled corticosteroid/ long-acting muscarinic antagonist/ long-acting beta agonist)

Once daily dose of 55 µg umeclidinium (LAMA) and 22 µg vilanterol (LABA) 92 µg fluticasone furoate (ICS): Trelegy™ Ellipta dry powder inhaler.

Placebo
Matched placebo dry powder inhaler.

The inhalers were provided as an unrestricted medical education grant from GlaxoSmithKline Research & Development Limited, Middlesex, UK.

Randomisation and allocation
Randomisation was via the Sealed Envelope System (a central, secure web-based system). Participants were randomised in a 2 : 2 : 1 ratio to dual therapy, triple therapy or placebo using random permuted blocks of variable length (5 and 10). Randomisation was stratified by two variables; the BSI score that factors in *Pseudomonas* status, prior exacerbations/hospitalisations and age (BSI score of 0–8 or 9+) and by baseline ICS drug therapy (ICS user or non-ICS user at baseline). The randomisation allocation sequence was produced by Sealed Envelope, and each inhaler was allocated a unique kit code as a blinded identifier. A unique kit code was allocated to participants via the randomisation system at randomisation and each subsequent investigational medicinal product (IMP) dispensation.

This was a double-blind trial. Participants and site staff, including the principal investigator, pharmacy and clinical team, did not know the treatment allocation assigned to each participant. All members of the Trial Management Group were blinded to the treatment allocation apart from the trial statistician(s) and database manager(s). The three trial IMPs/inhalers were manufactured, packaged and labelled in an identical manner in terms of appearance to maintain the blind. Newcastle Specials Pharmacy Production Unit (PPU) was unblinded due to their role in labelling of the product.

Outcomes

Primary outcome
Number of bronchiectasis exacerbations requiring treatment with antibiotics during the 12-month treatment period was measured using participant reports via completed weekly exacerbation diary. The protocol definition of an exacerbation is a continued worsening of one or more of the following symptoms, alongside antibiotic treatment for the exacerbation:

- increased cough
- sputum discolouration
- excess sputum production
- breathlessness
- fatigue.

Primary economic outcome
Incremental cost per QALY gained at 12 months was the primary outcome. Costs were based on the cost of the interventions, use of health services via a Health Care Utilisation Questionnaire (HCUQ) administered at baseline, 1, 6 and 12 months post randomisation and AEs. Transport and time for participants to utilise healthcare appointments were assessed via the Time and Travel questionnaire administered at 12 months post randomisation.[1]

Secondary outcomes
A number of secondary end points were planned;

- Number of hospital admissions for bronchiectasis exacerbations during 12-month treatment period was measured using participant reports and completed weekly exacerbation diary and was verified by hospital discharge summary data.
- Hospitalisation details due to bronchiectasis exacerbation data were collected up to 24 months after visit 1: screening/baseline (note that due to early closure, data were only collected up to 12 months).
- Time to first exacerbation of bronchiectasis was measured using participant reports and completed weekly exacerbation diary.
- Number of emergency hospital admissions (all-cause) was ascertained at 1, 6 and 12 months visits and from primary care records.
- Number of serious AEs as a result of drug reactions or reactions to cessation of treatment was reported by participant to research team or at 1-, 6- and 12-month visits.
- Health-related quality of life was measured by St George's Respiratory Questionnaire (SGRQ), Quality of Life Bronchiectasis (QoL-B) and EuroQol-5 Dimensions, five-level version (EQ-5D-5L) at baseline, 1-, 6- and 12-month visits.
- Breathlessness was measured using Baseline Dyspnoea Index (BDI) at baseline and Transition Dyspnoea Index (TDI) at 1-, 6- and 12-month visits.
- Post-bronchodilator lung function (LABA within 8 hours, short-acting beta-2 agonist within 2 hours) was measured by spirometry [forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC)] performed to American Thoracic Society (ATS)/European Respiratory Society standards at baseline, 1-, 6- and 12-month visits.
- All-cause, respiratory and cardiac mortality.
- Incremental cost per exacerbation avoided with costs based on cost of the interventions (micro-costed), use of health services collected via a HCUQ administered at baseline, 1, 6 and 12 months post randomisation and AEs collected via case report forms.

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- Costs to the NHS and patients and lifetime cost-effectiveness based on extrapolation modelling using the trial data supplemented by Hospital Episode Statistics and Office for National Statistics (ONS) data (collected up to 24 months after visit 1: screening/baseline) and by relevant literature and expert opinion and extrapolated over a patient's lifetime.
- Number of pneumonia events and total number of participants suffering pneumonia was measured by asking the participants during follow-up visits.

Data collection

Data were collected during four research visits (screening/baseline, 1-month, 6-month and 12-month follow-up) or at additional phone calls to participants following the dispensing of each inhaler (up to a total of 13 dispensations) and 7 days after the last dose of IMP (see *Appendix 1*, *Figure 5*). Some data were also obtained from participants' medical records. Participants recorded bronchiectasis exacerbations using a weekly exacerbation diary. Completed exacerbation diaries were reviewed at the research visits and during the phone calls. AEs were collected by participant self-report or during questioning at research visits or telephone calls.[1]

Sample size

The original sample size calculation[1] was based on the number of exacerbations among a similar population in prior national audits.[22,23] The average number of exacerbations was 2.3 per year. Restricting trial entry to those who had ≥ 3, the original inclusion criteria (assuming a Poisson distribution) give an average of around 3.8. We therefore assumed, given Hawthorne effect and regression to the mean, there would be a lower mean exacerbation rate than this in the placebo arm, and a mean of 2.4 over 1 year. The sample size was chosen so as to ensure the trial was well powered to detect a clinically meaningful fall in mean exacerbation rates for bronchiectasis exacerbations to 1.9 years in dual therapy and triple therapy arms (approximately 20% reduction). This effect size was deemed as realistic when compared with the 20–30% reduction seen in COPD trials with dual bronchodilators/triple therapy where it has been accepted as clinically meaningful. Although likely studying a different subpopulation in bronchiectasis, a recent meta-analysis of inhaled antibiotic trials in bronchiectasis suggested a reduction in exacerbations by approximately 20% and nearly 50% for severe exacerbations.[24]

For 90% power (two-sided 5% significance level) to conclude that dual therapy is more effective than placebo with the above parameters, we calculated (assuming large-sample approximation of the Poisson distribution) that a sample size of 600 participants was needed, randomised 240 : 240 : 120 between dual therapy, ICS/LAMA/LABA and placebo. This allowed for a 5% loss to follow-up. This represented a conservative retention rate compared to over 95% observed in the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Theophylline With Inhaled CorticoSterial Study (TWICS) for people with COPD[25] with a similar pragmatic design and limited patient burden. This calculation assumed a difference between placebo and LABA/LAMA of 0.5 exacerbations per year (21% relative reduction).[1]

If superiority of dual therapy versus placebo was concluded, we would then test the non-inferiority of dual therapy against ICS/LAMA/LABA. The sample size would have given 90% power (one-sided 5% type I error) with a 0.38 non-inferiority margin (reflecting 20% of the assumed LAMA/LABA rate).

Since we assumed a normal approximation to the Poisson, we confirmed the power with 100,000 simulated replicates. The simulated power of the superiority and non-inferiority hypotheses are actually slightly higher than from the large-sample approximation formulae (91% and 90.3%, respectively). We had also considered overdispersion by simulating from a negative binomial distribution (with a negative binomial regression used to analyse the simulated replicates).[1] Overdispersion did cause the power to drop, but our sample size remained robust: for example, if overdispersion caused a 30% increase in the variance, the power to declare superiority was still 85%. We expect that power would have been gained from including partial information from participants who were lost to follow-up.

In the early stages of the trial, it was found that the exacerbation rates in pre-baseline periods were lower than they had been historically, most probably due to the effect of COVID-19 restrictions. The inclusion criteria were therefore updated in February 2022 to allow patients with two or more exacerbations in any preceding 12-month period across 2 years,[1] the previous requirement being a history of three or more exacerbations in the preceding 12 months. A recalculation of the power of the trial was conducted, assuming that there would be lower exacerbation rates in the follow-up period. We assumed that the placebo exacerbation rate would be an average of 1.9 per year. We recalculated the power for two scenarios: (1) assuming the same absolute difference (0.5) between dual therapy A versus placebo and the

same non-inferiority margin (0.38) as previously and (2) the same relative difference (21%) between dual therapy versus placebo and relative non-inferiority margin (20%) as before. *Appendix 1*, *Table 5* shows the power of the trial to conclude non-inferiority and superiority under these scenarios compared to the original calculation.

Statistical analysis

Due to the trial closing with only 33 participants instead of the planned 600 participants, the original analysis described in the protocol was unsuitable.[1]

All outcome data were analysed on an intention-to-treat basis, with participants being analysed according to the randomisation arm they were allocated to. Safety tabulations were completed on all those who received any trial treatment. Due to the reduced sample size, no analysis was completed on a per-protocol population.

The analysis used was descriptive with the aim to inform future studies. Continuous outcomes were reported using the mean and standard deviation (SD) and/or the median and range (minimum and maximum values). Change from baseline to each follow-up time point was calculated as the follow-up score minus the baseline score. Categorical outcomes were reported as frequencies and percentages. For the SGRQ and QoL-B, we also reported the proportion of participants who improved from baseline to follow-up by the minimum clinically important difference (MCID) of 4 for SGRQ[26] and 8 for QoL-B.[27] A swimmer plot has been used to visualise individual trajectories over time.

For the primary outcome of the number of exacerbations, it was planned that if at least 30 participants had at least 6 months of follow-up data and there were at least 6 participants in the placebo arm, a negative binomial regression model would be used to provide exploratory estimates of the difference between randomised groups. This was the case, and this analysis was performed. The model was adjusted for stratification factors of BSI score and baseline ICS drug therapy and two-sided 95% confidence intervals (CIs) were provided for the incident rate ratio (IRR) between dual therapy, triple therapy and placebo. Results were also provided without adjustment. The time at risk was considered to be the time not spent in exacerbation (hence, while a participant was experiencing an exacerbation, they were not included as at risk of another).

For time to first exacerbation, median, upper and lower quartile time to first exacerbation (with 95% CIs) were calculated (where possible), using the reverse Kaplan–Meier estimate. Kaplan–Meier estimates of survivor functions by randomised arm were plotted.

Apart from the exploratory analysis of the primary outcome and the secondary outcome time to first exacerbation, no hypothesis testing was performed.

The SGRQ, QoL-B and BSI questionnaires were scored according to the scale developers' manual or published scoring methods. Treatment compliance was calculated during a participant's time on treatment. The full definition is given in *Appendix 2*.

Statistical analyses were conducted in Stata® version 18.0 (StataCorp LP, College Station, TX, USA). Independent trial steering and data monitoring committees had oversight throughout the trial and convened at least annually.

Health economic analysis

Similar to the statistical analysis, the economic analysis described in the protocol was unsuitable due to the trial closing.[22] The reported economic analysis uses data from the recruited participants who were followed up until their 12-month visit (N = 33). The outcomes of the economic analysis were revised based on this new sample size to the following:

1. presentation of health service utilisation data in the form of summary statistics
2. presentation of quality-of-life data (EQ-5D-5L) in the form of summary statistics
3. presentation of time and travel data in the form of summary statistics.

The design, conduct and analysis of the economic analysis followed guidelines for best practice throughout.[28] The economic analysis was undertaken from the perspective of the UK NHS and PSS.

National Health Service health and social care resource use

Data on health and social care resource use were collected using a bespoke, self-reported questionnaire, the HCUQ, which was administered to all participants at baseline, 1, 6 and 12 months post randomisation. The HCUQ also collected information on any direct and indirect costs to participants associated with managing their bronchiectasis, including any privately paid for health care and/or personal care and any time away from usual activities, including paid work, due to a bronchiectasis exacerbation.

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Firstly, response rates to the HCUQ were recorded at each time point. The data were presented by randomised arm. Descriptive statistics (mean and median) with their measure of variance [SD and interquartile range (IQR)] were used to summarise the data at each time point.

Unit costs, from routine sources, were assigned to self-reported resource use to estimate the average total cost per participant and the average total cost per randomised arm.[29,30] Costs were estimated only for participants who had completed the HCUQ at 1, 6 and 12 months. It was assumed that if a participant did not complete one of the questions, then they did not use this service, which potentially underestimated the average total resource-use costs. The costs were presented as the average total cost for each healthcare resource, the average total secondary care costs, average total primary care costs and average total primary and secondary care costs. Conclusions on potential differences in costs should not be drawn, given the small sample size.

Utility and quality-adjusted life-years

The economic analysis reported the completion rates and domain scores for the EQ-5D-5L and visual analogue scale (VAS). The VAS asks participants to report their health today on a scale of 0–100, where 0 = worst possible health and 100 = best possible health.

Responses to the EQ-5D-5L were converted into utility values by cross-walking responses on to the EQ-5D-3L, as recommended by the National Institute of Health and Care Excellence.[31,32] QALYs were estimated using the area under the curve. As there were EQ-5D-5L data from at least 90% (N = 30) of participants, the analysis was extended to summarise the data by the three trial arms. Due to the small sample size, no formal statistical testing was undertaken.

Time and travel

The Time and Travel questionnaire collected information on the direct and indirect costs incurred by participants to access care. The data were summarised as descriptive statistics and are presented in *Appendix 5*, *Tables 21* and *22*.

All economic analyses were undertaken in Stata version 18.0.

Results

Trial set-up, sponsorship and ethical approval took 14 months. From the initial call for expressions of interest, 25 sites returned completed feasibility questionnaires; 15 of these were selected for the pilot phase of the trial. Of these, two sites in advance stages of set-up had to withdraw from participation due to changes in respiratory services or staffing in light of the COVID-19 pandemic. Site set-up time ranged from sending the Local Information Pack (LIP) to contract execution (27–269 days) and from sending the LIP to opening to recruitment (Green Light, 98–374 days); by contrast, the sites' initial estimates of this time period, given at feasibility, ranged from 14 to 84 days (see *Appendix 3*, *Figure 6*).

The first site opened to recruitment on 29 July 2021, with 13 sites in total being open by 22 August 2022. One of the 13 sites open to recruitment recruited from two different hospitals within the same NHS Trust due to a merger of the initial two NHS Trusts in set-up. At the time that the trial was closed, five sites were in set-up to contribute to the main phase of the trial.

Participants were randomised between 22 September 2021 and 21 October 2022 through Respiratory Departments at 9 of the 13 open UK NHS secondary care sites. Projected versus actual recruitment is given in *Appendix 3*, *Figure 7*.

For the nine sites that recruited at least one participant, the rate of recruitment per month varied from 0.1 to 0.9, with the overall recruitment rate being 0.3 participants per site-month (see *Appendix 3*, *Table 8*). This was below the minimum target for the pilot trial of 1.25 participants per site-month.

Details of participant flow through the trial is given in the Consolidated Standards of Reporting Trials (CONSORT) diagram (*Figure 1*). Eighty-five potentially eligible patients were screened, of whom 26 (31%) declined at screening, 26 (31%) were ineligible and 33 (39%) were randomised. Screening and recruitment data are shown by site in *Appendix 3*, *Table 8*. The majority of recruitment was from one centre [14/33 (42%)]. The reasons due to which the participants failed screening or declined the trial are given in *Appendix 3*, *Table 9*. Of the 26 patients who failed screening, reasons were given for 23; and the most common reasons were bronchiectasis, which is not the predominant primary respiratory disease in the view of the investigator [4/23 (17%)]; the predominant disease COPD or asthma [4/23 (17%)]; unwilling to change or stop ICS, LAMA or LABA treatment prior to recruitment [3/23 (13%)]; and contraindications to ICS withdrawal [3/23 (13%)]. In the 26 patients who declined the trial, the most frequent reasons given were the trial was too time-consuming [8/26 (31%)] or not interested in research [5/26 (19%)].

Of the 33 randomised participants, 14 were randomised to dual therapy (LAMA/LABA), 12 to triple therapy (ICS/LAMA/LABA) and 7 to placebo. All participants started therapy. Three participants withdrew from the trial [3/33 (9%)]; one was from each randomised group due to personal circumstances [dual therapy: 1/14 (7%)], unacceptable side effects [triple therapy: 1/12 (8%)] and the inhaler not giving relief [placebo: 1/7 (14%)]. Five participants [5/33 (15%)] discontinued therapy [dual therapy: 1/14 (7%), triple therapy: 2/12 (17%), placebo 2/7 (29%)]. The reasons for discontinuation were intolerable side effects (one per arm), raised fractional exhaled nitric oxide (NO) due to airway inflammation from non-tuberculous mycobacterial lung disease (one triple therapy) and loss of confidence in trial medication due to two chest infections (one placebo). Retention of participants on the trial was high, as 30 participants (91%) had a 12-month visit (13 dual therapy, 11 triple therapy and 6 placebo). Missing data were minimal across outcomes (see *Appendix 3*, *Table 10*). Treatment compliance was high, with 81% (25/31) participants taking at least 75% of their medication while on treatment [dual therapy: 11/13 (85%), triple therapy: 9/12 (75%), placebo: 5/6 (83%)]. See *Appendix 2*, *Tables 6* and *7* for further details.

Baseline summaries

Baseline characteristics look balanced at baseline (*Table 1* and *Appendix 3*, *Table 11*) apart from sex at birth [number of males – dual 5/14 (36%), triple (5/12 (42%) and placebo 5/7 (71%)] and smoking history [number of ex-smokers – dual 3/14 (21%), triple 2/12 (17%) and placebo 5/7 (71%)]. In general, the sample population was representative of the target population similar to large cohort studies in bronchiectasis. The average age was 69.4 (SD: 10.7) years and a range of 40–89. There was a slight female predominance with a 55% : 45% female-to-male ratio. The baseline disease severity had a mean BSI score of 9.7 (SD: 4.6; severe bronchiectasis). Fifty-five per cent of participants (18/33) were classed as having severe bronchiectasis (BSI score of ≥ 9), with 45% (15/33) classed as having mild–moderate bronchiectasis (BSI score of 0–8). Eleven participants had *Pseudomonas* colonisation at baseline [11/33 (33%)]. The mean number of exacerbations in the preceding 12-month period was 3.2 (SD: 1.2). There was a significant impairment of health-related quality of life, with a mean SGRQ of 44.4 (SD: 21.0) and a QoL-B respiratory symptoms score of 57.1 (SD: 19.6). Notably, 14 (42%) were ICS users at baseline. Ethnicity showed a predominance of White British [30/33 (91%)], followed by any other White background [2/33 (6%)] and Asian or Asian British Pakistani [1/33 (3%)].

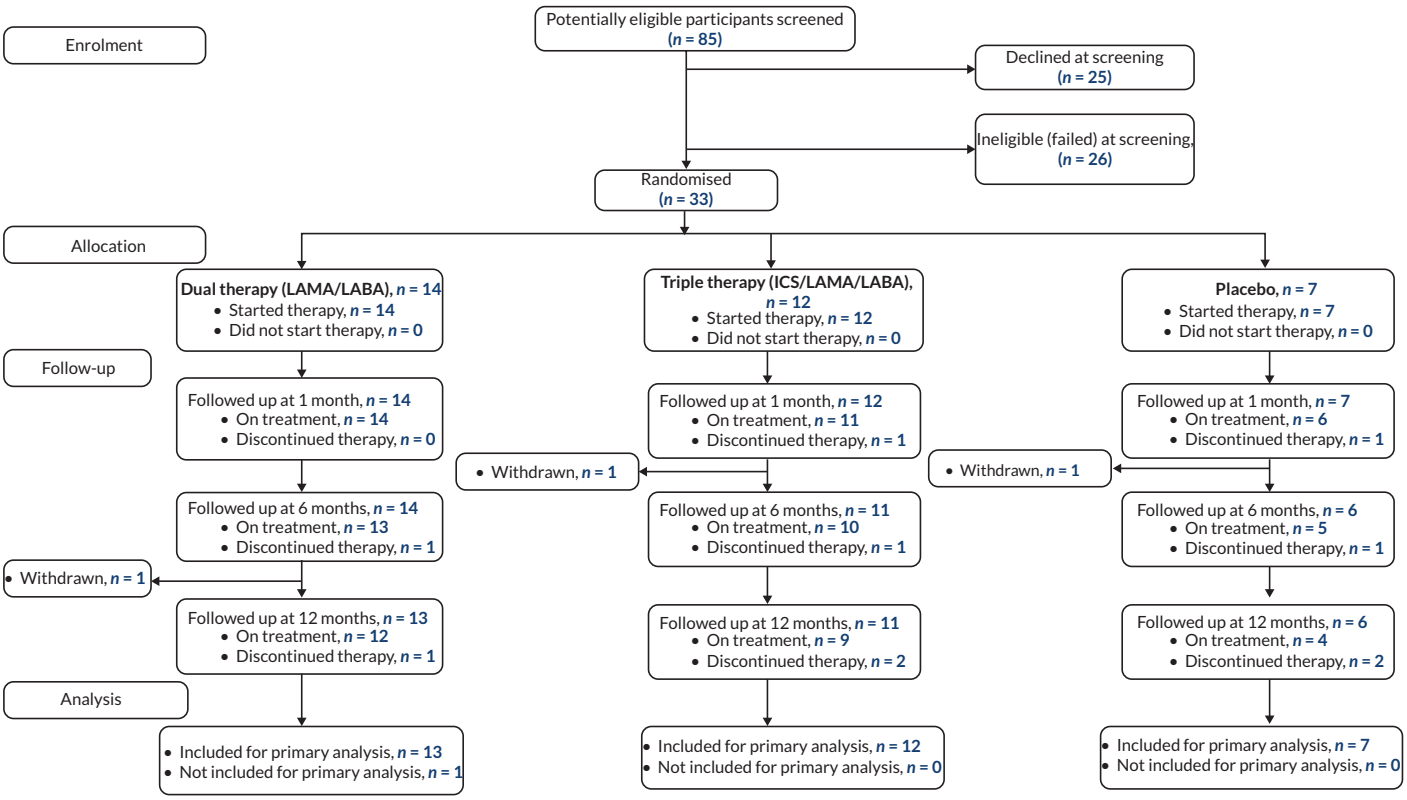

FIGURE 1 The CONSORT flow diagram.

TABLE 1 Baseline characteristics

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
N	14	12	7	33
Demographics				
Sex at birth				
Female	9 (64%)	7 (58%)	2 (29%)	18 (55%)
Male	5 (36%)	5 (42%)	5 (71%)	15 (45%)
Age at randomisation in years				
Median (IQR)	72.4 (60.9–75.7)	70.7 (58.5–77.1)	71.3 (65.9–74.7)	71.3 (60.9–75.7)
Mean (SD)	69.2 (11.1)	68.9 (10.2)	70.5 (12.2)	69.4 (10.7)
Range	(48.8–86.0)	(52.1–82.2)	(48.3–89.1)	(48.3–89.1)
Ethnicity				
White British	13 (93%)	12 (100%)	5 (71%)	30 (91%)
Any other White background	0 (0%)	0 (0%)	2 (29%)	2 (6%)
Asian or Asian British Pakistani	1 (7%)	0 (0%)	0 (0%)	1 (3%)
Stratification factors				
BSI score used at randomisation				
BSI score (category)				
Score of 0–8	7 (50%)	5 (42%)	3 (43%)	15 (45%)
Score of 9+	7 (50%)	7 (58%)	4 (57%)	18 (55%)
BSI score				
Median (IQR)	8.5 (6–12)	9.5 (7, 11.5)	11 (4, 13)	9 (6, 12)
Mean (SD)	9.6 (5.0)	9.5 (3.0)	10.1 (6.0)	9.7 (4.5)
Range	(4.0–21.0)	(5.0–15.0)	(3.0–20.0)	(3.0–21.0)
BSI score calculated from raw data				
BSI score (category)				
Score of 0–8	7 (50%)	5 (42%)	3 (43%)	15 (45%)
Score of 9+	7 (50%)	7 (58%)	4 (57%)	18 (55%)
BSI score				
Median (IQR)	8.5 (6–12)	9.5 (7–11.5)	11 (4–13)	9 (7–12)
Mean (SD)	9.6 (5.2)	9.5 (3.0)	10.1 (6.0)	9.7 (4.6)
Range	(1.0–21.0)	(5.0–15.0)	(3.0–20.0)	(1.0–21.0)
Baseline ICS drug therapy				
ICS user	6 (43%)	4 (33%)	4 (57%)	14 (42%)
Non-ICS user	8 (57%)	8 (67%)	3 (43%)	19 (58%)
Medical history				
Number of bronchiectasis exacerbations in the year prior to joining the trial				
Median (IQR)	3 (3–4)	3 (2–4)	3 (2–4)	3 (3–4)

TABLE 1 Baseline characteristics (continued)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Mean (SD)	3.4 (1.2)	3.1 (1.3)	3.1 (1.1)	3.2 (1.2)
Range	(2–7)	(1–6)	(2–5)	(1–7)
Number of bronchiectasis hospitalisations in the year prior to joining the trial	0 (0–1)	0 (0–0)	0 (0–1)	0 (0–1)
Median (IQR)	0 (0–1)	0 (0–0)	0 (0–1)	0 (0–1)
Mean (SD)	0.4 (0.8)	1.0 (3.2)	0.6 (0.8)	0.7 (2.0)
Range	(0–2)	(0–11)	(0–2)	(0–11)
Pseudomonas colonisation (from BSI)				
Yes	5 (36%)	4 (33%)	2 (29%)	11 (33%)
No	9 (64%)	8 (67%)	5 (71%)	22 (67%)
Spirometry				
FEV1				
Median (IQR)	1.4 (1.1–1.7)	1.6 (1.2–2.1)	2.0 (1.2–2.9)	1.5 (1.1–2.1)
Mean (SD)	1.6 (0.8)	1.8 (0.8)	2.1 (1.0)	1.8 (0.9)
Range	(0.7–3.3)	(0.8–3.8)	(0.8–3.9)	(0.7–3.9)
	(*n* = 13)			(*n* = 32)
FEV1% of predicted values				
Median (IQR)	67.0 (45.0–95.0)	69.6 (54.5–89.5)	84.0 (60.3–99.0)	68.5 (49.0–95.0)
Mean (SD)	71.3 (32.2)	70.1 (22.2)	76.3 (27.7)	72.0 (27.0)
Range	(34.0–129.0)	(33.0–103.6)	(25.0–103.0)	(25.0–129.0)
	(*n* = 13)			(*n* = 32)
FVC				
Median (IQR)	2.1 (1.7–2.7)	2.5 (1.9–3.0)	2.9 (1.9–4.1)	2.5 (1.8–3.0)
Mean (SD)	2.3 (0.8)	2.6 (1.0)	3.0 (1.3)	2.6 (1.0)
Range	(0.9–4.0)	(1.7–5.4)	(1.5–5.2)	(0.9–5.4)
	(*n* = 13)			(*n* = 32)
FVC% of predicted values				
Median (IQR)	77.0 (70.0–93.0)	85.0 (72.0–91.0)	93.0 (73.0–104.0)	80.6 (72.0–96.5)
Mean (SD)	80.8 (23.7)	82.5 (18.8)	86.6 (23.1)	82.7 (21.3)
Range	(38.0–126.0)	(48.7–116.9)	(44.0–112.0)	(38.0–126.0)
	(*n* = 13)			(*n* = 32)
FEV1/FVC ratio				
Median (IQR)	0.6 (0.6–0.7)	0.7 (0.6–0.7)	0.7 (0.6–0.7)	0.7 (0.6–0.7)
Mean (SD)	0.7 (0.1)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)
Range	(0.5–0.9)	(0.4–0.8)	(0.4–0.7)	(0.4–0.9)
	(*n* = 13)			(*n* = 32)

continued

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TABLE 1 Baseline characteristics (continued)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Questionnaires, indices and scores				
Modified Reiff scoring				
Median (IQR)	3.5 (2–6)	6 (3.5–8)	5 (3–6)	5 (3–6)
Mean (SD)	4.4 (2.6)	6.3 (3.2)	6.3 (5.4)	5.5 (3.5)
Range	(1–9)	(2–13)	(2–18)	(1–18)
BDI (score 0–12)				
Median (IQR)	7 (4–8)	7 (6–11)	8.5 (6–10)	7 (6–9)
Mean (SD)	6.1 (2.3)	8.2 (2.5)	7.7 (3.8)	7.1 (2.8)
Range	(2–10)	(6–12)	(1–12)	(1–12)
	(*n* = 13)	(*n* = 10)	(*n* = 6)	(*n* = 29)
MRCD score (1–5), *n* (%)				
1. Not troubled by breathlessness except on strenuous exercise	0 (0%)	6 (50%)	2 (29%)	8 (24%)
2. Short of breath when hurrying or walking up a slight hill	5 (36%)	2 (17%)	2 (29%)	9 (27%)
3. Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace	6 (43%)	3 (25%)	1 (14%)	10 (30%)
4. Stops due to breathlessness after walking 100 m	2 (14%)	1 (8%)	1 (14%)	4 (12%)
5. Housebound due to breathlessness, or breathless on dressing or undressing	1 (7%)	0 (0%)	1 (14%)	2 (6%)
Median (IQR)	3 (2–3)	1.5 (1–3)	2 (1–4)	2 (2–3)
Mean (SD)	3.0 (0.9)	1.9 (1.1)	2.6 (1.5)	2.5 (1.2)
Range	(2–5)	(1–4)	(1–5)	(1–5)
SGRQ				
Total SGRQ score				
Median (IQR)	46.8 (33.9–68.3)	42.8 (16.5–57.6)	50.7 (13.2–73.5)	42.8 (29.2–59.2)
Mean (SD)	49.8 (17.1)	37.1 (20.8)	46.2 (28.6)	44.4 (21.0)
Range	(28.5–79.0)	(6.8–64.1)	(12.9–76.5)	(6.8 79.0)
			(*n* = 6)	(*n* = 32)
QoL-B				
Physical				
Median (IQR)	40.0 (13.3–73.3)	60.0 (33.3–96.7)	46.7 (33.3–100.0)	53.3 (26.7–86.7)
Mean (SD)	43.3 (33.6)	62.2 (30.9)	57.1 (36.5)	53.1 (33.4)
Range	(0.0–93.3)	(20.0–100.0)	(6.7–100.0)	(0.0–100.0)
Role				
Median (IQR)	66.7 (20.0–93.3)	76.7 (56.7–90.0)	80.0 (50.0–93.3)	73.3 (50.0–93.3)
Mean (SD)	58.6 (34.7)	73.9 (19.0)	73.8 (26.7)	67.4 (28.4)
Range	(0.0–100.0)	(46.7–100.0)	(26.7–100.0)	(0.0–100.0)

TABLE 1 Baseline characteristics (continued)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Vitality				
Median (IQR)	44.4 (33.3–55.6)	55.6 (44.4–72.2)	33.3 (22.2–66.7)	44.4 (33.3–66.7)
Mean (SD)	41.3 (19.2)	57.4 (16.3)	46.0 (23.5)	48.1 (20.0)
Range	(0.0–66.7)	(33.3–77.8)	(22.2–77.8)	(0.0–77.8)
Emotional				
Median (IQR)	87.5 (58.3–91.7)	91.7 (75.0–100.0)	91.7 (83.3–100.0)	91.7 (66.7–100.0)
Mean (SD)	75.0 (27.7)	84.7 (20.4)	88.1(11.6)	81.3 (22.6)
Range	(16.7–100.0)	(33.3–100.0)	(66.7–100.0)	(16.7–100.0)
Social				
Median (IQR)	62.5 (33.3–75.0)	50.0 (25.0–58.3)	66.7 (33.3–75.0)	50.0 (33.3–75.0)
Mean (SD)	52.0 (25.6)	48.4 (23.0)	58.3 (21.0)	52.0 (23.3)
Range	(0.0–77.8)	(22.2–91.7)	(25.0–75.0)	(0.0–91.7)
Treatment burden				
Median (IQR)	77.8 (55.6–100)	77.8 (50.0–88.9)	77.8 (44.4–77.8)	77.8 (55.6–88.9)
Mean (SD)	75.9 (22.7)	70.8 (23.7)	61.1 (33.3)	70.4 (24.7)
Range	(44.4–100.0)	(33.3–100.0)	(11.1–77.8)	(11.1–100.0)
	(*n* = 6)	(*n* = 8)	(*n* = 4)	(*n* = 18)
Health perceptions				
Median (IQR)	50.0 (33.3–58.3)	45.8 (37.5–70.8)	66.7 (33.3–75.0)	50.0 (33.3–66.7)
Mean (SD)	44.0 (22.3)	50.7 (20.6)	59.1 (23.7)	49.7 (22.0)
Range	(0.0–75.0)	(16.7–75.0)	(25.0–88.9)	(0.0–88.9)
Respiratory symptoms				
Median (IQR)	53.7 (44.4–66.7)	61.1 (40.7–79.6)	62.5 (48.2–74.1)	59.3 (48.1–70.4)
Mean (SD)	55.3 (15.9)	58.6 (24.4)	58.1 (19.7)	57.1 (19.6)
Range	(29.6–81.5)	(18.5–92.6)	(22.2–81.5)	(18.5–92.6)

MRCD, Medical Research Council Dyspnoea.

Note
Data are *n*; %, mean (SD) or median (IQR); range, unless otherwise stated.

Primary outcome

The distribution of the number of exacerbations during the trial by treatment group and overall is given in *Appendix 3*, *Figures 8* and *9*. The median number of exacerbations was 1 (IQR 0–3) for dual therapy, 2 (1–2.5) for triple therapy and 3 (2–3) for placebo group (*Table 2*) over a median of 12-month follow-up (IQR: 12.0–12.0, range: 2.5–12.7). From the exploratory models (*Table 3*), the adjusted IRR (95% CI) for the number of exacerbations was 0.59 (0.26 to 1.32) for dual therapy versus placebo and 0.54 (0.23 to 1.27) for triple therapy versus placebo and 0.92 (0.45 to 1.92) for triple therapy versus dual therapy. This means that, on average, participants were 41% and 46% less likely to experience an exacerbation during the trial in the dual therapy and triple therapy arms compared to placebo, respectively, but as can be seen by the CIs crossing 1, there is a lot of uncertainty in these estimates; so, the possibility of participants being more likely to have exacerbations in the treatment groups cannot be ruled out. From the same exploratory models, the adjusted mean difference (95% CI)

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TABLE 2 Number of bronchiectasis exacerbations requiring antibiotics during the follow-up period, per treatment group

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
N	14	12	7	33
Number of bronchiectasis exacerbations requiring antibiotics				
0	4 (30.8%)	1 (8.3%)	1 (14.3%)	6 (18.8%)
1	4 (30.8%)	4 (33.3%)	0 (0.0%)	8 (25.0%)
2	0 (0.0%)	4 (33.3%)	2 (28.6%)	6 (18.8%)
3	3 (23.1%)	2 (16.7%)	3 (42.9%)	8 (25.0%)
4+	2 (15.4%)	1 (8.3%)	1 (14.3%)	4 (12.5%)
Mean (SD)	2.0 (2.3)	1.8 (1.1)	2.6 (1.5)	2.1 (1.7)
Median (IQR, range)	1 (0–3) (0–7)	2 (1–2.5) (0–4)	3 (2–3) (0–5)	2 (1–3) (0–7)
n	13[a]	12	7	32[a]

a There was one participant who did not return any diaries, and there was no information in the comments at visits to state whether they had had exacerbations or not; therefore, they are not included in the analysis of the primary outcome.

Note
Note that for the three participants who withdrew early, their number of episodes has not been adjusted for their shorter time in study.

TABLE 3 Comparison of the number of bronchiectasis exacerbations requiring antibiotics during the trial between treatment groups (*n* = 32)

	Dual therapy vs. placebo	Triple therapy vs. placebo	Triple therapy vs. dual therapy
Unadjusted IRR (95% CI)	0.59 (0.26 to 1.33)	0.54 (0.24 to 1.26)	0.92 (0.44 to 1.91)
Adjusted[a] IRR (95% CI)	0.59 (0.26 to 1.32)	0.54 (0.23 to 1.27)	0.92 (0.45 to 1.92)
Unadjusted mean difference (95% CI)	−1.37 (−3.74 to 1.00)	−1.52 (−3.89 to 0.85)	−0.15 (−1.53 to 1.23)
Adjusted[a] mean difference (95% CI)	−1.39 (−3.78 to 1.00)	−1.54 (−3.96 to 0.89)	−0.15 (−1.52 to 1.23)

IRR, incidence rate ratio.
a Adjusted for the stratification factors of BSI score and baseline ICS drug therapy.

in exacerbations during the trial was −1.39 (−3.78 to 1.00) for dual therapy versus placebo and −1.54 (−3.96 to 0.89) for triple therapy versus placebo and −0.15 (−1.52 to 1.23) for triple therapy versus dual therapy.

Secondary outcomes

A summary of the secondary outcome descriptive analysis follows. We must note that this analysis is descriptive and is based on a small sample size and therefore this should not be used to draw conclusions.

Time to first exacerbation

The Kaplan–Meier survival curves for the time to first exacerbation are presented in *Figures 2* and *3*. The lower quartile for the time to first exacerbation is the time at which the probability of being exacerbation-free is 0.75. From *Table 4*, the lower quartile in dual therapy was 88 days (95% CI: 20 to 167), that in triple therapy group was 54 days (95% CI: 13 to 81) and that in placebo was 13 days (95% CI: 5 to 41). This indicates that, in this trial, participants in the placebo group had their first episode earlier than the treatment groups, but there is a lot of uncertainty in these estimates (indicated by the overlapping CIs). We must note that the placebo group contains only seven participants, of whom one withdrew from the trial at 2.5 months, having not had an episode. The six remaining participants in the placebo arm all had their first episode by 4.4 months. This analysis is descriptive and is based on a small sample size and therefore this should not be used to draw firm conclusions.

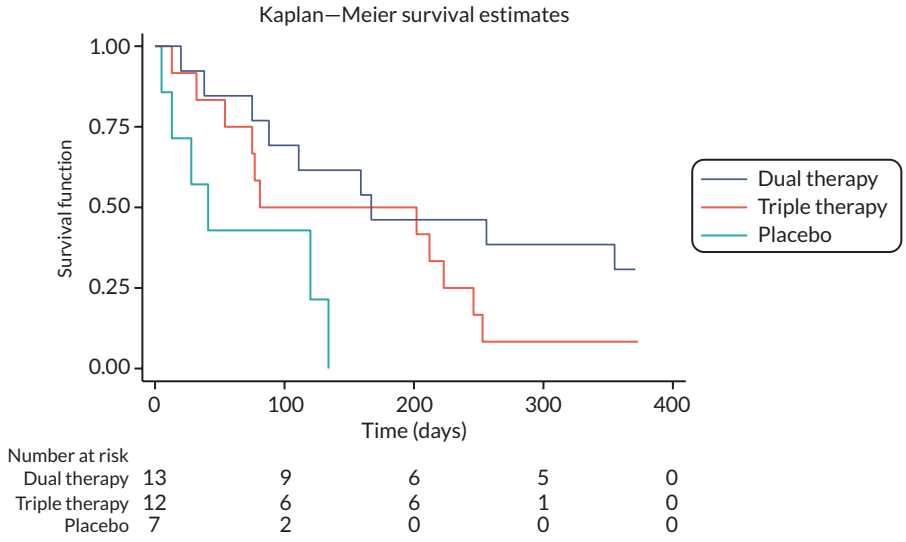

FIGURE 2 Kaplan–Meier estimates of survivor functions by randomised treatment groups.

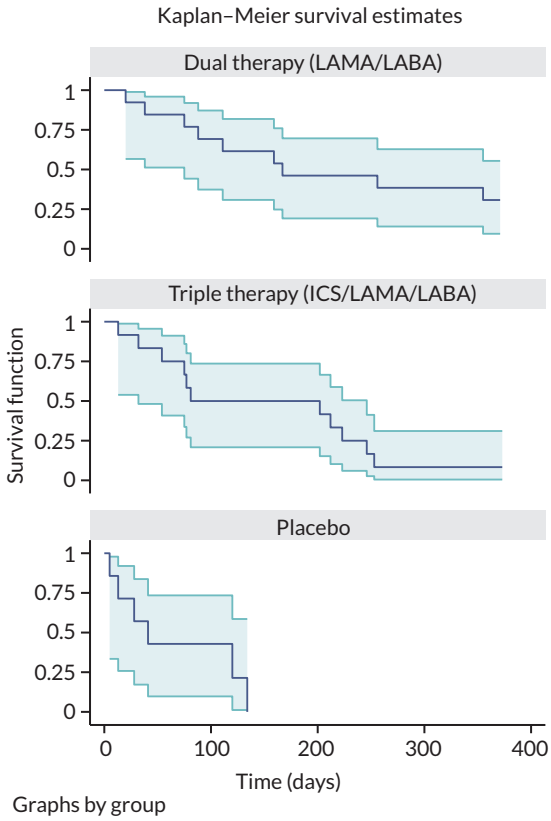

FIGURE 3 Kaplan–Meier estimates of survivor functions with 95% CI by randomised treatment groups.

A swimmer plot (*Figure 4*) shows the individual trajectories of participants during the trial. We have included information on ICS use at baseline, time to first exacerbation, time on treatment, follow-up duration and randomised arm.

The plot includes treatment group (dual therapy is blue, triple therapy is orange and placebo is green), time to first bronchiectasis exacerbation (black dot), the time a participant stopped treatment (red triangle) and ICS use at baseline (solid lines represent non-ICS user, and dashed lines represent ICS user).

Lung function

Looking at the change from baseline, participants on average had a lower FEV1 and FVC at 12 months than at baseline in the placebo arm, whereas in the treatment arms, the FEV1 and FVC was higher than baseline at the 12-month visit (see *Appendix 3*, *Table 12*, *Figures 10* and *11*).

Breathlessness

Breathlessness/change in breathlessness was similar across the arms at 12 months as indicated by the MRCD scale and the TDI (see *Appendix 3*, *Table 13*).

Health-related quality of life

For the QoL-B, most of the domains have no clear pattern in the change from baseline; however, for the respiratory and health perception domains, on average, participants in the placebo group had a lower score at 12 months compared to baseline, whereas there was little change on average in the treatment groups (see *Appendix 3*, *Tables 12* and *13*, *Figure 13*). On the respiratory domain 5/13 (38.5%), 1/11 (9.1%) and 1/6 (16.7%) in dual therapy, triple therapy and placebo, respectively, achieved at least an eight-point increase in their score from baseline to 12 months (see *Appendix 3*, *Table 14*). For the health perceptions domain, this was 5/13 (38.5%), 5/11 (45.5%) and 1/6 (16.7%), respectively. There was no clear pattern in the change in SGRQ total score at 12 months, however, 6/12 (50%), 4/11 (36%) and 2/5 (40%) of participants achieved at least a four-point (the MCID) reduction in SGRQ total

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TABLE 4 Summary statistics of the time to first episode (days)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
N	14	12	7	33
Median (95% CI)	167 (75 to [a])	81 (32 to 246)	41 (5 to [a])	120 (75 to 212)
Lower quartile (95% CI)	88 (20 to 167)	54 (13 to 81)	13 (5 to 41)	41 (13 to 81)
Upper quartile (95% CI)	[a](159 to [a])	223 (81 to [a])	120 (28 to [a])	253 (167 to [a])
n	13	12	7	32

a Cannot be estimated due to too few participants at this time who go on to experience a first episode.

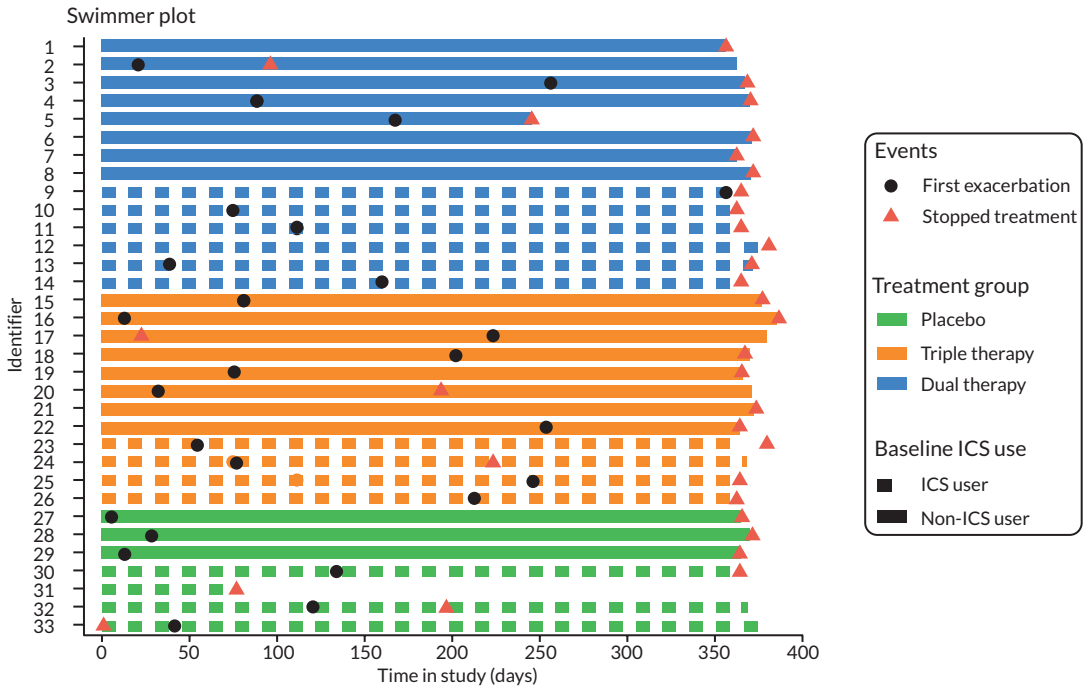

FIGURE 4 A swimmer plot showing the individual trajectories of a participants' time in the trial.

score at 12 months in dual therapy, triple therapy and placebo, respectively (see *Appendix 3*, *Tables 12*, *13* and *15*, *Figure 12*).

Safety

There were five bronchiectasis exacerbations in three participants who required hospital admission (one admission in dual, one in triple and three for one participant in placebo) (see *Appendix 4*, *Table 16*). There were 10 emergency hospital admissions (dual: five in three participants, triple: two in two participants and placebo: three in one participant). There was one case of radiologically confirmed pneumonia in triple therapy (see *Appendix 4*, *Table 16*).

There were no key safety signals noted, with most participants experiencing some AEs ranging from 71% in placebo arm to 100% in the triple therapy arm (see *Appendix 4*, *Table 17*). In total, there were 169 AEs in 30 participants (dual: 75 AEs in 13 participants, triple: 68 AEs in 12 participants and placebo: 26 AEs in 5 participants) (see *Appendix 4*, *Table 17*). Note that given the randomisation ratio, we only have half the participants in the placebo group compared to the treatment groups, so we would expect roughly half the AEs in the placebo group compared to the treatment groups. The median number of AEs per participant was 5 (IQR: 1–8), 4 (IQR: 2.5–6.5) and 3 (IQR: 0–6) in the dual, triple and placebo arms, respectively, indicating there were more AEs, on average, in the treatment groups than placebo. In total, six of the AEs on two participants were related to treatment. There were 10 serious AEs from six participants (18% of participants), all considered unrelated to treatment (see *Appendix 4*, *Table 18*). This was 21% of participants

(3/14) on dual therapy, 17% of participants (2/12) on triple therapy and 14% of participants (1/7) for placebo. The serious adverse events (SAEs) were five cases of bronchiectasis exacerbation in two participants, attempted suicide, chronic pain, mycobacterium abscesses infection, UTI and vomiting (see *Appendix 4*, *Table 19*). There were no safety concerns linked to the interventions. Further details on AEs are given in *Appendix 4*, *Table 20*.

Economic analysis

The response rates to both the HCUQ and EQ-5D-5L questionnaires are presented in *Appendix 5*, *Tables 23* and *24*. The majority (range: 86–100%) of participants responded to both questionnaires at each time point.

For those who completed the HCUQ at 1, 6 and 12 months (N = 30), their data were combined to estimate their total self-reported resource use over the previous 12 months; these data are presented in *Appendix 5*, *Table 25*.

Unit costs (see *Appendix 5*, *Table 26*) were assigned to the resources reported in *Appendix 5*, *Table 23* to estimate the average total costs for all participants and for each randomised arm (see *Appendix 5*, *Table 27*). The average total self-reported NHS resource-use cost was £2447 (SD £4793); £2420 (SD £5011) in the dual therapy arm, £2691 (SD £5875) in the triple therapy arm and £1187 (SD £1080) in the placebo arm. Recent data, in 2021, estimated the average NHS spend per person to be £4188.[33] It should be noted that there are additional costs herein not captured in the estimation of NHS costs, including inhaled treatments.

No conclusions should be drawn on the potential differences in QALYs (see *Appendix 5*, *Table 28*) between the treatment groups due to the small number of participants and the observed imbalances in baseline utility scores that were not adjusted for in the estimation of QALYs.

Discussion/interpretation

Bronchiectasis remains a condition with no specifically licensed medications. Since the inception of this trial, emergent data have provided a better understanding of the complex heterogeneous pathophysiology of this condition; large-scale observational studies suggest the potential benefits of inhaled steroids and bronchiectasis.[20] Cohort studies have also suggested that there is a specific eosinophilic subtype of bronchiectasis that may support a subgroup of patients with a greater response to inhaled steroids.[34] Prospective trial data on the role of inhaled steroids and long-acting bronchodilators are of significant interest to the clinical community.

This trial was designed to answer this important clinical question but failed to recruit to target. This likely reflects a number of factors, including the COVID-19 pandemic and changes in post-COVID-19 pandemic behaviours in both patients, research sites and research teams. Firstly, patients were more hesitant to be involved in research that required travel to research sites, all of which were NHS hospitals. Secondly, there is good evidence that the eligible pool of patients with the requisite number of exacerbations was likely to have reduced during the COVID-19 pandemic: COVID-19-related 'shielding' (advised between 22 March 2020 and 31 July 2021), that is, remaining at home with minimal external contacts beyond the immediate household, was standard advice to patients with long-term lung conditions, such as those with bronchiectasis. After 'lockdown' restrictions were lifted in the UK, many patients chose to continue lockdown behaviours within daily routines. This was observed in other UK-based studies of bronchiectasis to be associated with a fall in bronchiectasis-related associated exacerbation rates in the UK,[35] and similar data were seen in the USA.[36] A reduction of exacerbations in other respiratory diseases has also been observed, with a 30% reduction in exacerbations of COPD reported.[37] Collectively, this reduced those patients who were both eligible (experiencing fewer exacerbations than required for trial entry) and willing to participate (attending trial sites/changing baseline medications) in this trial.

Sites took considerable amounts of time to set up and open to recruitment, which was much longer than that in the pre-pandemic period, and sites had less capacity following the diversion of staff to the COVID-19 response and COVID-19 research. This was well recognised within the UK healthcare research environment at the time, reflecting many studies that had been paused during COVID-19 pandemic and then restarted plus a number of new studies starting related to the COVID-19 pandemic. This 'surge' of studies was due to all trying to open and compete for approvals/governance of teams' times. This also meant more competition post approvals delivery for a finite number of nurses/research delivery teams at site. Interestingly, a trial using the same drug therapies but with a shorter trial design of 3 months on active therapy conducted in the Netherlands also failed to recruit; The FORZA trial only recruited 34 patients and could not show in this sample size any benefit on cough at 3 months.[38]

This synopsis should be referenced as follows:
Wilson N, Morton M, Homer T, Konkoth AB, Joyce R, Kershaw A, *et al.* A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis [published online ahead of print February 4 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GGCC1111

Other issues on study delivery are notable from this trial. Significant variations in the screening process were observed across sites; this left some uncertainty on the eligible population. Some centres reported nearly 100% screening to recruitment levels, and others reported screening to recruitment levels as low as 5%. This likely reflects differences between centres definitions of 'pre-screening', for example, remote review of note compared to face-to-face screening, where patients have had pre-screening and then face-to-face screening occurs. Adopting a consistent approach of how pre-screening and face-to-face screening are recorded across sites would be helpful to understand the feasibility in future studies and track the effect of any changes to the protocol.

Routes to improving recruitment in bronchiectasis trials need to be considered; work in this trial had already attempted to have strong patient and public engagement through workshops and discussions on patient information, leaflets and advice on messaging for the trial. These gave the trial management team significant support and will be strongly recommended for future studies. The trial management team found this advice was excellent, but simply, it was a very challenging time to convince patients who had been counselled to avoid risk and shield for 18 months to attend a hospital with perceived potential risk. For research studies, one future option may well be to try and develop study designs that can be delivered remotely or embedded within routine clinical care. The option for patients to have consent, undergo study procedures, either through telephone calls, mobile phone app or text-based messaging were all suggested as possibilities but were not within the funding of the trial award. Potentially, as these advances become more mainstream in clinical trials, the cost of these may drop and they can become more integrated into trials. Noting the older age population involved, informal feedback during the study made it clear that not all patients could contribute to trial designs that were solely electronic. Additional routes to improving recruitment were pursued during the course of the trial, including doing database searches of the BronchUK registry (www.bronch.ac.uk) and the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) European registry (www.bronchiectasis.eu). The filtering for UK-based patients recruited into EMBARC – revealed from 7700 patients with bronchiectasis that over 600 had exacerbations and could be eligible for the trial and who had already indicated their consent to be contacted about further research studies. This database search was not available at the beginning of the trial, in part because the COVID-19 pandemic had meant the databases had not been curated and quality checks completed. Targeting this potential patient group was presented as a potential rescue strategy for the trial to the funder in November 2022, but it was not deemed viable to rescue the trial within the time frame needed. Future trials in this area may wish to build in early database searches and seek permissions from the national database holders. Alternatively, models such as recruiting through national primary care data linkages should be considered. A primary care search strategy was not built into the trial design at inception, considering that most specialised bronchiectasis care, particularly for those with ongoing exacerbations, is secondary care-based; this again should be reconsidered in future trials.

There is no ideal test for excluding asthma and/or COPD in the bronchiectasis population. Recent data show that there is very significant mislabelling of COPD in a bronchiectasis population.[39] We allowed sites to decide if the bronchiectasis was the predominant disease, which is imprecise but reflects the pragmatic nature of HTA trials and clinical practice.

The trial recruited 33 patients as compared to a target of 120 at the time of stopping (the target required to meet the overall target of 600 participants). This means the trial was underpowered by some margin and no firm conclusions can be drawn. The available results suggest that there may be a signal of efficacy with either the dual therapy or the triple therapy based on the adjusted IRRs, which indicates that, on average, participants were 41% in dual and 46% in triple less likely than placebo to have an exacerbation; however, these estimates have very wide CIs, which do not rule out an effect in the opposite direction. Expressed in a different way, the number of patients who had one or fewer exacerbations during the trial was 62% for dual therapy, 42% for triple therapy and 14% (1/7) for placebo. The one participant who did not have an exacerbation in the placebo group withdrew from the trial at 2.5 months as the inhaler was not giving relief. Additionally, the median time to first exacerbation was 167 days for dual bronchodilators compared to 81 days for triple therapy and 41 days for placebo. More than half of the patients in the placebo arm had exacerbated by 100 days, and all participants remaining in the trial in the placebo arm had had an exacerbation by 4.5 months. The small sample size in placebo arm of seven means strong conclusions should not be made, but these data raise the potential for a future study design to consider time to first exacerbation as a study end point. An additional limitation is a very significant imbalance in the proportion of patients with smoking history, who received placebo versus active treatments. In a larger trial, this would be expected to be more balanced, but some of the observations in our small study may be influenced by this imbalance. These data are highly liable to the potential for bias due to small sample sizes, but they suggest that future studies are required to provide evidence.

Reflecting the pragmatic nature of the trial and standard clinical practice, lung function testing was conducted across sites using local equipment with local calibration and servicing. These approaches mean that the level of accuracy may not reflect that seen in commercial inhaler studies, which have proprietary spirometers in each centre that are calibrated before each patient with a quality control over read. In this trial, each arm had a small increase in FEV1 absolute vales and percentage predicted by the end of the trial. No trends in clinically meaningful differences were observed, with a 2–4% increase in median FEV1 seen over the course of the year. As these tests are more variable, effort- and equipment-dependent, then uncertainty remains. It is possible should, remote trials designs be favoured, that future study design may not include lung function. The MRCD score at baseline was 2 across the whole study population; 'On level ground, I walk slower than people of my age because of breathlessness, or I have to stop for breath when walking at my own pace on the level'. This was the same at the end of the trial. The test is simple to administer and is part of routine clinical care. It may not be particularly responsive in this population to the proposed interventions, but future studies should consider including it to explore this further. The mean SGRQ score of the whole population at baseline was 61.5, suggesting a significantly impaired quality of life. There appeared to be a large range reported throughout the trial. Interestingly, the total SGRQ score improved in each of the arms. It is unclear if this was specific to the trial and may have occurred through patient interaction with study teams or was seen during the wider non-trial population as the COVID-19 pandemic diminished.

Patient and public involvement

Patient and public involvement (PPI) has been incorporated throughout the trial. At the design stage, the British Lung Foundation (now AsthmaLung UK) Breathe Easy PPI groups gave their opinions and concerns over the use of inhaled drugs for bronchiectasis, an acceptable trial design and key questions to be answered. This feedback fed into the trial design, which was developed to have participant involvement for 12 months following PPI advice that any involvement longer than 12 months would not be acceptable. Work with the European Lung Foundation was also carried out to access their patient priorities' data, which showed that over 1000 patients' survey indicated that trials of inhaled therapy were key.

On a trial level, there were four PPI representatives: two who were co-applicants for the trial and were non-independent members of the TSC, and two who were independent members of the TSC. The PPI representatives were both patients with bronchiectasis and members of the public with extensive knowledge of respiratory disease and the impact on patients, friends and family.

The PPI co-applicants had input into development of trial documentation, in particular patient-facing documentation, ensuring that they were accessible to the target audience. During the challenges faced with trial site set-up and recruitment through the COVID-19 pandemic, the PPI participants were consulted about plans to alter eligibility criteria and recruitment strategies and then again when the trial was reviewed as part of the Research Reset programme, providing their support. Additionally, the independent PPI participants were involved in oversight of the trial as members of the TSC.

The PPI members have been involved in the plans for disseminating the results of the trial to participants and the wider public.

Equality, diversity and inclusion

The trial was terminated early before a sufficient sample size was attained. There was limited scope to develop specific targeting for underrepresented groups, as the main focus was trying to get sites open and encourage screening. The sites opened (or in process of opening) consistently reported issues with staffing and patient hesitancy in engagement, likely reflecting the early post peak pandemic timing. The sites were geographically spread and included several sites within the highest prevalence areas for bronchiectasis identified within the British Lung Foundation report, including North-East, North-West England and Yorkshire and Humberside regions.[40]

Impact and learning

The impact of this trial is that it shows that even in a post-pandemic period some patients and centres are willing to randomise patients into a study where triple therapy is compared to dual bronchodilator and placebo.[2] Significant proportions of the randomised group were on inhaled therapies at baseline and willing to stop these therapies to enter the trial. The data collected confirms good participant retention and completion of questionnaires.[2] The available data do suggest a possible signal of efficacy and a future large-scale study would be helpful to resolve the uncertainty. Indeed, the results of this trial being publicised may aid good recruitment in further studies given the indication of an important effect to be detected.

This synopsis should be referenced as follows:
Wilson N, Morton M, Homer T, Konkoth AB, Joyce R, Kershaw A, *et al.* A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis [published online ahead of print February 4 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GGCC1111

The available sample size and possible effects of the post-COVID-19 pandemic behaviours of patients suggests that caution should be used to extrapolate the future sample size calculations of such a trial; the observed exacerbation rates may not be representative in future trials. Future studies should consider the potential for using large disease specific registries and/or primary care databases to enhance recruitment opportunities and consider designs not solely based on hospital attendance for research visits.

Lessons learned

Several elements of this trial and its' challenges in delivery trial delivery are notable from this trial and may be useful for further studies. Significant variations in the screening process were observed across sites: this left some uncertainty on the eligible population. Some centres reported nearly 100% screening for potential eligibility to recruitment levels and others reported levels as low as 5%. This likely reflects differences between centres definitions of 'pre-screening', for example remote review of note compared to face-to-face screening where patients have had pre-screening and then face-to-face screening occurs. Adopting a consistent approach of how pre-screening and face-to-face screening are recorded across sites would be helpful to understand the feasibility in future studies and track the effect of any changes to the protocol.

Routes to improving recruitment were pursued during the course of the trial, including conducting database searches of the BronchUK registry (www.bronch.ac.uk) and the EMBARC European registry (www.bronchiectasis.eu). With filtering for UK-based patients recruited into EMBARC, this revealed from that 7700 patients with bronchiectasis over 600 had exacerbations and could be eligible for the trial and who had already indicated their consent to be contacted about further research studies. This database search was not available at the beginning of the trial, in part because the COVID-19 pandemic had meant the databases had not had curation, quality checks completed and access to the site containing the data. Future trials in this area (and other areas) may wish to build in early database searches and seek permissions from the national database holders. Alternatively, models such as recruiting through national primary care data linkages should be considered. A primary care search strategy was not built into the trial design at inception considering that most specialised bronchiectasis care particularly for those with ongoing exacerbations is secondary care-based, this again should be reconsidered in future trials.

Routes to improving recruitment also include leveraging PPI. We had strong PPI through workshops and discussions on patient information leaflets and advice on messaging of the trial. These gave the trial management team significant support, and we strongly recommend these for future studies. More recent areas to consider are using health forums/online communities such as HealthUnlocked (https://healthunlocked.com/newsfeed) to help raise awareness of the study for patients. Additionally, the NIHR support study dissemination via their volunteer registry Be Part of Research (https://bepartofresearch.nihr.ac.uk/) so clinicians and patients can be signposted to register interest.

One future option may well be to try and develop research study designs that can be delivered remotely or embedded within routine clinical care. The option for patients to have remote consent and undergo study procedures (such as complete questionnaires), either through telephone calls, via e-mail, mobile phone app or text-based messaging were all suggested as possibilities to boost recruitment to the trial, but these approaches were not within the funding of the study award. Future studies should discuss the importance of making certain elements of studies optional where permitted, for example, lung function testing to both patients and research sites. The study team had looked into this previously but felt the cost may have been too high at time of application. As these advances become more mainstream in clinical trials, the cost of these may drop then they can become more easily integrated into trials. Noting the older age population involved, PPI feedback made it clear that not all patients could contribute to trial designs that were solely electronic.

Research recommendations

The role of inhaled therapy with dual bronchodilators and/or triple inhaled therapy in bronchiectasis remains unclear and future trials conducted in a post-pandemic period should be considered.

The potential for, and acceptability of, remote trial delivery to be conducted and accepted into practice should be explored with both participants and guideline groups.

Specific discussions on future trial designs that may have open label, or no placebo arm, should be explored with stakeholders, such as participants and guideline groups.

Conclusions

This trial was prematurely terminated primarily because of slow recruitment. The trial suffered from multiple post-COVID-19 pandemic challenges. The patients who did consent into the trial had excellent retention rates and

a possible signal of efficacy of dual bronchodilators and triple therapy was observed, but no firm conclusions can be drawn.

Future studies are still required to understand the role of inhaled therapies in bronchiectasis.

Additional information

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Data-sharing statement

The deidentified data set from the trial will be prepared and stored by Newcastle University. Data sharing is subject to request providing detail of the purpose, analysis plan, results dissemination and authorship. If approved, data transfer is subject to completion of a Data-Sharing Agreement between Newcastle University and the requester. Data-sharing requests should be directed to anthony.de-soyza@ncl.ac.uk.

Ethics statement

The trial was given a favourable opinion by the UK NHS Research Authority's Northeast – Newcastle & North Tyneside 2

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Research Ethics Committee (reference: 21/NE/0020) on the 1 March 2021.

Information governance statement

The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) and Newcastle University are committed to processing personal information in accordance with the General Data Protection Regulation (EU GDPR) 2016/679 and UK Data Protection Act (2018). NuTH is the data controller, the Data Protection Officer (DPO) can be contacted by emailing nuth.dpo@nhs.net. Further information about how personal data are handled, how individuals can exercise their rights and details of the DPO are found here: www.newcastle-hospitals.nhs.uk/help/privacy/privacy-notice-for-patients/.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GGCC1111.

Primary conflicts of interest: Nina Wilson reports receiving grants from the NIHR. James Wason reports being funded by a NIHR Research Professorship (NIHR301614), being a member on NIHR HTA Clinical Evaluation and Trials Committee (2020–4) and selection panel Chair for NIHR Undergraduate Internship scheme (2024–current). Laura Ternent reports receiving grants from the NIHR. John Steer reports receiving grants from Chiesi Ltd Institution Research Grant, Astra Zeneca. James D Chalmers reports receiving grants from NIHR, AstraZeneca, Boehringer Ingelheim, GSK, Zambon, Insmed and Gilead, and receiving personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Zambon, Insmed, Novartis, Gilead and Cheisi. Adam T Hill reports being Chair of British Thoracic Society Standards of Care Committee. Charles S Haworth reports receiving grants from NIHR, receiving consulting fees and on advisory boards for 30 Technology, Astra Zeneca, CSL Behring, Chiesi, Infex, Insmed, Janssen, LifeArc, Meiji, Mylan, Pneumagen, Shionogi, Vertex and Zambon, receiving fees for advisory and educational work from Chiesi, Insmed, Mylan and Zambon, a board member for European Cystic Fibrosis Society and holding stock/stock option in Pneumagen. John R Hurst reports received grants from AstraZeneca, receiving consulting fees for advisory and educational work from AstraZeneca, Boehringer Ingleheim, Chiesi, GSK, Novartis and Sanofi. Anthony De-Soyza reports receiving grant awards from NIHR and grant support from Astra Zeneca, Chiesi and GSK, receiving speaker fees for bureau/advisory committee work from Astra Zeneca, Bayer, GSK, 30T pharmaceuticals and Insmed and NIHR committee membership (HTA CET Funding Committee HTA Post Funding (CET and GB) Programme Oversight Committee – 1 November 2017–31 December 2026, HTA Commissioning Funding Committee – 1 May 2020–30 September 2022, Prioritisation Committee B Membership – 1 March 2020–31 December 2027, HTA Programme Oversight Committee – 1 June 2020–1 October 2027).

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Publications

Morton M, Wilson N, Homer TM, Simms L, Steel A, Maier R, *et al.*, Dual bronchodilators in Bronchiectasis study (DIBS): protocol for a pragmatic, multicentre, placebo-controlled, three-arm, double-blinded, randomised controlled trial studying bronchodilators in preventing exacerbations of bronchiectasis. *BMJ Open* 2023;**13**:e071906. https://doi.org/10.1136/bmjopen-2023-071906

Wilson N, Morton M, Homer T, Konkoth AB, Joyce R, Kershaw A, *et al.* Dual Bronchodilators in Bronchiectasis Study (DIBS): a randomised controlled trial. *ERJ Open Research* 2025;**11**:01079-2024. https://doi.org/10.1183/23120541.01079-2024

Trial registration

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This synopsis provided an overview of the research award *Dual Bronchodilators in Bronchiectasis Study (DIBS)*. For other articles from this thread and for more information about this research, please view the award page [www.fundingawards.nihr.ac.uk/award/NIHR127460].

About this article

The contractual start date for this research was in July 2021. This article began editorial review in July 2024 and was accepted for publication in June 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' article and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

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List of abbreviations

AE	adverse event
BDI	Baseline Dyspnoea Index
BSI	Bronchiectasis Severity Index
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CT	computed tomography
DIBS	Dual Bronchodilators in Bronchiectasis Study
EMBARC	European Multicentre Bronchiectasis Audit and Research Collaboration
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
HCUQ	Health Care Utilisation Questionnaire
HTA	Health Technology Assessment
ICS	inhaled corticosteroid
IMP	investigational medicinal product
IQR	interquartile range
IRR	incident rate ratio
LABA	long-acting beta agonist
LAMA	long-acting muscarinic antagonist
LIP	Local Information Pack
MCID	minimum clinically important difference
MRCD	Medical Research Council Dyspnoea
NIHR	National Institute for Health and Care Research
ONS	Office for National Statistics
PPI	patient and public involvement
PSS	Personal Social Services
QALY	quality-adjusted life-year
QoL-B	Quality of Life Bronchiectasis
SAE	serious adverse event
SAR	serious adverse reaction
SGRQ	St Georges Respiratory questionnaire
TDI	Transition Dyspnoea Index
TSC	Trial Steering Committee
VAS	visual analogue scale

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1 Morton M, Wilson N, Homer TM, Simms L, Steel A, Maier R, *et al*. Dual Bronchodilators in Bronchiectasis Study (DIBS): protocol for a pragmatic, multicentre, placebo-controlled, three-arm, double-blinded, randomised controlled trial studying bronchodilators in preventing exacerbations of bronchiectasis. *Br Med J Open* 2023;**13**:e071906.

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Appendix 1 Trial design

Inclusion and exclusion criteria

Inclusion criteria

Patients are eligible for the trial if all of the following apply:

1. Adult patients with CT scans that confirmed bronchiectasis is the predominant primary respiratory disease in the view of the investigator (CT images/CT reports must be available to complete radiological scoring for BSI).
2. History of two or more exacerbations in any 12-month period in the preceding 2 years requiring antibiotics and/or steroids.
3. Evidence of airflow limitation with an FEV1/FVC ratio < 0.7 and/or daily mucus expectoration.
4. Have either:
   a. < 20 pack-year history of smoking
   or
   b. > 20 pack-year history of smoking with an FEV1 > 79% predicted (to exclude COPD).
5. For patients taking ICS, LAMA or LABA treatment prior to recruitment, they are willing to have these treatments changed or stopped.
6. Stable bronchiectasis with no exacerbations for 4 weeks prior to baseline.
7. Stable dose of oral steroid for 4 weeks prior to baseline (only applicable for patients taking oral steroid as part of standard care).

Exclusion criteria

Patients are excluded from the trial if any of the following apply:

1. Cystic fibrosis-related bronchiectasis.
2. Where bronchiectasis is not the main disease or there are contraindications to ICS withdrawal.
3. Predominant COPD or asthma [Patients who have a historical diagnosis of asthma and/or COPD, but where the investigator has sufficient evidence to refute, these diagnoses can still be included. This is to be documented in the source documentation (i.e. patient medical records) and the CRF.].
4. Indication to remain on ICS (e.g. asthma, COPD, allergic bronchopulmonary aspergillosis and inflammatory bowel disease) or known intolerance to any of the trial drugs or their ingredients.
5. Patients with galactose intolerance, total lactase deficiency or glucose–galactose malabsorption.
6. Inability to perform spirometry or quality-of-life questionnaires.
7. Patients who are:
   a. pregnant
   b. breastfeeding
   c. of childbearing potential with a positive urine pregnancy test prior to starting trial IMP
   d. male or female of childbearing potential unwilling to use contraception throughout the trial (postmenopausal women must be amenorrhoeic for at least 12 months to be considered for non-childbearing potential).
8. Anyone with cognitive impairment who may not be able to consent.
9. Those who do not speak English or cannot comply with trial procedures.
10. Any potential participant who the investigator believes will not be able to complete the trial visits and procedures.
11. A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, β2-agonist, lactose/milk protein or magnesium stearate or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the investigator, contraindicates trial participation.
12. Use of acute antibiotics or systemic steroids within 4 weeks of baseline (except for antibiotics and/or stable doses of prednisone ≤ 5 mg used to treat non-respiratory conditions).
13. Malignancy diagnosed within 5 years of the first trial medication administration where the investigator feels the trial may be affected by recurrence or progression of the malignancy (e.g. patients with stable breast cancer, current prostate cancer or 'expected curative' cancer surgery may not be excluded at the investigator's discretion).
14. Administration of an investigational agent within 30 days of the first dose of trial medication.

BOX 1 Amendments to eligibility criteria during the trial

- Exclusion criterion number 12 updated for clarity.
- Inclusion criterion number 2 updated to allow inclusion of patients experiencing two or more exacerbations within 12 months of each other in any 2-year period in the preceding 2 years.
- Statistics section updated to include updated calculations accounting for the change in inclusion criterion number 2.
- Expansion of inclusion criterion number 4 (aimed at excluding patients with likely COPD) to allow patients with > 20 pack-year history of smoking to enter the trial if there are no spirometric indications of COPD, i.e. an FEV1 > 79% predicted.
- Exclusion criterion number 13 updated to enable patients with stable cancers to be included in the trial.

In the two scenarios, we assumed that the placebo exacerbation rate would be an average of 1.9 per year. We recalculated the power for two scenarios: (1) assuming the same absolute difference (0.5) between LAMA/LABA versus placebo and the same non-inferiority margin (0.38) as previously and (2) the same relative difference (21%) between LAMA/LABA versus placebo and relative non-inferiority margin (20%) as before.

TABLE 5 The power of the trial to conclude non-inferiority (NI) and superiority under two scenarios compared to the original calculation sample size calculation of 600 participants

	Mean exacerbation rate				Power[a]	
Scenario	Placebo	ICS/LAMA/LABA (intervention)	LAMA/LABA (active control)	NI margin (relative to active control)	Non-inferiority	Superiority
Presented in original grant application	2.4	1.9	1.9	0.38 (20%)	90.3%	89.8%
Updated inclusion criteria (same absolute differences)	1.9	1.4	1.4	0.38 (26.7%)	96.3%	95.8%
Updated inclusion criteria (same relative differences)	1.9	1.5	1.5	0.3 (20%)	83.4%	83.4%

a Note this is assuming analytical formulae, with simulations giving consistent but slightly higher powers.

Source

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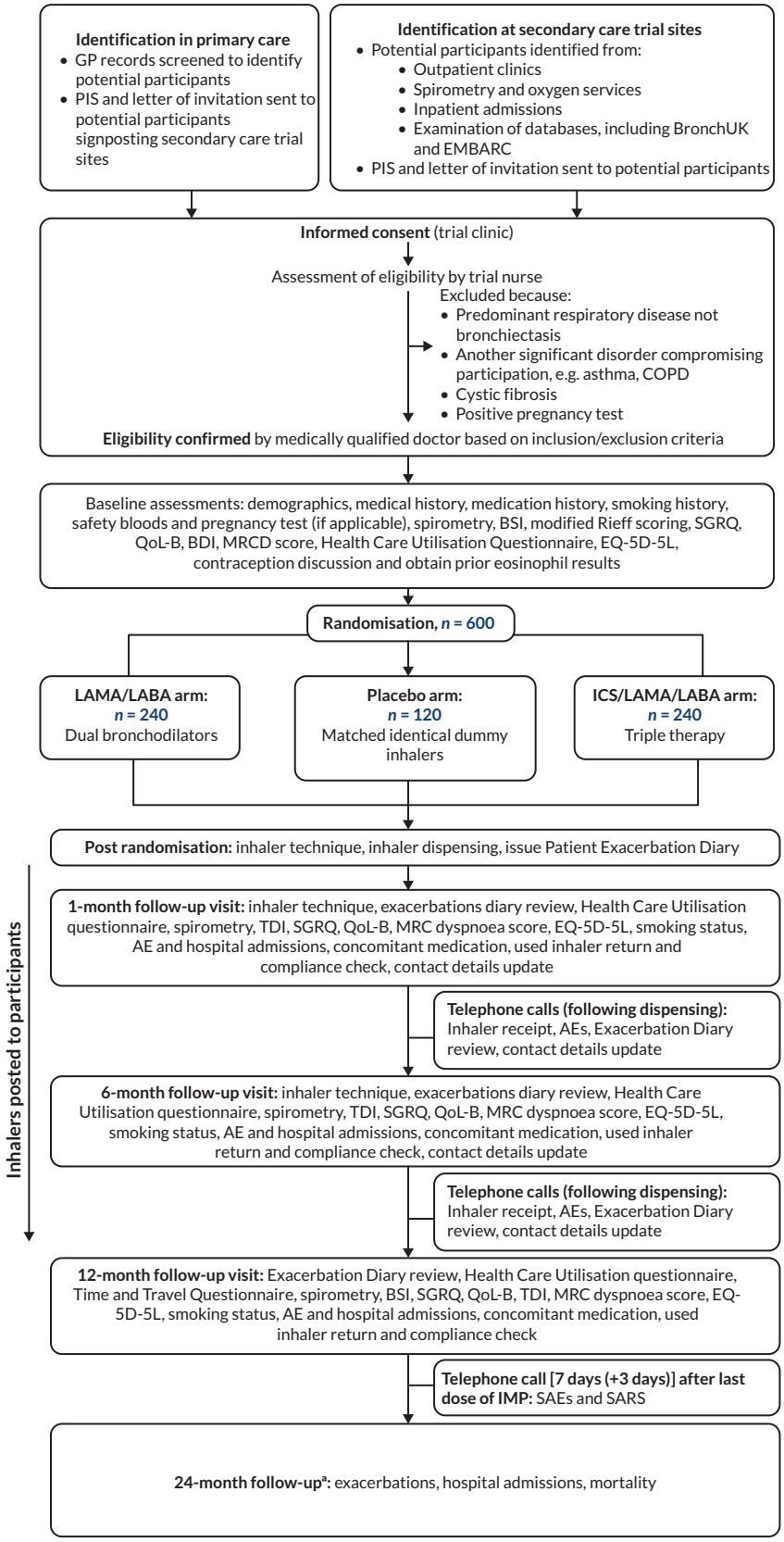

FIGURE 5 Trial flow chart. GP, general practitioner; HES, Hospital Episode Statistics; PIS, patient information sheet; SAR, serious adverse reaction. a, Required only if the participant reaches this time point within the lifetime of the trial. Follow-up is via review of medical records, BronchUK and EMBARC requests or ONS/HES requests. Participants will not attend a visit/receive a telephone call for this follow-up.

Appendix 2 Compliance

The participants in this trial were randomised in a 2 : 2 : 1 ratio to receive either dual therapy dry powder inhaler, triple therapy dry powder inhaler or matched placebo dry powder inhaler. Participants took dose (one inhalation) of the IMP they have been randomised to once a day for the 12-month (365 days total) treatment period. No dose modifications were allowed. The quantity of product within each inhaler allowed for 30 doses, and participants were expected to use all doses within the inhaler before starting a new inhaler. A total of 13 inhalers were required by each participant for the 12-month (365 days total) treatment period.

The number of doses taken were calculated as 30*(number of returned inhalers)-total doses left.

For each individual participant, the potential treatment duration (i.e. the number of days the participant could have potentially taken the IMP) was calculated from randomisation until the date of their last visit (when they last return IMP) or the date of withdrawal or death if treatment was discontinued early. This duration is summarised as the median, IQR and range in each randomised group.

Compliance with the IMP dosing protocol was calculated as 100*(number of doses taken)/(potential treatment duration) and is summarised in each randomised group by the median, IQR and range and also tabulated as a binary variable; compliance < 75% and compliance ≥ 75%. If participants did not return inhalers at all visits, we adjusted the potential treatment time to reflect this, for example, if a participant returned inhalers at 6 months but not 12 months, we calculated their adherence over the 6 months only. However, if participants returned inhalers at the 12-month visit but had not returned all inhalers, we assumed the inhalers were unused.

Time in study was defined from randomisation until the last study visit completed or date of death/complete withdrawal. Note that for those who continued to follow-up but discontinued treatment, this is from randomisation until date of last follow-up or death.

The number of patients who received some treatment and the number who discontinued prematurely is reported.

TABLE 6 Summary of allocated treatment received

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
N	14	12	7	33
Received at least one dose of allocated treatment	14 (100.0%)	12 (100.0%)	7 (100.0%)	33 (100.0%)
Treatment compliance while on treatment (%)[a]				
Median (IQR)	94.6 (84.1–98.7)	95.2 (75.0–99.1)	97.8 (86.0–100.0)	95.6 (83.3–99.5)
Range	(55.5–100.0)	(46.6–100.0)	(32.8–100.0)	(32.8–100.0)
n	(*n* = 13)	(*n* = 12)	(*n* = 6)	(*n* = 31)
Treatment compliance while on treatment,[a] ***n (%)***				
< 75%	2 (15.4%)	3 (25.0%)	1 (16.7%)	6 (19.4%)
75–100%	11 (84.6%)	9 (75.0%)	5 (83.3%)	25 (80.7%)
Discontinued treatment prematurely	1 (7.1%)	2 (16.7%)	2 (28.6%)	5 (15.2%)
Reason				
Intolerable side effects	1	1	1	3
Other	0	1^	1$	2^$

continued

TABLE 6 Summary of allocated treatment received (continued)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Participant withdrawal	1 (7.1%)	1 (8.3%)	1 (14.3%)	3 (9.1%)
Reason				
Unacceptable side effects	0	1	0	1
Personal circumstances	1	0	0	1
Inhaler not giving relief	0	0	1	1
Investigator withdrawal	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Duration of treatment (months)[b]				
Median (IQR)	12.0 (11.9–12.2)	12.0 (9.6–12.3)	12.0 (2.5–12.0)	12.0 (11.7–12.2)
Range	(3.2–12.5)	(0.8–12.7)	(0.0–12.2)	(0.3–12.7)

TABLE 7 Summary of time in study per participant

	Dual therapy (LAMA/LABA) (*n* = 14)	Triple therapy (ICS/LAMA/LABA) (*n* = 12)	Placebo (*n* = 7)	Total (*n* = 33)
Time in study per participant (months)[a]				
Mean (SD)	11.8 (1.1)	11.7 (1.7)	10.7 (3.6)	11.5 (2.0)
Median (IQR)	12.0 (11.9–12.2)	12.1 (12.0–12.4)	12.0 (12.0–12.1)	12.0 (12.0–12.2)
Range	(8.1–12.5)	(6.3–12.7)	(2.5–12.2)	(2.5–12.7)
Categorical time in study per participant (months) (%)[b]				
< 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 1, < 6	0 (0.0%)	1 (8.3%)	1 (14.3%)	2 (%)
≥ 6, < 12	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (%)
12	13 (9.3%)	11 (91.7%)	6 (85.7%)	30 (%)

a Calculated based on time from randomisation to 12-month visit or withdrawal date.
b Calculated based on attendance at 1-, 6- and 12-month study visits.

Appendix 3 Results

TABLE 8 Summary of screening and recruitment by site

Site	Time open for recruitment (in months)	Number screened for potential eligibility (NS)	Number of participants potentially eligible screened (PE) (% of NS)	Number of participants declined (% of PE)	Number of participants ineligible-failed at screening (% of PE)	Number randomised (% of PE)	Recruitment per site-month
1	14.8	14	14 (100.0%)	0 (0.0%)	0 (0.0%)	14 (100%)	0.9
2	12.0	60	54 (90.0%)	26 (48.2%)	23 (42.6%)	5 (9.3%)	0.4
3	12.0	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100%)	0.1
4	11.1	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100%)	0.1
5	10.4	4	4 (100.0%)	0 (0.0%)	0 (0.0%)	4 (100%)	0.4
6	10.6	0	–	–	–	–	–
7	10.1	6	6 (100.0%)	0 (0.0%)	3 (50.0%)	3 (50.0%)	0.3
8	7.5	0	–	–	–	–	–
9	7.3	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100%)	0.1
10	6.7	0	–	–	–	–	–
11	6.9	3	3 (100.0%)	0 (0.0%)	0 (0.0%)	3 (100%)	0.4
12	3.6	0	–	–	–	–	–
13	2.0	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100%)	0.5
Total	111.4	91	85	26 (30.6%)	26 (30.6%)	33 (38.8%)	0.3

TABLE 9 Summary by reasons participants were not recruited

Failed screening, *n*	**26**
Reason given, *n*	**23**
Main reason for declining/not entering the trial for those who failed screening, n (%)	
A3. Bronchiectasis is not the predominant primary respiratory disease in the view of the investigator	4 (17%)
A4. < 2 exacerbations in any 12-month period in the preceding 2 years requiring antibiotics and/or steroids	1 (4%)
A5. No evidence of airflow limitation with an FEV1/FVC ratio < 0.7 and/or daily mucus expectoration	1 (4%)
A7. Unwilling to change or stop ICS, LAMA or LABA treatment prior to recruitment	3 (13%)
A8. Has unstable bronchiectasis	1 (4%)
A11. Predominant COPD or asthma (does not include patients with historical diagnosis of asthma and/or COPD where investigators have sufficient evidence to refute these diagnoses)	4 (17%)
A12. Contraindications to ICS withdrawal	3 (13%)
A15. Patient is pregnant, breastfeeding, of childbearing potential with a positive urine pregnancy test prior to starting trial IMP, male or female of childbearing potential but unwilling to use contraception throughout the trial	2 (9%)
A18. Cannot comply with trial procedures	1 (4%)
A19. Investigator believes patient will not be able to complete the study visits and procedures	1 (4%)

continued

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TABLE 9 Summary by reasons participants were not recruited (continued)

A21. Use of acute antibiotics or systemic steroids within 4 weeks of baseline	1 (4%)
B7. Other, please give details if provided	1 (4%)
Reason missing	9
If other reason, please enter details	
Airflow obstruction	1 (100%)
Declined trial, *n*	**26**
Reason given, *n*	**26**
Main reason for declining/not entering the trial for those that declined, n (%)	
A18. Cannot comply with trial procedures	1 (4%)
B4. Not willing to be on a placebo inhaler	1 (4%)
B5. Trial is too time-consuming	8 (31%)
B6. No reason given	3 (12%)
B7. Other, please give details if provided	13 (50%)
Reason missing	0
If other reason, please enter details	
Bronchiectasis diagnosis of 12 months. Patient would like to establish current treatment first	1 (8%)
Declined due potential side effect – dry mouth and unable to commit to study schedule	1 (8%)
Dislikes inhalers	2 (15%)
Not interested in research	5 (38%)
Patient has previously tried inhalers, found them to be of no benefit	1 (8%)
Patient is concerned about trial medication, as she has allergies, therefore declined	1 (8%)
Patient is going aboard to commence active treatment	1 (8%)
Wants to minimise face-to-face appointments	1 (8%)

TABLE 10 Missing data

		Baseline			1-month follow-up			6-month follow-up			12-month follow-up		
		Dual (*n* = 14)	Triple (*n* = 12)	Placebo (*n* = 7)	Dual (*n* = 14)	Triple (*n* = 12)	Placebo (*n* = 7)	Dual (*n* = 14)	Triple (*n* = 11)	Placebo (*n* = 6)	Dual (*n* = 13)	Triple (*n* = 11)	Placebo (*n* = 6)
MRCD		–	–	–	–	–	–	–	–	–	–	–	–
BDI (baseline), TDI (1, 6, 12 months)	Functional Impairment	–	1 (8.3%)	1 (14.3%)	–	–	–	–	–	–	1 (7.7%)	1 (9.1%)	–
	Magnitude of task	–	2 (16.7%)	1 (14.3%)	–	–	–	1 (7.1%)	–	–	1 (7.7%)	1 (9.1%)	–
	Magnitude of effort	1 (7.1%)	2 (16.7%)	1 (14.3%)	–	–	–	–	–	–	1 (7.7%)	1 (9.1%)	–
	BDI/TDI	1 (7.1%)	2 (16.7%)	1 (14.3%)	–	–	–	1 (7.1%)	–	–	1 (7.7%)	1 (9.1%)	–
QoL-B	Physical functioning	–	–	–	–	–	–	–	–	–	–	-	–
	Role functioning	–	–	–	–	–	–	–	–	–	–	-	–
	Vitality	–	–	–	–	–	–	–	–	–	–	-	–
	Emotional functioning	–	–	–	–	–	–	–	–	–	–	-	–
	Social functioning	–	–	–	–	–	–	–	–	–	–	-	–
	Treatment burden	8 (57.1%)	4 (33.3%)	3 (42.9%)	3 (21.4%)	2 (16.7%)	1 (14.3%)	5 (35.7%)	1 (9.1%)	1 (16.7%)	5 (38.5%)	3 (27.3%)	2 (33.3%)
	Health perceptions	–	–	–	–	–	–	–	–	–	-	-	-
	Respiratory symptoms	–	–	–	–	–	–	–	–	–	-	-	-
SGRQ	Symptoms score	–	–	–	–	–	–	–	–	–	-	-	-
	Activities score	–	–	1 (14.3%)	–	–	–	–	–	–	1 (7.7%)	-	-
	Impacts score	–	–	–	–	–	–	–	–	–	-	-	-
	Total SGRQ score	–	–	1 (14.3%)	–	–	–	–	–	–	1 (7.7%)	-	-
FEV1		1 (7.1%)	–	–	1 (7.1%)	–	–	–	–	–	-	-	1 (16.7%)
FVC		1 (7.1%)	–	–	1 (7.1%)	–	–	–	–	–	-	-	1 (16.7%)

Note
Figures presented as *n (%)*.

This synopsis should be referenced as follows: Wilson N, Morton M, Homer T, Konkoth AB, Joyce R, Kershaw A, *et al.* A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis [published online ahead of print February 4 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GGCC1111

TABLE 11 Additional baseline characteristics

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
N	14	12	7	33
Medical history				
Has the participant been diagnosed with any of the following?				
Asthma (refuted past diagnosis)				
Yes	2 (14%)	0 (0%)	0 (0%)	2 (6%)
No	12 (86%)	12 (100%)	7 (100%)	31 (94%)
Nasal polyps				
Yes	1 (7%)	2 (17%)	2 (29%)	5 (15%)
No	13 (93%)	10 (83%)	5 (71%)	28 (85%)
COPD (refuted past diagnosis)				
Yes	0 (0%)	0 (0%)	1 (14%)	1 (3%)
No	14 (100%)	12 (100%)	6 (86%)	32 (97%)
Rhinosinusitis				
Yes	5 (36%)	4 (33%)	3 (43%)	12 (36%)
No	9 (64%)	8 (67%)	4 (57%)	21 (64%)
Angina				
Yes	3 (21%)	0 (0%)	1 (14%)	4 (12%)
No	11 (79%)	12 (100%)	6 (86%)	29 (88%)
Atrial fibrillation				
Yes	1 (7%)	0 (0%)	0 (0%)	1 (3%)
No	13 (93%)	12 (100%)	7 (100%)	32 (97%)
Myocardial infarction				
Yes	1 (7%)	0 (0%)	1 (14%)	2 (6%)
No	13 (93%)	12 (100%)	6 (86%)	31 (94%)
Cardiac failure				
Yes	1 (7%)	0 (0%)	0 (0%)	1 (3%)
No	13 (93%)	12 (100%)	7 (100%)	32 (97%)
Liver cirrhosis				
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No	14 (100%)	12 (100%)	7 (100%)	33 (100%)
Osteoporosis				
Yes	6 (43%)	2 (17%)	0 (0%)	8 (24%)
No	8 (57%)	10 (83%)	7 (100%)	25 (76%)
Anxiety				
Yes	2 (14%)	3 (25%)	0 (0%)	5 (15%)
No	12 (86%)	9 (75%)	7 (100%)	28 (85%)

TABLE 11 Additional baseline characteristics (continued)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Depression				
Yes	4 (29%)	1 (8%)	0 (0%)	5 (15%)
No	10 (71%)	11 (92%)	7 (100%)	28 (85%)
Chronic renal failure				
Yes	0 (0%)	0 (0%)	1 (14%)	1 (3%)
No	14 (100%)	12 (100%)	6 (86%)	32 (97%)
eGFR > 90 ml/min/1.73 m^2	6 (43%)	5 (42%)	2 (29%)	20 (61%)
eGFR ≤ 90 ml/min/1.73 m^2	8 (57%)	7 (58%)	5 (71%)	13 (39%)
If eGFR ≤ 90 ml/min/1.73 m^2:				
Median (IQR)	67 (56–80)	68 (60–74)	74.5 (51–78)	69.5 (60–77)
Mean (SD)	68.0 (14.6)	66.7 (7.8)	64.5 (24.5)	66.7 (14.3)
Range	(44–85)	(57–77)	(28–81)	(28–85)
	(*n* = 7)	(*n* = 7)	(*n* = 4)	(*n* = 18)
Diabetes				
Yes	1 (7%)	0 (0%)	2 (29%)	3 (9%)
No	13 (93%)	12 (100%)	5 (71%)	30 (91%)
Has the participant had any of the following cancers?				
Lung cancer				
Yes	1 (7%)	0 (0%)	0 (0%)	1 (3%)
No	13 (93%)	12 (100%)	7 (100%)	32 (97%)
Haematological malignancy				
Yes	0 (0%)	0 (0%)	1 (14%)	1 (3%)
No	14 (100%)	12 (100%)	6 (86%)	32 (97%)
Other solid tumours				
Yes	0 (0%)	0 (0%)	2 (29%)	2 (6%)
No	14 (100%)	12 (100%)	5 (71%)	31 (94%)
Surgical interventions for bronchiectasis (previous and planned)				
Lobectomy				
Yes	2 (14%)	4 (33%)	0 (0%)	6 (18%)
No	12 (86%)	8 (67%)	7 (100%)	27 (82%)
Completed pulmonary rehab				
In the last 12 months	0 (0%)	1 (8%)	1 (14%)	2 (6%)
Ever	2 (14%)	4 (33%)	2 (29%)	8 (24%)
Never	12 (86%)	7 (58%)	4 (57%)	23 (70%)

continued

This synopsis should be referenced as follows:
Wilson N, Morton M, Homer T, Konkoth AB, Joyce R, Kershaw A, *et al.* A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis [published online ahead of print February 4 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GGCC1111

TABLE 11 Additional baseline characteristics (continued)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Physiotherapy training				
Yes	10 (71%)	8 (67%)	5 (71%)	23 (70%)
No	4 (29%)	4 (33%)	2 (29%)	10 (30%)
Current physio regimen				
Infrequent physio	0 (0%)	1 (8%)	0 (0%)	1 (3%)
No regular physio	4 (31%)	5 (42%)	2 (29%)	11 (34%)
Regular physio with active cycle	4 (31%)	5 (42%)	5 (71%)	14 (44%)
Regular physio with active cycle and device	5 (38%) (*n* = 13)	1 (8%)	0 (0%)	6 (19%) (*n* = 32)
Has the participant received influenza vaccination in the past year?				
Yes	11 (79%)	12 (100%)	5 (83%)	28 (88%)
No	3 (21%)	0 (0%)	1 (17%)	4 (12%)
			(*n* = 6)	(*n* = 32)
Has the participant received Pneumococcal polysaccharide vaccination?				
Yes	12 (86%)	11 (92%)	4 (67%)	27 (84%)
No	2 (14%)	1 (8%)	2 (33%)	5 (16%)
			(*n* = 6)	(*n* = 32)
Has the participant received COVID-19 vaccination?				
Yes	14 (100%)	12 (100%)	7 (100%)	33 (100%)
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Smoking history				
Ex-smoker	3 (21%)	2 (17%)	5 (71%)	10 (30%)
Never smoked	11 (79%)	10 (83%)	2 (29%)	23 (70%)
Smoking exposure in pack years				
Median (IQR)	0 (0–3)	0 (0–0)	1 (1–13)	0 (0–2.5)
Mean (SD)	2.4 (4.1)	1.3 (3.3)	6.4 (8.0)	2.8 (5.0)
Range	(0–10)	(0–10)	(0–17)	(0–17)
	(*n* = 10)	(*n* = 9)	(*n* = 5)	(*n* = 24)
Questionnaires, indices and scores				
BDI (score 0–12)				
Median (IQR)	7 (4–8)	7 (6–11)	8.5 (6–10)	7 (6–9)
Mean (SD)	6.1 (2.3)	8.2 (2.5)	7.7 (3.8)	7.1 (2.8)
Range	(2–10)	(6–12)	(1–12)	(1–12)
	(*n* = 13)	(*n* = 10)	(*n* = 6)	(*n* = 29)

TABLE 11 Additional baseline characteristics (continued)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Baseline functional impairment (score 0–4)				
Median (IQR)	3 (2–3)	3 (2–4)	3 (3–4)	3 (2–4)
Mean (SD)	2.4 (0.9)	3.1 (0.9)	2.8 (1.5)	2.7 (1.1)
Range	(1–4)	(2–4)	(0–4)	(0–4)
		(*n* = 11)	(*n* = 6)	(*n* = 31)
Baseline magnitude of task (score 0–4)				
Median (IQR)	2 (1–2)	2 (2–4)	2.5 (2–3)	2 (2–3)
Mean (SD)	1.6 (0.7)	2.7 (0.9)	2.5 (1.0)	2.2 (1.0)
Range	(0–3)	(2–4)	(1–4)	(0–4)
		(*n* = 10)	(*n* = 6)	(*n* = 30)
Baseline magnitude of effort (score 0–4)				
Median (IQR)	2 (1–3)	2 (2–3)	3 (1–3)	2 (2–3)
Mean (SD)	2.0 (1.0)	2.5 (0.7)	2.3 (1.5)	2.2 (1.0)
Range	(1–4)	(2–4)	(0–4)	(0–4)
	(*n* = 13)	(*n* = 10)	(*n* = 6)	(*n* = 29)
SGRQ				
Symptoms score				
Median (IQR)	64.4 (57.9–77.1)	66.2 (30.2–83.7)	74.7 (21.2–81.9)	64.9 (56.9–81.2)
Mean (SD)	66.1 (11.2)	57.9 (30.2)	59.2 (29.3)	61.6 (23.3)
Range	(45.5–83.9)	(9.5–95.2)	(17.3–85.1)	(9.5–95.2)
Activities score				
Median (IQR)	63.2 (53.5–92.5)	50.6 (14.3–66.3)	57.3 (17.9–87.0)	59.5 (32.3–76.0)
Mean (SD)	64.5 (24.3)	41.6 (28.8)	54.9 (32.4)	54.1 (28.6)
Range	(18.5–93.4)	(0.0–79.7)	(17.4–92.5)	(0.0–93.4)
			(*n* = 6)	(*n* = 32)
Impacts score				
Median (IQR)	33.1 (20.4–49.6)	29.0 (8.6–44.3)	26.6 (9.5–62.1)	30.1 (18.8–48.2)
Mean (SD)	36.5 (18.0)	28.0 (17.5)	35.4 (24.5)	33.2 (19.1)
Range	(14.6–69.2)	(4.2–53.2)	(7.4–65.6)	(4.2–69.2)
Total SGRQ score				
Median (IQR)	46.8 (33.9–68.3)	42.8 (16.5–57.6)	50.7 (13.2–73.5)	42.8 (29.2–59.2)
Mean (SD)	49.8 (17.1)	37.1 (20.8)	46.2 (28.6)	44.4 (21.0)
Range	(28.5–79.0)	(6.8–64.1)	(12.9–76.5)	(6.8 79.0)
			(*n* = 6)	(*n* = 32)
Baseline bloods				
Haemoglobin (g/dl)				
Median (IQR)	14.0 (13.3–14.3)	13.6 (12.7–14.5)	14.0 (12.3–15.0)	14.0 (13.0–14.3)

continued

TABLE 11 Additional baseline characteristics (continued)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Mean (SD)	13.8 (0.8)	13.6 (1.5)	13.9 (1.4)	13.7 (1.2)
Range	(12.4–14.9)	(10.9–16.5)	(12.3–16.2)	(10.9–16.5)
	(*n* = 13)			(*n* = 32)
White blood cell count (×10⁹/l)				
Median (IQR)	7.4 (6.1–8.7)	8.4 (6.4–9.3)	7.3 (5.1–8.7)	7.7 (6.4–9.1)
Mean (SD)	7.9 (2.8)	8.2 (1.6)	7.3 (2.2)	7.9 (2.2)
Range	(4.3–13.8)	(5.6–10.5)	(4.7–10.5)	(4.3–13.8)
	(*n* = 13)	(*n* = 11)	(*n* = 6)	(*n* = 30)
Platelets count (×10⁹/l)				
Median (IQR)	240 (227–323)	276.5 (229–303.5)	245 (171–414)	253 (217.5–317.5)
Mean (SD)	264.2 (64.7)	267.1 (45.0)	282.3 (118.5)	269.2 (71.5)
Range	(171–377)	(201–338)	(164–417)	(164–417)
	(*n* = 13)			(*n* = 32)
Red blood cell count (×10¹²/l)				
Median (IQR)	4.5 (4.3–4.8)	4.5 (3.9–4.8)	4.6 (4.3–4.8)	4.5 (4.2–4.8)
Mean (SD)	4.5 (0.4)	4.5 (0.5)	4.6 (0.3)	4.5 (0.4)
Range	(3.7–5.4)	(3.9–5.3)	(4.2–4.9)	(3.7–5.4)
	(*n* = 13)	(*n* = 11)		(*n* = 31)
Neutrophils (×109/l)				
Median (IQR)	4.4 (3.6–5.5)	5.2 (3.7–6.8)	4.9 (3.4–6.8)	5.0 (3.7–6.7)
Mean (SD)	4.6 (1.4)	5.2 (1.6)	4.8 (1.6)	4.9 (1.5)
Range	(2.8–7.5)	(3.0–7.5)	(2.8–6.8)	(2.8–7.5)
	(*n* = 12)			(*n* = 31)
Lymphocytes (×10⁹/l)				
Median (IQR)	1.6 (1.4–2.2)	2.1 (1.7–2.3)	1.6 (1.2–1.8)	1.8 (1.5–2.2)
Mean (SD)	1.9 (0.9)	2.0 (0.4)	1.5 (0.4)	1.9 (0.7)
Range	(0.4–3.9)	(1.5–2.6)	(0.9–2.0)	(0.4–3.9)
	(*n* = 13)			(*n* = 32)
Monocytes (×10⁹/l)				
Median (IQR)	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.5 (0.4–0.7)	0.6 (0.5–0.7)
Mean (SD)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)
Range	(0.2–1.1)	(0.3–1.0)	(0.4–1.0)	(0.2–1.1)
	(*n* = 13)			(*n* = 32)
Eosinophils [×10⁹/l (or ×10³/μl)]				
Median (IQR)	0.18 (0.10–0.28)	0.13 (0.10–0.25)	0.16 (0.13–0.25)	0.16 (0.10–0.27)
Mean (SD)	0.22 (0.18)	0.18 (0.10)	0.2 (0.2)	0.20 (0.15)
Range	(0.05–0.65)	(0.08–0.37)	(0.02–0.60)	(0.02–0.65)
	(*n* = 13)			(*n* = 32)

TABLE 11 Additional baseline characteristics (continued)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Eosinophils %				
Median (IQR)	2.2 (2.0–2.4)	1.7 (1.2–3.0)	3.4 (3.4–3.4)	2.0 (1.4–3.4)
Mean (SD)	2.2 (0.3)	2.1 (1.3)	3.4 (0.0)	2.3 (1.1)
Range	(2.0–2.4)	(1.0–4.0)	(3.4–3.4)	(1.0–4.0)
	(*n* = 2)	(*n* = 4)	(*n* = 1)	(*n* = 7)
Basophils (×10^9/l)				
Median (IQR)	0.04 (0.3–0.08)	0.07 (0.05–0.10)	0.06 (0.00–0.07)	0.06 (0.04–0.08)
Mean (SD)	0.05 (0.03)	0.07 (0.03)	0.05 (0.04)	0.06 (0.03)
Range	(0.00–0.10)	(0.03–0.10)	(0.00–0.10)	(0.00–0.10)
	(*n* = 13)			(*n* = 32)

eGFR, estimated glomerular filtration rate.

Note
Data are *n*; %, mean (SD) or median (IQR); range, unless otherwise stated. (*n* =) is only given for where there are missing data.

TABLE 12 Summary of change from baseline for FEV1, FVC, SGRQ and QoL-B

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
1 month	*N*	14	12	7	33
	FEV1				
	Median (IQR)	0.18 (−0.02 to 0.24)	0.16 (0.0–0.27)	−0.07 (−0.18 to −0.03)	0.12 (−0.07 to 0.21)
	Mean (SD)	0.07 (0.35)	0.13 (0.18)	−0.08 (0.11)	0.06 (0.26)
	Range	(−0.87 to 0.49)	(−0.16 to 0.4)	(−0.25 to 0.09)	(−0.87 to 0.49)
		(*n* = 13)			(*n* = 32)
	FVC				
	Median (IQR)	0.17 (0.04–0.24)	0.10 (−0.07 to 0.28)	−0.16 (−0.24 to 0.21)	0.1 (−0.10 to 0.25)
	Mean (SD)	0.15 (0.25)	0.14 (0.28)	−0.04 (0.28)	0.11 (0.27)
	Range	(−0.28 to 0.73)	(−0.21 to 0.84)	(0.36–0.41)	(−0.36 to 0.84)
		(*n* = 13)			(*n* = 32)
	SGRQ				
	Median (IQR)	0.79 (−10.4 to 4.1)	−4.2 (−8.6 to 0.49)	−2.9 (−5.9 to 0.05)	−1.5 (−8.2 to 2.5)
	Mean (SD)	−1.4 (10.9)	−3.5 (6.9)	−1.6 (6.1)	−2.2 (8.6)
	Range	(−22.3 to 19.0)	(−12.1 to 11.8)	(−7.5 to 9.4)	(−22.3 to 19.0)
				(*n* = 6)	(*n* = 32)

continued

This synopsis should be referenced as follows:
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TABLE 12 Summary of change from baseline for FEV1, FVC, SGRQ and QoL-B (continued)

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
QoL-B, median (IQR), mean (SD), range	Physical functioning				
	Median (IQR)	−3.3 (−13.3 to 6.7)	0.0 (−3.3 to 6.7)	−6.7 (−6.7 to 0)	0.0 (−6.7 to 6.7)
	Mean (SD)	−2.8 (13.8)	−2.2 (14.0)	−5.5 (8.1)	−3.2 (12.6)
	Range	(−33.3 to 20.0)	(−33.3 to 13.3)	(−20.0 to 6.7)	(−33.3 to 20.0)
	Role functioning				
	Median (IQR)	3.3 (0.0–6.7)	−6.7 (16.7–0.0)	0.0 (−3.3 to 6.7)	0.0 (−6.7 to 6.7)
	Mean (SD)	3.8 (11.0)	−6.1 (10.8)	−1.4 (9.0)	−0.9 (11.2)
	Range	(−13.3 to 33.3)	(−20.0 to 13.3)	(−20.0 to 6.7)	(−20.0 to 33.3)
	Vitality				
	Median (IQR)	0.0 (−11.1 to 11.1)	−5.6 (−11.1 to 0)	0.0 (−11.1 to 11.1)	0.0 (−11.1 to 0.0)
	Mean (SD)	0.0 (15.1)	−6.5 (11.1)	1.6 (15.0)	−2.0 (13.7)
	Range	(−22.2 to 22.2)	(−33.3 to 11.1)	(−22.2 to 22.2)	(−33.3 to 22.2)
	Emotional functioning				
	Median (IQR)	0.0 (−8.3 to 8.3)	0.0 (−12.5 to 8.3)	0.0 (−8.3 to 8.3)	0.0 (−8.3 to 8.3)
	Mean (SD)	−2.4 (14.0)	−8.3 (25.9)	−1.2 (7.5)	−4.3 (18.1)
	Range	(−41.7 to 16.7)	(−83.3 to 8.3)	(−8.3 to 8.3)	(−83.3 to 16.7)
	Social functioning				
	Median (IQR)	8.3 (0.0–13.9)	0.0 (−8.3 to 13.9)	8.3 (0.0–25.0)	8.3 (0.0–13.9)
	Mean (SD)	8.1 (11.6)	3.0 (13.2)	9.5 (14.8)	6.6 (12.8)
	Range	(−11.1 to 33.3)	(−16.7 to 25.0)	(−8.3 to 33.3)	(−16.7 to 33.3)
	Treatment burden				
	Median (IQR)	0.0 (−11.1 to 11.1)	0.0 (−5.6 to 16.7)	16.7 (−5.6 to 22.2)	0.0 (−11.1 to 22.2)
	Mean (SD)	1.9 (13.0)	5.6 (20.6)	8.3 (21.0)	4.9 (17.6)
	Range	(−11.1 to 22.2)	(−22.2 to 44.5)	(−22.2 to 22.2)	(−22.2 to 44.5)
		(*n* = 6)	(*n* = 8)	(*n* = 4)	(*n* = 18)
	Health perceptions				
	Median (IQR)	0.0 (0.0–8.3)	−4.2 (−8.3 to 16.7)	0.0 (−30.6 to 0.0)	0.0 (−8.3 to 8.3)
	Mean (SD)	1.4 (7.2)	−0.7 (14.4)	−9.9 (17.8)	−1.8 (13.1)
	Range	(−8.3 to 16.7)	(−25.0 to 16.7)	(−38.9 to 18.3)	(−38.9 to 16.7)
	Respiratory symptoms				
	Median (IQR)	5.6 (0.0–7.4)	7.4 (1.9–11.1)	3.7 (0.0–14.8)	7.4 (0.0–7.4)
	Mean (SD)	3.9 (11.5)	6.8 (14.6)	5.9 (10.5)	5.4 (12.2)
	Range	(−12.5 to 33.3)	(−14.8 to 44.5)	(−10.7 to 22.2)	(−14.8 to 44.4)

TABLE 12 Summary of change from baseline for FEV1, FVC, SGRQ and QoL-B (continued)

			Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
6 months	*N*		14	11	6	31
	FEV1					
	Median (IQR)		0.12 (−0.03 to 0.17)	0.0 (−0.05 to 0.12)	−0.16 (−0.19 to −0.07)	−0.01 (−0.15 to 0.13)
	Mean (SD)		0.07 (0.38)	0.03 (0.20)	−0.14 (0.08)	0.02 (0.29)
	Range		(−0.87 to 0.49)	(−0.16 to 0.4)	(−0.25 to 0.09)	(−0.87 to 0.49)
			(*n* = 13)			(*n* = 30)
	FVC					
	Median (IQR)		0.17 (−0.06 to 0.17)	−0.08 (−0.18 to 0.06)	0.13 (−0.25 to 0.10)	0.0 (−0.23 to 0.18)
	Mean (SD)		0.12 (0.33)	−0.05 (0.32)	−0.14 (0.27)	0.01 (0.32)
	Range		(−0.47 to 0.7)	(−0.52 to 0.46)	(−0.59 to 0.14)	(−0.59 to 0.7)
			(*n* = 13)			(*n* = 30)
	SGRQ					
	Median (IQR)		−0.58 (−9.7 to 8.5)	−4.5 (−11.5 to 3.0)	−2.4 (−6.4 to 4.2)	−1.9 (−9.7 to 7.1)
	Mean (SD)		−0.6 (12.5)	−3.9 (8.7)	1.0 (15.6)	−1.6 (11.5)
	Range		(−22.3 to 20.0)	(−19.1 to 9.7)	(−16.1 to 25.7)	(−22.3 to 25.7)
					(*n* = 5)	(*n* = 30)
	QoL-B, median (IQR), mean (SD), range	Physical functioning				
		Median (IQR)	−3.3 (−26.7 to 6.7)	−6.7 (−26.7 to 0.0)	−6.7 (−13.3 to 20.0)	−6.7 (−26.7 to 6.7)
		Mean (SD)	−9.1 (21.8)	−9.1 (16.7)	−4.4 (37.9)	−8.2 (23.3)
		Range	(−53.3 to 20.0)	(−33.3 to 20.0)	(−66.7 to 46.7)	(−66.7 to 46.7)
		Role functioning				
		Median (IQR)	−10.0 (−20.0 to 6.7)	−6.7 (−13.3 to 6.7)	−3.3 (−6.7 to 6.7)	−6.7 (−20.0 to 6.7)
		Mean (SD)	−2.4 (22.6)	−5.5 (10.3)	−4.4 (16.2)	−3.9 (17.4)
		Range	(−26.7 to 46.7)	(−20.0 to 6.7)	(−33.3 to 13.3)	(−33.3 to 46.7)
		Vitality				
		Median (IQR)	0.0 (−22.2 to 11.1)	0.0 (−11.1 to 11.1)	0.0 (−33.3 to 22.2)	0.0 (−11.1 to 11.1)
		Mean (SD)	−5.6 (18.9)	0.0 (8.6)	3.7 (23.0)	−1.8 (16.8)
		Range	(−33.3 to 22.2)	(−11.1 to 11.1)	(−33.3 to 33.3)	(−33.3 to 33.3)
		Emotional functioning				
		Median (IQR)	0.0 (−8.3 to 8.3)	0.0 (0.0 to 8.3)	8.3 (0.0 to 8.3)	0.0 (0.0 to 8.3)
		Mean (SD)	4.8 (17.5)	0.76 (8.7)	4.2 (7.0)	3.2 (13.0)
		Range	(−16.7 to 50.0)	(−16.7 to 16.7)	(−8.3 to 8.3)	(−16.7 to 50.0)

continued

TABLE 12 Summary of change from baseline for FEV1, FVC, SGRQ and QoL-B (continued)

			Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
		Social functioning				
		Median (IQR)	8.3 (0.0 to 16.7)	8.3 (−16.7 to 16.7)	5.6 (0.0 to 25.0)	8.3 (−2.8 to 16.7)
		Mean (SD)	7.1 (15.6)	6.1 (20.9)	10.2 (15.9)	7.4 (17.2)
		Range	(−25.0 to 33.3)	(−25.0 to 41.7)	(−8.3 to 33.3)	(−25.0 to 41.7)
		Treatment burden				
		Median (IQR)	11.1 (5.6 to 16.7)	−11.1 (−22.2 to −11.1)	0.0 (−11.1 to 22,2)	−5.6 (−11.1 to 11.1)
		Mean (SD)	11.1 (9.1)	−11.1 (11.1)	3.7 (17.0)	−1.6 (15.0)
		Range	(0.0 to 22.2)	(−22.2 to 11.1)	(−11.1 to 22.2)	(−22.2 to 22.2)
			(*n* = 4)	(*n* = 7)	(*n* = 3)	(*n* = 14)
		Health perceptions				
		Median (IQR)	0.0 (−8.3 to 8.3)	0.0 (−16.7 to 8.3)	−12.5 (−22.2 to 0.0)	0.0 (−16.7 to 8.3)
		Mean (SD)	−0.2 (15.1)	−1.5 (17.8)	−13.4 (13.2)	−3.2 (16.1)
		Range	(−25.0 to 33.3)	(−25.0 to 33.3)	(−33.3 to 0.0)	(−33.3 to 33.3)
		Respiratory symptoms				
		Median (IQR)	0.0 (−14.8 to 11.1)	0.0 (−5.1 to 18.5)	0.0 (−10.7 to 7.4)	0.0 (−10.7 to 11.1)
		Mean (SD)	0.30 (15.9)	4.6 (16.8)	0.7 (11.5)	1.9 (15.1)
		Range	(−25.5 to 25.9)	(−18.5 to 37.0)	(−11.1 to 18.5)	(−25.5 to 37.0)
12 months	***N***		13	11	6	30
	FEV1					
	Median (IQR)		0.1 (−0.08 to 0.24)	0.06 (0.03 to 0.19)	−0.06 (−0.07 to −0.05)	0.06 (−0.06 to 0.21)
	Mean (SD)		0.01 (0.41)	0.11 (0.19)	−0.07 (0.12)	0.03 (0.30)
	Range		(−1.2 to 0.35)	(−0.27 to 0.44)	(−0.25 to 0.1)	(−1.2 to 0.44)
			(*n* = 12)		(*n* = 5)	(*n* = 28)
	FVC					
	Median (IQR)		0.02 (−0.13 to 0.19)	0.05 (−0.04 to 0.41)	−0.23 (−0.28 to 0.17)	0.03 (−0.17 to 0.24)
	Mean (SD)		0.04 (0.29)	0.12 (0.38)	−0.12 (0.39)	0.04 (0.34)
	Range		(−0.47 to 0.63)	(−0.55 to 0.89)	(−0.62 to 0.37)	(−0.62 to 0.89)
			(*n* = 12)		(*n* = 5)	(*n* = 28)
	SGRQ					
	Median (IQR)		−3.0 (−10.5 to 9.5)	0.5 (−13.1 to 12.1)	13. 4 (−8.6 to 13.5)	0.4 (−10.5 to 12.3)
	Mean (SD)		0.2 (15.4)	1.4 (14.7)	−2.2 (25.6)	0.3 (16.6)
	Range		(−23.5 to 32.5)	(−20.3 to 30.3)	(−44.4 to 15.3)	(−44.4 to 32.5)
			(*n* = 12)		(*n* = 5)	(*n* = 28)

TABLE 12 Summary of change from baseline for FEV1, FVC, SGRQ and QoL-B (continued)

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
QoL−B, median (IQR), mean (SD), Range	Physical functioning				
	Median (IQR)	−6.7 (−13.3 to 13.3)	0.0 (−6.7 to 6.7)	−3.3 (−26.7 to 0.0)	−3.3 (−10.0 to 6.7)
	Mean (SD)	−3.6 (19.7)	0.3 (17.9)	−2.2 (30.6)	−1.9 (20.9)
	Range	(−46.7 to 26.7)	(−40.0 to 33.3)	(−33.3 to 53.3)	(−46.7 to 53.3)
	Role functioning				
	Median (IQR)	−6.7 (−20.0 to 13.3)	0.0 (0.0 to 6.7)	−10.0 (−20.0 to 20.0)	−3.3 (−20.0 to 6.7)
	Mean (SD)	−3.6 (20.1)	0.6 (14.1)	−6.7 (15.2)	−2.7 (16.9)
	Range	(−33.3 to 40.0)	(−26.7 to 26.7)	(−20.0 to 20.0)	(−33.3 to 40.0)
	Vitality				
	Median (IQR)	0.0 (−11.11 to 11.11)	−11.11 (−22.2 to 11.1)	−16.67 (−22.2 to 11.1)	−11.1 (−22.2 to 11.1)
	Mean (SD)	−1.71 (16.88)	−6.1 (15.2)	−5.6 (28.8)	−4.1 (18.6)
	Range	(−33.3 to 22.2)	(−22.2 to 22.2)	(−33.3 to 44.5)	(−33.3 to 44.5)
	Emotional functioning				
	Median (IQR)	0.0 (−8.3 to 16.7)	0.0 (0.0 to 16.7)	4.2 (−8.3 to 8.3)	0.0 (0.0 to 8.3)
	Mean (SD)	−1.3 (20.4)	5.3 (10.1)	2.8 (10.1)	1.9 (15.3)
	Range	(−50.0 to 41.7)	(9−8.3 to 25.0)	(−8.3 to 16.7)	(−50.0 to 41.7)
	Social functioning				
	Median (IQR)	8.3 (0.0–16.7)	8.3 (−8.3 to 16.7)	8.3 (0.0–25.0)	8.3 (−8.3 to 16.7)
	Mean (SD)	5.1 (21.2)	4.8 (16.5)	12.5 (33.2)	6.5 (21.9)
	Range	(−33.3 to 33.3)	(−16.7 to 33.3)	(−33.3 to 66.7)	(−33.3 to 66.7)
	Treatment burden				
	Median (IQR)	−11.1 (−22.2 to 0.0)	−11.1 (−33.3 to 0.0)	11.1 (0.0 to 22.2)	−5.6 (−22.2 to 11.1)
	Mean (SD)	−11.1 (18.1)	−9.5 (23.5)	11.1 (11.1)	−5.6 (20.8)
	Range	(−33.3 to 11.1)	(−33.3 to 33.3)	(0.0–22.2)	(−33.3 to 33.3)
		(*n* = 4)	(*n* = 7)	(*n* = 3)	(*n* = 14)
	Health perceptions				
	Median (IQR)	0.0 (−16.7 to 8.3)	0.0 (−8.3 to 16.7)	−19.5 (−33.3 to 0.0)	0.0 (−16.7 to 8.3)
	Mean (SD)	−3.9 (22.2)	4.6 (24.0)	−12.0 (35.3)	−2.4 (25.6)
	Range	(−50.0 to 33.3)	(−33.3 to 58.3)	(−50.0 to 50.0)	(−50.0 to 58.3)
	Respiratory symptoms				
	Median (IQR)	3.7 (−11.1 to 14.8)	−3.7 (−7.4 to 3.7)	−12.7 (−22.2 to −3.7)	−1.9 (−14.4 to 7.4)
	Mean (SD)	0.6 (19.8)	−2.0 (12.98)	−16.0 (29.1)	−3.7 (20.2)
	Range	(−37.0 to 29.6)	(−18.5 to 29.6)	(−66.7 to 22.2)	(−66.7 to 29.6)

This synopsis should be referenced as follows:
Wilson N, Morton M, Homer T, Konkoth AB, Joyce R, Kershaw A, *et al.* A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis [published online ahead of print February 4 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GGCC1111

TABLE 13 Summary of secondary outcomes of MRC, QoL-B, SGRQ and TDI over time by randomised treatment group

Baseline	*N*		14	12	7	33
	MRCD score	Median (IQR)	3 (2–3)	1.5 (1–3)	2 (1–4)	2 (2–3)
		Mean (SD)	3.0 (0.9)	1.9 (1.1)	2.6 (1.5)	2.5 (1.2)
		Range	(2–5)	(1–4)	(1–5)	(1–5)
	QoL-B, median (IQR, range), mean (SD)	Physical functioning				
		Median (IQR)	40.0 (13.3–73.3)	60.0 (33.3–96.7)	46.7 (33.3–100.0)	53.3 (26.7–86.7)
		Mean (SD)	43.3 (33.6)	62.2 (30.9)	57.1 (36.5)	53.1 (33.4)
		Range	(0.0–93.3)	(20.0–100.0)	(6.7–100.0)	(0.0–100.0)
		Role functioning				
		Median (IQR)	66.7 (20.0–93.3)	76.7 (56.7–90.0)	80.0 (50.0–93.3)	73.3 (50.0–93.3)
		Mean (SD)	58.6 (34.7)	73.9 (19.0)	73.8 (26.7)	67.4 (28.4)
		Range	(0.0–100.0)	(46.7–100.0)	(26.7–100.0)	(0.0–100.0)
		Vitality				
		Median (IQR)	44.4 (33.3–55.6)	55.6 (44.4–72.2)	33.3 (22.2–66.7)	44.4 (33.3–66.7)
		Mean (SD)	41.3 (19.2)	57.4 (16.3)	46.0 (23.5)	48.1 (20.0)
		Range	(0.0–66.7)	(33.3–77.8)	(22.2–77.8)	(0.0–77.8)
		Emotional functioning				
		Median (IQR)	87.5 (58.3–91.7)	91.7 (75.0–100.0)	91.7 (83.3–100.0)	91.7 (66.7–100.0)
		Mean (SD)	75.0 (27.7)	84.7 (20.4)	88.1(11.6)	81.3 (22.6)
		Range	(16.7–100.0)	(33.3–100.0)	(66.7–100.0)	(16.7–100.0)
		Social functioning				
		Median (IQR)	62.5 (33.3–75.0)	50.0 (25.0–58.3)	66.7 (33.3–75.0)	50.0 (33.3–75.0)
		Mean (SD)	52.0 (25.6)	48.4 (23.0)	58.3 (21.0)	52.0 (23.3)
		Range	(0.0–77.8)	(22.2–91.7)	(25.0–75.0)	(0.0–91.7)
		Treatment burden				
		Median (IQR)	77.8 (55.6–100)	77.8 (50.0–88.9)	77.8 (44.4–77.8)	77.8 (55.6–88.9)
		Mean (SD)	75.9 (22.7)	70.8 (23.7)	61.1 (33.3)	70.4 (24.7)
		Range	(44.4–100.0)	(33.3–100.0)	(11.1–77.8)	(11.1–100.0)
			(*n* = 6)	(*n* = 8)	(*n* = 4)	(*n* = 18)
		Health perceptions				
		Median (IQR)	50.0 (33.3–58.3)	45.8 (37.5–70.8)	66.7 (33.3–75.0)	50.0 (33.3–66.7)
		Mean (SD)	44.0 (22.3)	50.7 (20.6)	59.1 (23.7)	49.7 (22.0)
		Range	(0.0–75.0)	(16.7–75.0)	(25.0–88.9)	(0.0–88.9)
		Respiratory symptoms				
		Median (IQR)	53.7 (44.4–66.7)	61.1 (40.7–79.6)	62.5 (48.2–74.1)	59.3 (48.1–70.4)
		Mean (SD)	55.3 (15.9)	58.6 (24.4)	58.1 (19.7)	57.1 (19.6)
		Range	(29.6–81.5)	(18.5–92.6)	(22.2–81.5)	(18.5–92.6)

TABLE 13 Summary of secondary outcomes of MRC, QoL-B, SGRQ and TDI over time by randomised treatment group (continued)

Baseline	*N*		14	12	7	33
	SGRQ	Symptoms score				
		Median (IQR)	64.4 (57.9–77.1)	66.2 (30.2–83.7)	74.7 (21.2–81.9)	64.9 (56.9–81.2)
		Mean (SD)	66.1 (11.2)	57.9 (30.2)	59.2 (29.3)	61.6 (23.3)
		Range	(45.5–83.9)	(9.5–95.2)	(17.3–85.1)	(9.5–95.2)
		Activities score				
		Median (IQR)	63.2 (53.5–92.5)	50.6 (14.3–66.3)	57.3 (17.9–87.0)	59.5 (32.3–76.0)
		Mean (SD)	64.5 (24.3)	41.6 (28.8)	54.9 (32.4)	54.1 (28.6)
		Range	(18.5–93.4)	(0.0–79.7)	(17.4–92.5)	(0.0–93.4)
		Impacts score				
		Median (IQR)	33.1 (20.4–49.6)	29.0 (8.6–44.3)	26.6 (9.5–62.1)	30.1 (18.8–48.2)
		Mean (SD)	36.5 (18.0)	28.0 (17.5)	35.4 (24.5)	33.2 (19.1)
		Range	(14.6–69.2)	(4.2–53.2)	(7.4–65.6)	(4.2–69.2)
		Total SGRQ score				
		Median (IQR)	46.8 (33.9–68.3)	42.8 (16.5–57.6)	50.7 (13.2–73.5)	42.8 (29.2–59.2)
		Mean (SD)	49.8 (17.1)	37.1 (20.8)	46.2 (28.6)	44.4 (21.0)
		Range	(28.5–79.0)	(6.8–64.1)	(12.9–76.5)	(6.8 79.0)
					(*n* = 6)	(*n* = 32)
	BDI (TDI)	Baseline functional impairment				
		Median (IQR)	3 (2–3)	3 (2–4)	3 (3–4)	3 (2–4)
		Mean (SD)	2.4 (0.9)	3.1 (0.9)	2.8 (1.5)	2.7 (1.1)
		Range	(1–4)	(2–4)	(0–4)	(0–4)
				(*n* = 11)	(*n* = 6)	(*n* = 31)
		Baseline magnitude of task				
		Median (IQR)	2 (1–2)	2 (2–4)	2.5 (2–3)	2 (2–3)
		Mean (SD)	1.6 (0.7)	2.7 (0.9)	2.5 (1.0)	2.2 (1.0)
		Range	(0–3)	(2–4)	(1–4)	(0–4)
				(*n* = 10)	(*n* = 6)	(*n* = 30)
		Baseline magnitude of effort				
		Median (IQR)	2 (1–3)	2 (2–3)	3 (1–3)	2 (2–3)
		Mean (SD)	2.0 (1.0)	2.5 (0.7)	2.3 (1.5)	2.2 (1.0)
		Range	(1–4)	(2–4)	(0–4)	(0–4)
			(*n* = 13)	(*n* = 10)	(*n* = 6)	(*n* = 29)
		BDI				
		Median (IQR)	7 (4–8)	7 (6–11)	8.5 (6–10)	7 (6–9)
		Mean (SD)	6.1 (2.3)	8.2 (2.5)	7.7 (3.8)	7.1 (2.8)
		Range	(2–10)	(6–12)	(1–12)	(1–12)
			(*n* = 13)	(*n* = 10)	(*n* = 6)	(*n* = 29)

continued

TABLE 13 Summary of secondary outcomes of MRC, QoL-B, SGRQ and TDI over time by randomised treatment group (continued)

1 month	*N*		14	12	7	33
	MRCD score	Median (IQR)	3 (2–4)	2 (1–3)	2 (1–4)	2 (2–3)
		Mean (SD)	2.9 (1.2)	2.1 (1.2)	2.6 (1.5)	2.5 (1.3)
		Range	(1–5)	(1–4)	(1–5)	(1–5)
	QoL-B, median (IQR, range), mean (SD)	Physical functioning				
		Median (IQR)	30.0 (0.0–80.0)	53.3 (33.3–100.0)	40.0 (26.7–93.3)	46.7 (20.0–80.0)
		Mean (SD)	40.5 (37.9)	60.0 (34.0)	51.4 (37.9)	49.9 (36.4)
		Range	(0.0–100.0)	(6.7–100.0)	(0.0–100.0)	(0.0–100.0)
		Role functioning				
		Median (IQR)	70.0 (46.7–80.0)	73.3 (50.0–83.3)	80.0 (46.7–93.3)	73.3 (46.7–86.7)
		Mean (SD)	62.4 (30.8)	67.8 (23.4)	72.4 (26.5)	66.5 (26.8)
		Range	(6.7–100.0)	(33.3–100.0)	(26.7–100.0)	(6.7–100.0)
		Vitality				
		Median (IQR)	50.0 (22.2–55.6)	50.0 (44.4–66.7)	44.4 (33.3–77.8)	44.4 (33.3–66.7)
		Mean (SD)	41.3 (22.8)	50.9 (17.4)	47.6 (27.0)	46.1 (21.7)
		Range	(0.0–66.7)	(22.2–77.8)	(11.1–88.9)	(0.0–88.9)
		Emotional functioning				
		Median (IQR)	83.3 (58.3–100.0)	83.3 (70.8–95.8)	91.7 (75.0–100.0)	83.3 (66.7–100.0)
		Mean (SD)	72.6 (30.6)	76.4 (26.6)	86.9 (15.1)	77.0 (26.4)
		Range	(8.3–100.0)	(16.7–100.0)	(58.3–100.0)	(8.3–100.0)
		Social functioning				
		Median (IQR)	66.7 (41.7–75.0)	43.1 (41.7–56.9)	66.7 (58.3–83.3)	58.3 (41.7–75.0)
		Mean (SD)	60.1 (25.6)	51.4 (18.6)	67.9 (14.8)	58.6 (21.5)
		Range	(0.0–91.7)	(33.3–91.7)	(41.7–83.3)	(0.0–91.7)
		Treatment burden				
		Median (IQR)	77.8 (66.7–88.9)	83.3 (77.8–88.9)	94.4 (55.6–100.0)	88.9 (66.7–88.9)
		Mean (SD)	77.8 (17.9)	77.8 (20.3)	77.8 (32.2)	77.8 (21.6)
		Range	(44.4–100.0)	(22.2–88.9)	(22.2–100.0)	(22.2–100.0)
			(*n* = 11)	(*n* = 10)	(*n* = 6)	(*n* = 27)
		Health perceptions				
		Median (IQR)	50.0 (41.7–58.3)	41.7 (29.2–75.0)	58.3 (25.0–75.0)	50.0 (25.0–66.7)
		Mean (SD)	45.4 (22.6)	50.0 (25.6)	49.2 (28.4)	47.9 (24.3)
		Range	(0.0–75.0)	(16.7–91.7)	(11.1–83.3)	(0.0–91.7)
		Respiratory symptoms				
		Median (IQR)	59.3 (51.9–70.4)	64.8 (51.9–79.6)	63.0 (51.9–81.5)	63.0 (51.9–77.8)
		Mean (SD)	59.2 (19.1)	65.4 (18.8)	64.0 (21.4)	62.5 (19.1)
		Range	(29.6–88.9)	(33.3–96.3)	(25.9–88.9)	(25.9–96.3)

TABLE 13 Summary of secondary outcomes of MRC, QoL-B, SGRQ and TDI over time by randomised treatment group (continued)

1 month	*N*		14	12	7	33
	SGRQ	Symptoms score				
		Median (IQR)	55.1 (36.6–74.3)	64.1 (17.8–71.9)	71.6 (32.7–79.5)	61.5 (32.7–74.3)
		Mean (SD)	55.2 (20.7)	49.3 (29.8)	57.5 (24.2)	53.6 (24.5)
		Range	(25.2–90.7)	(9.6–84.1)	(23.8–81.2)	(9.6–90.7)
		Activities score				
		Median (IQR)	57.3 (48.8–87.2)	51.0 (8.7–59.5)	60.2 (18.5–85.8)	54.4 (23.4–79.0)
		Mean (SD)	61.5 (27.1)	36.8 (27.4)	54.0 (36.1)	51.0 (30.4)
		Range	(12.2–93.4)	(0.0–66.2)	(11.5–100.0)	(0.0–100.0)
		Impacts score				
		Median (IQR)	31.4 (20.4–73.0)	22.5 (12.8–46.3)	36.0 (7.3–48.7)	28.6 (15.0–47.2)
		Mean (SD)	38.7 (25.8)	26.8 (17.2)	31.9 (21.6)	33.0 (22.1)
		Range	(5.1–76.1)	(3.9–49.2)	(1.6–62.3)	(1.6–76.1)
		Total SGRQ score				
		Median (IQR)	42.5 (31.8–71.1)	33.3 (10.3–55.8)	50.7 (13.3–67.6)	41.6 (25.7–58.6)
		Mean (SD)	48.4 (23.8)	33.6 (21.1)	42.7 (24.6)	41.8 (23.3)
		Range	(10.7–82.1)	(6.0–59.1)	(11.3–72.3)	(6.0–82.1)
	TDI	Change in functional impairment				
		Median (IQR)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
		Mean (SD)	0.3 (1.3)	0.3 (0.9)	−0.4 (1.1)	0.1 (1.1)
		Range	(−3–2)	(0–3)	(−3–0)	(−3–3)
		Change in magnitude of task				
		Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
		Mean (SD)	0.2 (0.7)	0.3 (0.6)	−0.1 (0.4)	0.2 (0.6)
		Range	(−1–2)	(0–2)	(−1–0)	(−1–2)
		Change in magnitude of effort				
		Median (IQR)	0 (0–0)	0 (0–1)	0 (−1–0)	0 (0–0)
		Mean (SD)	0.1 (0.7)	0.5 (0.9)	−0.6 (1.1)	0.1 (1.0)
		Range	(−1–2)	(0–3)	(−3–0)	(−3–3)
		TDI				
		Median (IQR)	0 (0–2)	0 (0–1)	0 (−1–0)	0 (0–1)
		Mean (SD)	0.6 (2.4)	1.0 (2.3)	−1.1 (2.6)	0.4 (2.5)
		Range	(−5–6)	(0,8)	(−7,0)	(−7,8)

continued

TABLE 13 Summary of secondary outcomes of MRC, QoL-B, SGRQ and TDI over time by randomised treatment group (continued)

6 months	*N*		14	11	6	31
	MRCD score	Median (IQR)	2.5 (2–4)	2 (1–3)	2.5 (1–3)	2 (1–3)
		Mean (SD)	2.8 (1.1)	2.1 (1.1)	2.5 (1.5)	2.5 (1.2)
		Range	(1–5)	(1–4)	(1–5)	(1–5)
	QoL-B, median (IQR, range), mean (SD)	Physical functioning				
		Median (IQR)	26.7 (0.0–40.0)	60.0 (20.0–93.3)	56.7 (33.3–93.3)	33.3 (20.0–80.0)
		Mean (SD)	34.3 (33.6)	52.1 (37.2)	56.7 (40.2)	44.9 (36.3)
		Range	(0.0–100.0)	(6.7–100.0)	(0.0–100.0)	(0.0–100.0)
		Role functioning				
		Median (IQR)	56.7 (33.3–73.3)	73.3 (40.0–86.7)	80.0 (60.0–100.0)	73.3 (40.0–86.7)
		Mean (SD)	56.2 (28.4)	67.9 (23.6)	73.3 (30.4)	63.7 (27.2)
		Range	(6.7–100.0)	(33.3–100.0)	(20.0–100.0)	(6.7–100.0)
		Vitality				
		Median (IQR)	27.8 (22.2–66.7)	66.7 (44.4–77.8)	50.0 (33.3–77.8)	44.4 (22.2–66.7)
		Mean (SD)	35.7 (29.3)	58.6 (18.0)	53.7 (27.6)	47.3 (26.9)
		Range	(0.0–88.9)	(22.2–77.8)	(22.2–88.9)	(0.0–88.9)
		Emotional functioning				
		Median (IQR)	87.5 (75.0–100.0)	91.7 (66.7–100.0)	95.8 (91.7–100.0)	91.7 (75.0–100.0)
		Mean (SD)	79.8 (25.5)	84.1 (18.0)	93.1 (9.8)	83.9 (20.7)
		Range	(16.7–100.0)	(50.0–100.0)	(75.0–100.0)	(16.7–100.0)
		Social functioning				
		Median (IQR)	66.7 (41.7–75.0)	58.3 (33.3–77.8)	66.7 (66.7–75.0)	66.7 (41.7–75.0)
		Mean (SD)	59.1 (27.2)	56.6 (23.0)	67.1 (9.7)	59.8 (23.0)
		Range	(0.0–100.0)	(16.7–88.9)	(50.0–77.8)	(0.0–100.0)
		Treatment burden				
		Median (IQR)	88.9 (66.7–100.0)	66.7 (55.6–88.9)	77.8 (66.7–88.9)	77.8 (66.7–94.4)
		Mean (SD)	81.5 (22.9)	68.9 (20.8)	66.7 (39.3)	73.1 (25.8)
		Range	(33.3–100.0)	(33.3–100.0)	(0.0–100.0)	(0.0–100.0)
			(*n* = 9)	(*n* = 10)	(*n* = 5)	(*n* = 24)
		Health perceptions				
		Median (IQR)	50.0 (25.0–58.3)	50.0 (25.0–66.7)	54.2 (25.0–66.7)	50.0 (25.0–66.7)
		Mean (SD)	43.9 (25.1)	50.0 (22.4)	47.2 (22.8)	46.7 (23.1)
		Range	(0.0–83.3)	(16.7–83.3)	(16.7–66.7)	(0.0–83.3)
		Respiratory symptoms				
		Median (IQR)	55.6 (51.9–66.7)	63.0 (48.1–85.2)	57.4 (51.9–85.2)	55.6 (51.9–74.1)
		Mean (SD)	55.6 (14.6)	63.5 (22.4)	59.9 (25.8)	59.2 (19.6)
		Range	(22.2–81.5)	(25.9–88.9)	(18.5–88.9)	(18.5–88.9)

TABLE 13 Summary of secondary outcomes of MRC, QoL-B, SGRQ and TDI over time by randomised treatment group (continued)

6 months	*N*		14	11	6	31
	SGRQ, median (IQR, range), mean (SD)	Symptoms score				
		Median (IQR)	64.0 (44.8–73.8)	41.1 (25.0–76.9)	68.7 (46.5–73.4)	61.7 (36.9–73.8)
		Mean (SD)	58.4 (19.6)	48.9 (27.1)	58.6 (22.2)	55.1(22.7)
		Range	(26.1–86.1)	(13.3–100.0)	(18.6–75.9)	(13.3–100.0)
		Activities score				
		Median (IQR)	68.9 (47.4–86.4)	41.7 (12.2–60.3)	38.7 (24.6–68.4)	55.0 (29.5–70.9)
		Mean (SD)	62.6 (26.3)	39.8 (22.6)	45.7 (29.9)	51.2 (27.1)
		Range	(5.3–92.5)	(5.3–67.6)	(11.2–92.5)	(5.3–92.5)
		Impacts score				
		Median (IQR)	37.7 (29.3–48.5)	22.0 (7.4–36.0)	27.0 (20.9–35.3)	31.2 (17.7–41.5)
		Mean (SD)	38.6 (18.6)	23.0 (14.0)	29.2 (16.9)	31.3 (17.7)
		Range	(8.9–73.5)	(4.1–43.7)	(7.5–57.5)	(4.1–73.5)
		Total SGRQ score				
		Median (IQR)	50.7 (38.9–59.8)	35.2 (12.3–50.2)	41.4 (26.3–45.5)	43.9 (26.3–54.8)
		Mean (SD)	49.2 (18.7)	32.4 (17.0)	39.2 (20.0)	41.3 (19.3)
		Range	(10.7–77.6)	(9.6–56.9)	(10.5–70.0)	(9.6–77.6)
	TDI, **median** (IQR, range) mean (SD)	Change in functional impairment				
		Median (IQR)	0 (0–1)	0 (0–3)	0 (0–0)	0 (0–1)
		Mean (SD)	0.4 (1.4)	0.8 (1.5)	−0.2 (0.4)	0.5 (1.3)
		Range	(−2 to 3)	(−1 to 3)	(−1 to 0)	(−2 to 3)
				(*n* = 11)	(*n* = 6)	(*n* = 31)
		Change in magnitude of task				
		Median (IQR)	0 (−1 to 1)	0 (0–2)	0 (0–0)	0 (0–0)
		Mean (SD)	0.2 (1.3)	0.6 (1.4)	0.0 (0.0)	0.3 (1.2)
		Range	(−2 to 3)	(−1 to 3)	(0–0)	(−2 to 3)
			(*n* = 13)	(*n* = 11)	(*n* = 6)	(*n* = 30)
		Change in magnitude of effort				
		Median (IQR)	0 (−1 to 1)	0 (0–3)	0 (0–0)	0 (−1 to 1)
		Mean (SD)	−0.1 (1.5)	0.5 (1.9)	0.0 (0.6)	0.1 (1.5)
		Range	(−3 to 3)	(−3 to 3)	(−1 to 1)	(−3 to 3)
				(*n* = 11)	(*n* = 6)	(*n* = 31)
		TDI				
		Median (IQR)	0 (−1 to 2)	0 (0–8)	0 (0–0)	0 (−1 to 2)
		Mean (SD)	0.6 (4.1)	1.9 (4.5)	−0.2 (1.0)	0.9 (3.8)
		Range	(−6 to 8)	(−3 to 9)	(−2 to 1)	(−6 to 9)
			(*n* = 13)	(*n* = 11)	(*n* = 6)	(*n* = 30)

continued

TABLE 13 Summary of secondary outcomes of MRC, QoL-B, SGRQ and TDI over time by randomised treatment group (continued)

12 months	*N*		13	11	6	30
	MRCD score	Median (IQR)	2 (2–3)	2 (1–3)	2 (1–2)	2 (1–3)
		Mean (SD)	2.5 (1.1)	1.9 (0.8)	2.0 (1.1)	2.2 (1.0)
		Range	(1–4)	(1–3)	(1–4)	(1–4)
	QoL-B, median (IQR, range), mean (SD)	Physical functioning				
		Median (IQR)	33.3 (6.7–80.0)	60.0 (33.3–93.3)	70.0 (46.7–80.0)	60.0 (33.3–80.0)
		Mean (SD)	43.1 (38.7)	61.5 (29.0)	58.9 (31.9)	53.0 (34.1)
		Range	(0.0–100.0)	(16.7–100.0)	(0.0–86.7)	(0.0–100.0)
		Role functioning				
		Median (IQR)	66.7 (40.0–80.0)	80.0 (60.0–86.7)	80.0 (73.3–93.3)	76.7 (46.7–86.7)
		Mean (SD)	58.5 (25.0)	73.9 (21.6)	71.1 (32.6)	66.7 (25.6)
		Range	(13.3–86.7)	(26.7–100.0)	(6.7–93.3)	(6.7–100.0)
		Vitality				
		Median (IQR)	44.4 (22.2–66.7)	55.6 (44.4–55.6)	44.4 (33.3–66.7)	44.4 (33.3–66.7)
		Mean (SD)	42.7 (25.2)	52.5 (18.7)	44.4 (27.2)	46.7 (23.0)
		Range	(0.0–77.8)	(22.2–88.9)	(0.0–77.8)	(0.0–88.9)
		Emotional functioning				
		Median (IQR)	91.7 (66.7–100.0)	100.0 (83.3–100.0)	95.8 (83.3–100.0)	91.7 (75.0–100.0)
		Mean (SD)	77.6 (28.1)	88.6 (16.8)	91.7 (10.5)	84.4 (22.0)
		Range	(0.0–100.0)	(50.0–100.0)	(75.0–100.0)	(0.0–100.0)
		Social functioning				
		Median (IQR)	58.3 (44.4–75.0)	50.0 (33.3–75.0)	66.7 (58.3–91.7)	58.3 (41.7–75.0)
		Mean (SD)	61.1 (17.2)	55.3 (19.1)	69.4 (20.2)	60.6 (18.6)
		Range	(33.3–83.3)	(33.3–83.3)	(41.7–91.7)	(33.3–91.7)
		Treatment burden				
		Median (IQR)	72.2 (66.7–88.9)	61.1 (50.0–77.8)	83.3 (50.0–94.4)	66.7 (55.6–88.9)
		Mean (SD)	73.6 (15.6)	62.5 (24.4)	72.2 (34.5)	68.9 (23.0)
		Range	(44.4–88.9)	(22.2–100.0)	(22.2–100.0)	(22.2–100.0)
			(*n* = 8)	(*n* = 8)	(*n* = 4)	(*n* = 20)
		Health perceptions				
		Median (IQR)	50 (16.7–58.3)	58.3 (41.7–75.0)	50.0 (25.0–75.0)	50.0 (25.0–75.0)
		Mean (SD)	43.6 (24.1)	56.1 (25.3)	48.6 (25.0)	49.2 (24.5)
		Range	(16.7–83.3)	(16.7–91.7)	(16.7–75.0)	(16.7–91.7)

TABLE 13 Summary of secondary outcomes of MRC, QoL-B, SGRQ and TDI over time by randomised treatment group (continued)

12 months *N*			13	11	6	30
		Respiratory symptoms				
		Median (IQR)	63.0 (44.4–66.7)	63.0 (29.6–77.8)	50.0 (18.5–70.4)	61.1 (40.7–70.4)
		Mean (SD)	57.8 (16.9)	56.9 (26.5)	43.2 (28.5)	54.6 (23.1)
		Range	(33.3–85.2)	(14.8–96.3)	(0.0–70.4)	(0.0–96.3)
	SGRQ, median (IQR, range), mean (SD)	Symptoms score				
		Median (IQR)	56.8 (48.5–76.7)	46.5 (34.7–84.2)	65.1 (52.0–67.2)	58.2 (42.9–72.8)
		Mean (SD)	60.7 (19.2)	53.2 (28.9)	57.1 (18.3)	57.2 (22.6)
		Range	(37.7–90.6)	(0.0–93.4)	(21.2–72.2)	(0.0–93.4)
		Activities score				
		Median (IQR)	56.9 (42.0–92.9)	41.8 (23.4–66.2)	43.9 (29.7–79.8)	48.5 (29.7–72.8)
		Mean (SD)	61.8 (31.3)	43.7 (24.5)	48.2 (30.2)	52.1 (28.9)
		Range	(5.3–100.0)	(0.0–72.8)	(6.3–85.8)	(0.0–100.0)
			(*n* = 12)	(*n* = 11)	(*n* = 6)	(*n* = 29)
		Impacts score				
		Median (IQR)	39.1 (22.6–51.5)	27.6 (14.1–39.9)	28.2 (14.1–43.1)	35.3 (19.3–49.3)
		Mean (SD)	39.1 (22.6)	29.6 (15.1)	29.5 (19.8)	33.7 (19.5)
		Range	(4.7–80.5)	(11.2–55.0)	(5.5–57.8)	(4.7–80.5)
		Total SGRQ score				
		Median (IQR)	47.1 (35.1–70.7)	35.0 (22.2–55.8)	37.1 (26.3–54.7)	43.6 (28.4–58.8)
		Mean (SD)	49.5 (24.1)	37.7 (17.7)	39.8 (19.7)	43.0 (21.0)
		Range	(9.5–83.1)	(11.2–62.3)	(15.6–67.9)	(9.5–83.1)
			(*n* = 12)	(*n* = 11)	(*n* = 6)	(*n* = 29)
	TDI, **median** (IQR, range), mean (SD)	Change in functional impairment				
		Median (IQR)	0 (0–2)	0 (0–2)	0 (−1–1)	0 (0–1.5)
		Mean (SD)	0.6 (1.7)	0.5 (1.4)	0.3 (1.5)	0.5 (1.5)
		Range	(−2 to 3)	(−2 to 3)	(−1 to 3)	(−2 to 3)
			(*n* = 12)	(*n* = 10)	(*n* = 6)	(*n* = 28)
		Change in magnitude of task				
		Median (IQR)	0 (−1 to 2.5)	0 (0–0)	0 (−1 to 1)	0 (−0.5 to 1)
		Mean (SD)	0.5 (1.9)	0.2 (1.1)	0.3 (1.5)	0.4 (1.5)
		Range	(−2 to 3)	(−1 to 3)	(−1 to 3)	(−2 to 3)
			(*n* = 12)	(*n* = 10)	(*n* = 6)	(*n* = 28)

continued

TABLE 13 Summary of secondary outcomes of MRC, QoL-B, SGRQ and TDI over time by randomised treatment group (continued)

12 months *N*		13	11	6	30
	Change in magnitude of effort				
	Median (IQR)	0 (−2 to 2.5)	0 (0–0)	0 (0–0)	0 (0–1)
	Mean (SD)	0.3 (2.1)	0.2 (1.2)	0.3 (1.4)	0.3 (1.6)
	Range	(−2 to 3)	(−2 to 3)	(−1 to 3)	(−2 to 3)
		(*n* = 12)	(*n* = 10)	(*n* = 6)	(*n* = 28)
	TDI				
	Median (IQR)	0 (−3 to 7)	0 (0 to 2)	0 (−2 to 2)	0 (−1 to 3)
	Mean (SD)	1.4 (5.6)	0.9 (3.5)	1.0 (4.3)	1.1 (4.5)
	Range	(−6 to 9)	(−5 to 9)	(−3 to 9)	(−6 to 9)
		(*n* = 12)	(*n* = 10)	(*n* = 6)	(*n* = 28)

TABLE 14 Response assessed using the MCID for QoL-B

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
1 month	***N***	**14**	**12**	**7**	**33**
	Number of participants who achieved increase in QoL-B score by at least 8 points from baseline in 1 month across each domain, n (%)				
	Physical	3 (21.4%)	1 (8.3%)	0 (0.0%)	4 (12.1%)
	Role	2 (14.3%)	1 (8.3%)	0 (0.0%)	3 (9.1%)
	Vitality	4 (28.6%)	1 (8.3%)	3 (42.9%)	8 (24.2%)
	Emotional	4 (28.6%)	4 (33.3%)	2 (28.6%)	10 (3.0%)
	Social	8 (57.1%)	5 (41.7%)	4 (57.1%)	17 (51.5%)
	Treatment burden	2 (33.3%) (*n* = 6)	3 (37.5%) (*n* = 8)	3 (75.0%) (*n* = 4)	8 (44.4%) (*n* = 18)
	Health perceptions	4 (28.6%)	4 (33.3%)	1 (14.3%)	9 (27.3%)
	Respiratory symptoms	2 (14.3%)	4 (33.3%)	2 (28.6%)	8 (24.2%)
6 months	***N***	**14**	**11**	**6**	**31**
	Number of participants who achieved increase in QoL-B by at least 8 points from baseline in 6 months across each domain, n (%)				
	Physical	3 (21.4%)	1 (9.1%)	2 (33.3%)	6 (19.4%)
	Role	3 (21.4%)	0 (0.0%)	1 (16.7%)	4 (12.9%)
	Vitality	4 (28.6%)	3 (27.3%)	2 (33.3%)	9 (29.0%)
	Emotional	6 (42.9%)	3 (27.3%)	4 (66.7%)	13 (41.9%)
	Social	8 (57.1%)	6 (54.6%)	3 (50.0%)	17 (54.8%)
	Treatment burden	3 (75.0%) (*n* = 4)	1 (14.3%) (*n* = 7)	1 (33.3%) (*n* = 3)	5 (35.7%) (*n* = 14)
	Health perceptions	4 (28.6%)	4 (36.4%)	0 (0.0%)	8 (25.8%)
	Respiratory symptoms	5 (35.7%)	3 (27.3%)	1 (16.7%)	9 (29.0%)

TABLE 14 Response assessed using the MCID for QoL-B (continued)

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
12 months	***N***	**13**	**11**	**6**	**30**
	Number of participants who achieved increase in QoL-B by at least 8 points from baseline in 12 months across each domain, n (%)				
	Physical	4 (30.8%)	2 (18.2%)	1 (16.7%)	7 (23.3%)
	Role	4 (30.8%)	1 (9.1%)	1 (16.7%)	6 (20.0%)
	Vitality	6 (46.2%)	3 (27.3%)	2 (33.3%)	11 (36.7%)
	Emotional	3 (23.1%)	4 (36.4%)	3 (50.0%)	10 (33.3%)
	Social	8 (61.5%)	6 (54.6%)	3 (50.0%)	17 (56.7%)
	Treatment burden	1 (25.0%) (*n* = 4)	1 (14.3%) (*n* = 7)	2 (66.7%) (*n* = 3)	4 (28.6%) (*n* = 14)
	Health perceptions	5 (38.5%)	5 (45.5%)	1 (16.7%)	11 (36.7%)
	Respiratory symptoms	5 (38.5%)	1 (9.1%)	1 (16.7%)	7 (23.3%)

AQ2 **TABLE 15** Response assessed using the MCID for SGRQ

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
1 month	*N*	14	12	7	33
	Number of participants who achieved reduction in SGRQ score by at least 4 points from baseline in 1 month, *n* (%)	5 (35.7%)	6 (50.0%)	3 (50.0%) (*n* = 6)	14 (43.8%) (*n* = 32)
6 months	*N*	14	11	6	31
	Number of participants who achieved reduction in SGRQ score by at least 4 points from baseline in 6 months, *n* (%)	5 (35.7%)	6 (54.6%)	2 (40.0%) (*n* = 5)	13 (43.3%) (*n* = 30)
12 months	*N*	13	11	6	30
	Number of participants who achieved reduction in SGRQ score by at least 4 points from baseline in 12 months, *n* (%)	6 (50.0%) (*n* = 12)	4 (36.4%)	2 (40.0%) (*n* = 5)	12 (42.9%) (*n* = 28)

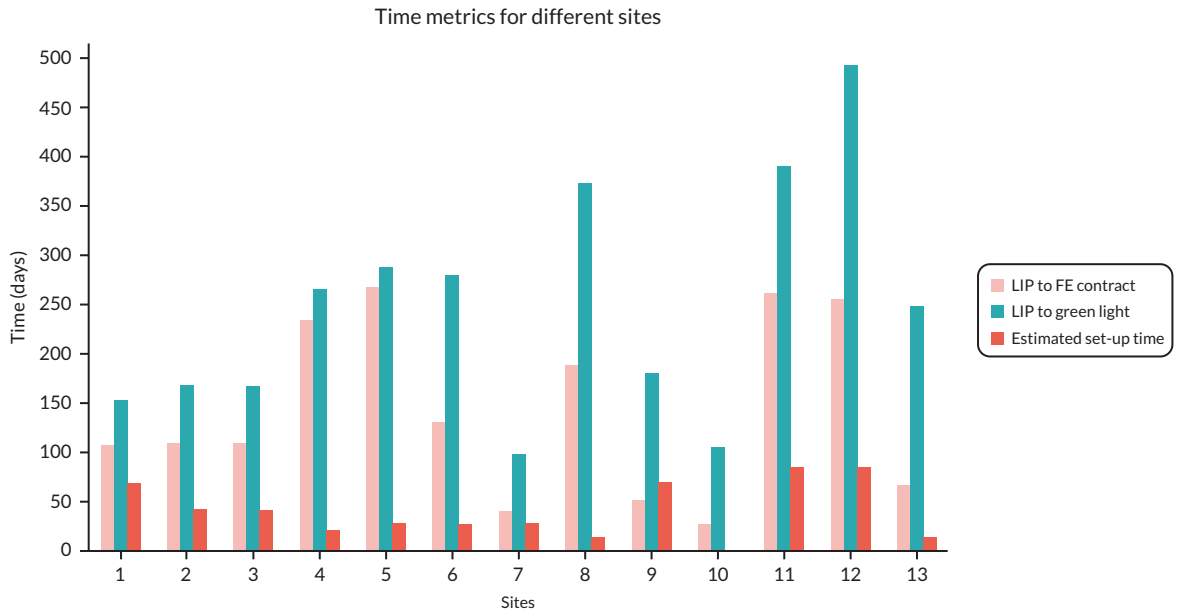

FIGURE 6 Time to set up metrics for different sites. Sites 2 and 3 had the same timings as they were within the same NHS Trust.

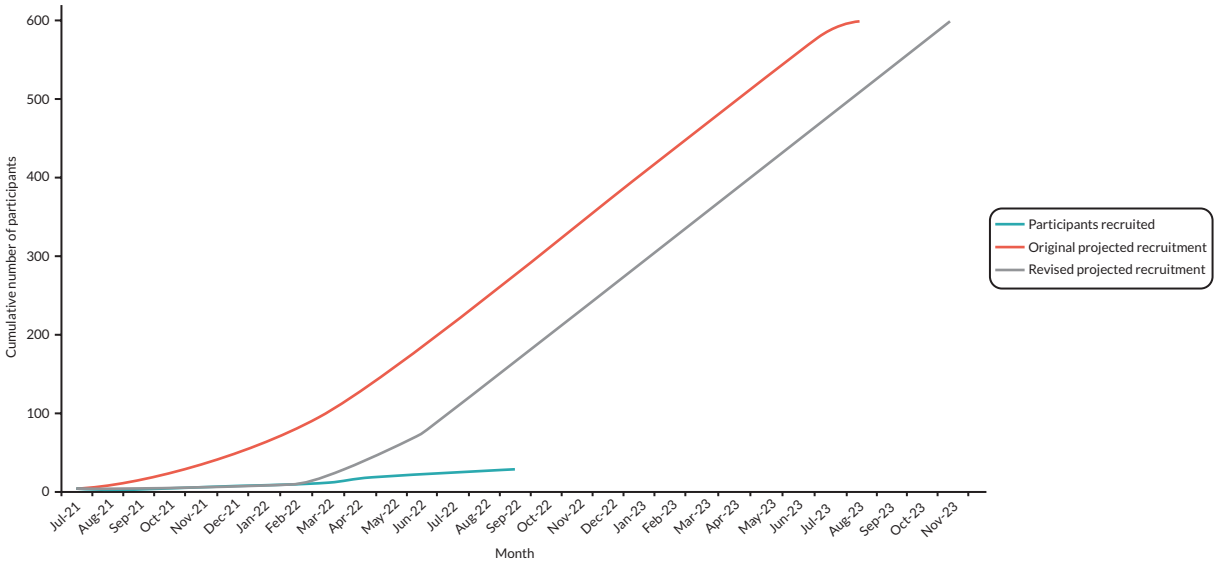

FIGURE 7 Plot of actual vs. projected recruitment.

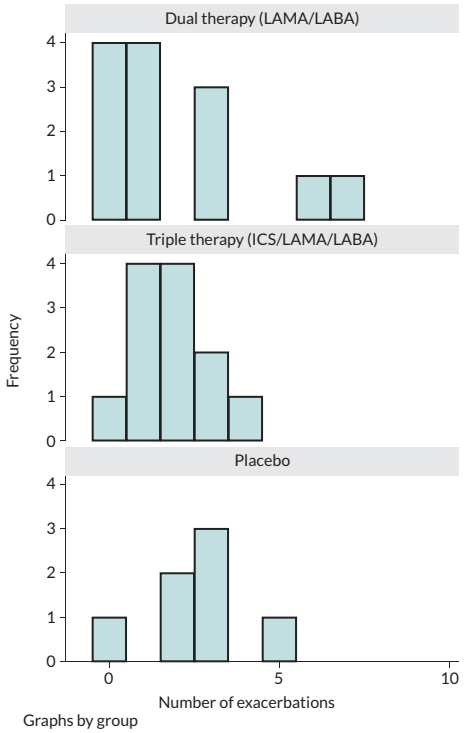

FIGURE 8 Histograms of number of bronchiectasis exacerbations requiring antibiotics during the trial per treatment group. This figure has been reproduced with permission from Wilson *et al.*[2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

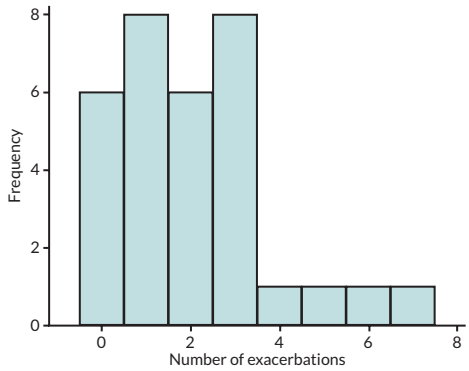

FIGURE 9 Histogram of number of bronchiectasis exacerbations requiring antibiotics during the trial.

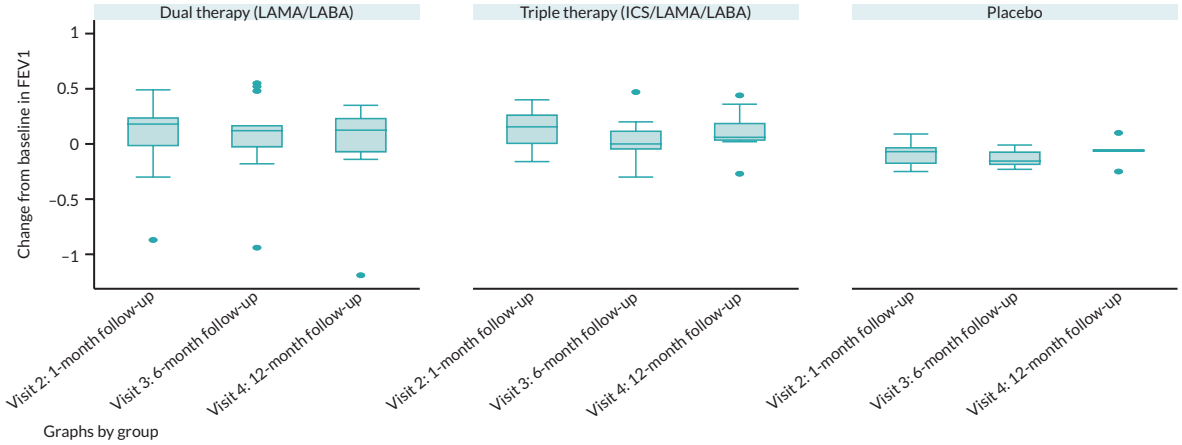

FIGURE 10 Boxplots for change from baseline in FEV1.

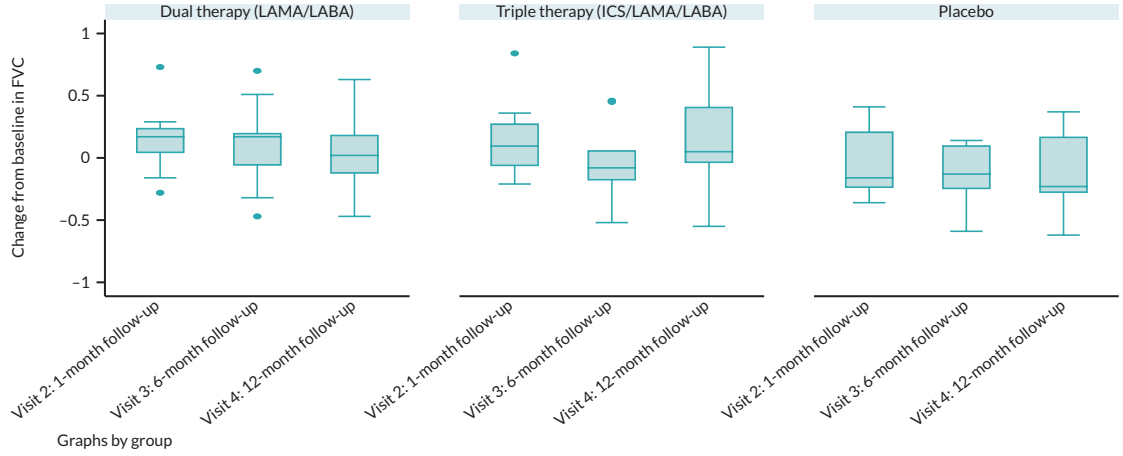

FIGURE 11 Boxplots for change from baseline in FVC.

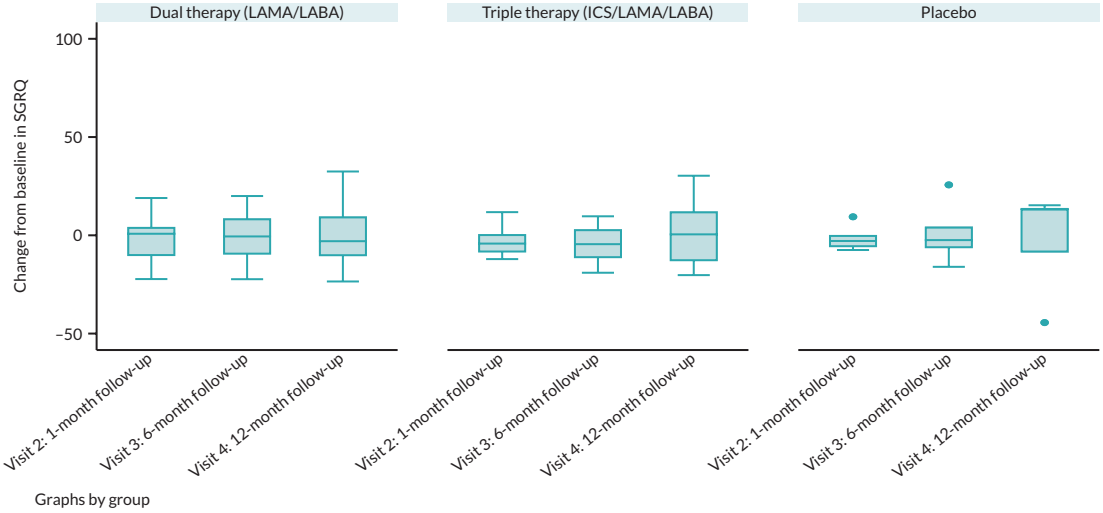

FIGURE 12 Boxplots for change from baseline in SGRQ.

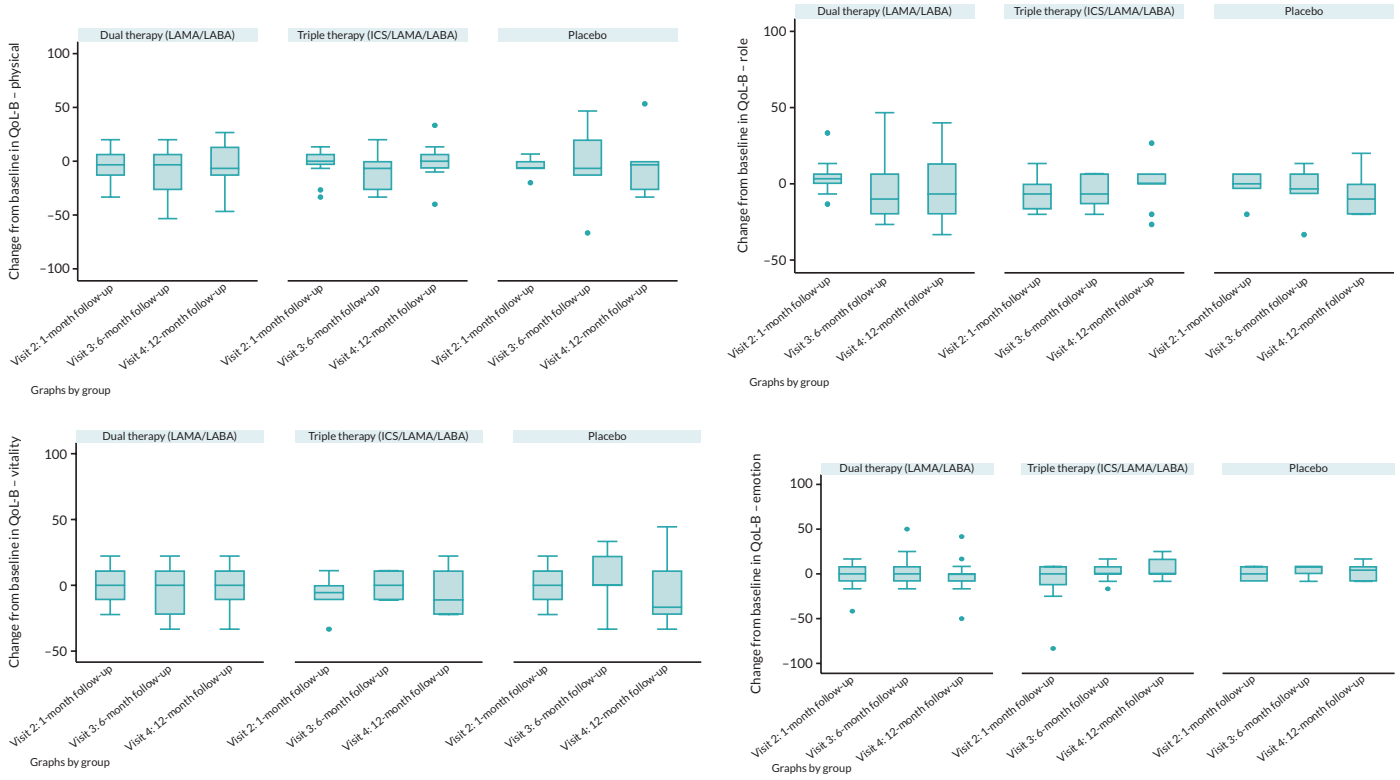

FIGURE 13 Summary of change from baseline in QoL-B across eight domains.

Appendix 4 Safety data

TABLE 16 Summary of the secondary outcomes of hospital admissions and pneumonia over time and by randomised treatment group

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
N	14	12	7	33
Total number of bronchiectasis exacerbations requiring hospital admission, n (%)				
0	13 (92.9%)	11 (91.7%)	6 (85.7%)	30 (90.9%)
1	1 (7.1%)	1 (8.3%)	0 (0.0%)	2 (6.1%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (3.0%)
Total number of emergency hospital admissions (all causes), n (%)				
0	11 (78.6%)	10 (83.3%)	6 (85.7%)	27 (81.8%)
1	2 (14.3%)	2 (17.7%)	0 (0.0%)	4 (12.1%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	1 (7.1%)	0 (0.0%)	1 (14.3%)	2 (6.1%)
Number of radiologically confirmed pneumonia, n (%)				
0	14 (100.0%)	11 (91.7%)	7 (100.0%)	32 (97.0%)
1	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.0%)

This synopsis should be referenced as follows:
Wilson N, Morton M, Homer T, Konkoth AB, Joyce R, Kershaw A, *et al.* A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis [published online ahead of print February 4 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GGCC1111

TABLE 17 Number of AEs (serious and non-serious)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Number of participants randomised	14	12	7	33
Number of AEs	75	68	26	169
Number of participants with AEs, *n* (%)	13 (92.9%)	12 (100.0%)	5 (71.4%)	30 (90.9%)

TABLE 18 Number of participants reporting SAEs, SARs and SUSARs

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
N	14	12	7	33
SAE				
Number of events	5	2	3	10
Number of participants with events, *n* (%)	3 (21.4%)	2 (16.7%)	1 (14.3%)	6 (18.2%)
SAR				
Number of events	0	0	0	0
Number of participants with events, *n* (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SUSAR				
Number of events	0	0	0	0
Number of participants with events, *n* (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

SAR, serious adverse reaction; SUSAR, suspected unexpected serious adverse reaction.

TABLE 19 Frequency and percentage of participants for each reported SAEs and adverse reactions (worst severity reported), organised by system organ class and level of severity and split by treatment arm

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Respiratory, thoracic and mediastinal disorders	*N*	14	12	7	33
	Bronchiectasis				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	1 (7.1%)	0	1 (14.3%)	2 (6.1%)
	Severe	0	0	0	0
	Life-threatening	0	0	0	0
	Death	0	0	0	0
	Missing	0	0	0	0

TABLE 19 Frequency and percentage of participants for each reported SAEs and adverse reactions (worst severity reported), organised by system organ class and level of severity and split by treatment arm (continued)

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
General system disorders NEC	***Pain***				
	Mild	0	0	0	0
	Moderate	1 (7.1%)	0	0	1 (3.0%)
	Severe	0	0	0	0
	Life-threatening	0	0	0	0
	Death	0	0	0	0
	Missing	0	0	0	0
Infections and infestations	***Urinary tract infection***				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Severe	0	0	0	0
	Life-threatening	0	0	0	0
	Death	0	0	0	0
	Missing	0	0	0	0
	Mycobacterium abscessus infection				
	Mild	0	0	0	0
	Moderate	0	1 (8.3%)	0	1 (3.0%)
	Severe	0	0	0	0
	Life-threatening	0	0	0	0
	Death	0	0	0	0
	Missing	0	0	0	0
Gastrointestinal disorder	***Vomiting***				
	Mild	0	0	0	0
	Moderate	1 (7.1%)	0	0	1 (3.0%)
	Severe	0	0	0	0
	Life-threatening	0	0	0	0
	Death	0	0	0	0
	Missing	0	0	0	0
Psychiatric disorders	***Suicide attempt***				
	Mild	0	0	0	0
	Moderate	1 (7.1%)	0	0	1 (3.0%)
	Severe	0	0	0	0
	Life-threatening	0	0	0	0
	Death	0	0	0	0
	Missing	0	0	0	0

NEC, necrotising enterocolitis.

TABLE 20 Frequency and percentage of participants for each reported non-SAEs and adverse reactions (worst severity reported), organised by system organ class and level of severity and split by treatment arm

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
	N	14	12	7	33
Blood and lymphatic system disorders	***Thrombocytopenia***				
	Mild	0	0	0	0
	Moderate	0	1 (8.3%)	0	1 (3.0%)
	Missing	0	0	0	0
	Anaemia				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
Cardiac disorders	***Left ventricular dysfunction***				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Palpitations				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
Gastrointestinal disorders	***Dental discomfort***				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Dysphagia				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Gastroenteritis viral				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Frequent bowel movements				
	Mild	0	0	1 (14.3%)	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0

TABLE 20 Frequency and percentage of participants for each reported non-SAEs and adverse reactions (worst severity reported), organised by system organ class and level of severity and split by treatment arm (continued)

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
	Haemorrhoids	1	–	–	–
	Mild	–7.10%	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Nausea	–	–	–	–
	Mild	0	0	0	0
	Moderate	0	1 (8.3%)	0	1 (3.0%)
	Missing	0	0	0	0
	Dysgeusia				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Vomiting				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Oropharyngeal pain				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
General disorders and administration	***Fatigue***				
	Mild	2 (14.3%)	2 (16.7%)	0	4 (12.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Hernia				
	Mild	0	0	1 (14.3%)	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Pyrexia				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
Immune system disorders	***Seasonal allergy***				
	Mild	1 (7.1%)	1 (8.3%)	1 (14.3%)	3 (9.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0

continued

TABLE 20 Frequency and percentage of participants for each reported non-SAEs and adverse reactions (worst severity reported), organised by system organ class and level of severity and split by treatment arm (continued)

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Infections and infestations	***COVID-19***				
	Mild	4 (28.6%)	2 (16.7%)	2 (28.6%)	8 (24.2%)
	Moderate	0	2 (16.7%)	0	2 (6.1%)
	Missing	0	0	0	0
	Ear infection				
	Mild	1 (7.1%)	1 (8.3%)	0	2 (6.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Herpes zoster				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Mycobacterial infection				
	Mild	0	0	0	0
	Moderate	0	1 (8.3%)	0	1 (3.0%)
	Missing	0	0	0	0
	Nasopharyngitis				
	Mild	1 (7.1%)	1 (8.3%)	0	2 (6.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Sinusitis				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	1 (8.3%)	0	1 (3.0%)
	Urinary tract infection				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Vulvovaginal candidiasis				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0

TABLE 20 Frequency and percentage of participants for each reported non-SAEs and adverse reactions (worst severity reported), organised by system organ class and level of severity and split by treatment arm (continued)

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Injury, poisoning and procedural complications	***Head injury***				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Nerve compression				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Skin laceration				
	Mild	0	0	1 (14.3%)	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
Investigations	***Blood glucose increased***				
	Mild	0	0	1 (14.3%)	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Blood iron decreased				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Body temperature increased				
	Mild	1 (7.1%)	1 (8.3%)	0	2 (6.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Fractional exhaled NO abnormalities				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Weight decreased				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0

continued

TABLE 20 Frequency and percentage of participants for each reported non-SAEs and adverse reactions (worst severity reported), organised by system organ class and level of severity and split by treatment arm (continued)

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Metabolism and nutrition disorders	***Abnormal loss of weight***				
	Mild	0	0	1 (14.3%)	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
Musculoskeletal and connective tissue disorders	***Wrist fracture***				
	Mild	0	0	0	0
	Moderate	1 (7.1%)	0	0	1 (3.0%)
	Missing	0	0	0	0
	Arthralgia				
	Mild	4 (28.6%)	1 (8.3%)	0	5 (15.2%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Axillary mass				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Back pain				
	Mild	2 (14.3%)	2 (16.7%)	0	4 (12.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Dupuytren's contracture				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Intervertebral disc protrusion				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	1 (8.3%)	0	1 (3.0%)
	Missing	0	0	0	0
	Muscle spasms				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	1 (8.3%)	0	1 (3.0%)
	Missing	0	0	0	0

TABLE 20 Frequency and percentage of participants for each reported non-SAEs and adverse reactions (worst severity reported), organised by system organ class and level of severity and split by treatment arm (continued)

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
	Muscle strain				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Musculoskeletal chest pain				
	Mild	2 (14.3%)	0	0	2 (6.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Pain in extremity				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
Nervous system disorders	***Dizziness***				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Headache				
	Mild	1 (7.1%)	3 (25.0%)	0	4 (12.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Neuralgia				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
Psychiatric disorders	***Depression***				
	Mild	0	1 (8.3%)	1 (14.3%)	2 (6.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Sleep disorder				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0

continued

This synopsis should be referenced as follows:
Wilson N, Morton M, Homer T, Konkoth AB, Joyce R, Kershaw A, *et al.* A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis [published online ahead of print February 4 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GGCC1111

TABLE 20 Frequency and percentage of participants for each reported non-SAEs and adverse reactions (worst severity reported), organised by system organ class and level of severity and split by treatment arm (continued)

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Renal and urinary disorders	***Haematuria***				
	Mild	0	1 (8.3%)	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0refer
Respiratory, thoracic and mediastinal disorders	***Anosmia***				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Bronchial secretion retention				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Bronchiectasis				
	Mild	3 (21.4%)	5 (41.7%)	4 (57.1%)	12 (36.4%)
	Moderate	0	0	1 (14.3%)	1 (3.0%)
	Missing	1 (7.1%)	0	0	1 (3.0%)
	Chest discomfort				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	1 (14.3%)	1 (3.0%)
	Missing	0	0	0	0
	Chest pain				
	Mild	1 (7.1%)	1 (8.3%)	1 (14.3%)	3 (9.1%)
	Moderate	0	1 (8.3%)	1 (14.3%)	2 (6.1%)
	Missing	0	0	0	0
	Cough				
	Mild	3 (21.4%)	1 (8.3%)	0	4 (12.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Dyspnoea				
	Mild	2 (14.3%)	1 (8.3%)	0	3 (9.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0

TABLE 20 Frequency and percentage of participants for each reported non-SAEs and adverse reactions (worst severity reported), organised by system organ class and level of severity and split by treatment arm (continued)

	Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
Haemoptysis				
Mild	1 (7.1%)	0	0	1 (3.0%)
Moderate	0	0	0	0
Missing	0	0	0	0
Nasal congestion				
Mild	1 (7.1%)	0	0	1 (3.0%)
Moderate	0	0	0	0
Missing	0	0	0	0
Pneumonia				
Mild	0	1 (8.3%)	0	1 (3.0%)
Moderate	0	0	0	0
Missing	0	0	0	0
Productive cough				
Mild	0	1 (8.3%)	0	1 (3.0%)
Moderate	0	0	0	0
Missing	0	0	0	0
Rales				
Mild	1 (7.1%)	0	0	1 (3.0%)
Moderate	0	0	0	0
Missing	0	0	0	0
Respiratory tract congestion				
Mild	1 (7.1%)	0	0	1 (3.0%)
Moderate	0	0	0	0
Missing	0	0	0	0
Rhinorrhoea				
Mild	0	1 (8.3%)	0	1 (3.0%)
Moderate	0	0	0	0
Missing	0	0	0	0
Sinus disorder				
Mild	1 (7.1%)	0	0	1 (3.0%)
Moderate	0	0	0	0
Missing	0	0	0	0

continued

TABLE 20 Frequency and percentage of participants for each reported non-SAEs and adverse reactions (worst severity reported), organised by system organ class and level of severity and split by treatment arm (continued)

		Dual therapy (LAMA/LABA)	Triple therapy (ICS/LAMA/LABA)	Placebo	Total
	Sputum increased				
	Mild	1 (7.1%)	1 (8.3%)	0	2 (6.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Wheezing				
	Mild	2 (14.3%)	0	0	2 (6.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
Skin and subcutaneous tissue disorders	***Rash***				
	Mild	1 (7.1%)	0	1 (14.3%)	2 (6.1%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
	Actinic keratosis				
	Mild	0	0	0	0
	Moderate	0	1 (8.3%)	0	1 (3.0%)
	Missing	0	0	0	0
	Transient acantholytic dermatosis				
	Mild	0	0	0	0
	Moderate	0	1 (8.3%)	0	1 (3.0%)
	Missing	0	0	0	0
	Rosacea				
	Mild	1 (7.1%)	0	0	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0
Vascular disorders	***Hypertension***				
	Mild	0	0	1 (14.3%)	1 (3.0%)
	Moderate	0	0	0	0
	Missing	0	0	0	0

Appendix 5 Health economics results

TABLE 21 Summary of the Time and Travel questionnaire completeness

	Dual therapy (LAMA/LABA) (*N* = 14)	Triple therapy (ICS/LAMA/LABA) (*N* = 12)	Placebo (*N* = 7)
Complete	11 (79%)	11 (92%)	5 (71%)
Missing	3 (21%)	1 (8%)	2 (29%)

N, number of participants.

TABLE 22 Summary of time and travel data

	N	Mean (SD)	Median (IQR)
Hospital admissions			
Ambulance	9	0.22 (0.44)	0 (0–0)
Hospital vehicle	9	0.00 (0.00)	0 (0–0)
Car	9	0.33 (0.50)	0 (0–1)
Taxi	9	0.11 (0.33)	0 (0–0)
Public transport	9	0.11 (0.33)	0 (0–0)
Other	9	0.22 (0.44)	0 (0–0)
Miles (one way)	3	7.00 (6.56)	8 (0–13)
Parking fee (£)	3	1.33 (2.30)	0 (0–4)
Fare (one way) (£)	3	6.67 (11.55)	0 (0–20)
Cost of other transport (£)	2	0.00 (0.00)	0 (0–0)
Time travelling – one way (minutes)	4	35.00 (26.46)	40 (15–55)
Main activity – paid work	8	0.00 (0.00)	0 (0–0)
Main activity – caring	8	0.00 (0.00)	0 (0–0)
Main activity – child care	8	0.00 (0.00)	0 (0–0)
Main activity – leisure	8	0.38 (0.52)	0 (0–1)
Main activity – housework	8	0.13 (0.35)	0 (0–1)
Main activity – voluntary	8	0.00 (0.00)	0 (0–0)
Main activity – other	8	0.50 (0.53)	0.5 (0–1)
Accompanied by carer	9	0.56 (0.53)	1 (0–1)
Carer time (minutes)	5	165 (65.73)	150 (150–150)
Carer activity – paid work	6	0.17 (0.41)	0 (0–0)
Carer activity – caring	6	0.17 (0.41)	0 (0–0)
Carer activity – child care	6	0.00 (0.00)	0 (0–0)
Carer activity – leisure	6	0.17 (0.41)	0 (0–0)
Carer activity – housework	6	0.33 (0.52)	0 (0–1)
Carer activity – voluntary	6	0.00 (0.00)	0 (0–0)
Carer activity – other	6	0.33 (0.52)	0 (0–1)

continued

This synopsis should be referenced as follows:
Wilson N, Morton M, Homer T, Konkoth AB, Joyce R, Kershaw A, *et al.* A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis [published online ahead of print February 4 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GGCC1111

TABLE 22 Summary of time and travel data (continued)

	N	Mean (SD)	Median (IQR)
Outpatient visits			
Ambulance	24	0.00 (0.00)	0 (0–0)
Hospital vehicle	24	0.67 (0.48)	1 (0–1)
Car	24	0.12 (0.34)	0 (0–0)
Taxi	24	0.21 (0.42)	0 (0–0)
Public transport	24	0.00 (0.00)	0 (0–0)
Other	24	0.00 (0.00)	0 (0–0)
Miles (one way)	16	11.81 (9.46)	9 (4.5–19.5)
Parking fee (£)	15	1.93 (2.69)	0 (0–4)
Fare (one way) (£)	5	6.60 (9.37)	0 (0–13)
Cost of other transport	–	–	–
Time travelling – one way (minutes)	23	30.61 (18.40)	30 (15–45)
Time spent at appointment (inc. waiting) (minutes)	22	92.73 (56.44)	90 (45–90)
Main activity – paid work	22	0.23 (0.43)	0 (0–0)
Main activity – caring	22	0.23 (0.43)	0 (0–0)
Main activity – child care	22	0.00 (0.00)	0 (0–0)
Main activity – leisure	22	0.27 (0.46)	0 (0–1)
Main activity – housework	22	0.27 (0.46)	0 (0–1)
Main activity – voluntary	22	0.00 (0.00)	0 (0–0)
Main activity – other	22	0.23 (0.43)	0 (0–0)
Accompanied by carer	22	0.27 (0.46)	0 (0–0)
Carer activity – paid work	10	0.00 (0.00)	0 (0–0)
Carer activity – caring	10	0.00 (0.00)	0 (0–0)
Carer activity – child care	10	0.00 (0.00)	0 (0–0)
Carer activity – leisure	10	0.10 (0.32)	0 (0–0)
Carer activity – housework	10	0.30 (0.48)	0 (0–1)
Carer activity – voluntary	10	0.00 (0.00)	0 (0–0)
Carer activity – other	10	0.50 (0.53)	0.5 (0–1)
Walk-in centre			
Ambulance	5	0.40 (0.55)	0 (0–1)
Hospital vehicle	5	0.20 (0.45)	0 (0–0)
Car	5	0.40 (0.55)	0 (0–1)
Taxi	5	0.00 (0.00)	0 (0–0)
Public transport	5	0.00 (0.00)	0 (0–0)
Other	5	0.00 (0.00)	0 (0–0)
Miles (one way)	3	4.33 (4.04)	5 (0–8)

TABLE 22 Summary of time and travel data (continued)

	N	Mean (SD)	Median (IQR)
Parking fee (£)	3	1.33 (2.31)	0 (0–4)
Fare (one way) (£)	3	2.17 (3.75)	0 (0–6.5)
Cost of other transport	–	–	–
Time travelling (one way) (minutes)	4	21.25 (8.54)	22.5 (15–27.5)
Time at appointment (inc. waiting) (minutes)	5	87 (106.81)	45 (15–90)
Main activity – paid work	5	0.00 (0.00)	0 (0–0)
Main activity – caring	5	0.00 (0.00)	0 (0–0)
Main activity – child care	5	0.00 (0.00)	0 (0–0)
Main activity – leisure	5	0.80 (0.45)	1 (1–1)
Main activity – housework	5	0.00 (0.00)	0 (0–0)
Main activity – voluntary	5	0.00 (0.00)	0 (0–0)
Main activity – other	5	0.20 (0.45)	0 (0–0)
Accompanied by carer	7	0.29 (0.49)	0 (0–1)
Carer activity – paid work	2	0.00 (0.00)	0 (0–0)
Carer activity – caring	2	0.00 (0.00)	0 (0–0)
Carer activity – child care	2	0.00 (0.00)	0 (0–0)
Carer activity – leisure	2	0.50 (0.71)	0.5 (0–1)
Carer activity – housework	2	0.50 (0.71)	0.5 (0–1)
Carer activity – voluntary	2	0.00 (0.00)	0 (0–0)
Carer activity – other	2	0.00 (0.00)	0 (0–0)
GP visits			
Ambulance	22	0.59 (0.50)	1 (0–1)
Hospital vehicle	22	0.05 (0.21)	0 (0–0)
Car	22	0.18 (0.39)	0 (0–0)
Taxi	22	0.18 (0.39)	0 (0–0)
Public transport	22	0.00 (0.00)	0 (0–0)
Other	22	0.00 (0.00)	0 (0–0)
Miles (one way)	16	2.50 (0.89)	2.5 (2–4)
Parking fee (£)	11	0.00 (0.00)	0 (0–0)
Fare (one way) (£)	4	0.78 (1.55)	0 (0–1.55)
Cost of other transport (£)	4	0.78 (1.55)	0 (0–1.55)
Time travelling (one way) (minutes)	21	10.48 (5.14)	10 (6–15)
Time at appointment (inc. waiting) (minutes)	22	37.50 (29.19)	30 (15–45)
Main activity – paid work	21	0.19 (0.40)	0 (0–0)
Main activity – caring	21	0.19 (0.40)	0 (0–0)

continued

TABLE 22 Summary of time and travel data (continued)

	N	Mean (SD)	Median (IQR)
Main activity – child care	21	0.00 (0.00)	0 (0–0)
Main activity – leisure	21	0.24 (0.44)	0 (0–0)
Main activity – housework	21	0.38 (0.50)	0 (0–1)
Main activity – voluntary	21	0.00 (0.00)	0 (0–0)
Main activity – other	21	0.19 (0.40)	0 (0–0)
Accompanied by carer	23	0.04 (0.21)	0 (0–0)
Carer activity – paid work	3	0.00 (0.00)	0 (0–0)
Carer activity – caring	3	0.00 (0.00)	0 (0–0)
Carer activity – child care	3	0.00 (0.00)	0 (0–0)
Carer activity – leisure	3	0.33 (0.58)	0 (0–1)
Carer activity – housework	3	0.00 (0.00)	0 (0–0)
Carer activity – voluntary	3	0.00 (0.00)	0 (0–0)
Carer activity – other	3	0.33 (0.58)	0 (0–1)
Care from family/friends			
Car	5	0.60 (0.55)	1 (0–1)
Taxi	5	0.20 (0.45)	0 (0–0)
Public transport	5	0.20 (0.45)	0 (0–0)
Other	5	0.00 (0.00)	0 (0–0)
Miles (one way)	4	3.00 (4.08)	1.5 (0.5–5.5)
Parking fee (£)	2	0.00 (0.00)	0 (0–0)
Fare (one way) (£)	2	0.00 (0.00)	0 (0–0)
Cost of other transport (£)	–	–	–
Time spent travelling (one way)	5	12.80 (17.24)	2 (2–20)
Carer activity – paid work	5	0.20 (0.45)	0 (0–0)
Carer activity – caring	5	0.20 (0.45)	0 (0–0)
Carer activity – child care	5	0.00 (0.00)	0 (0–0)
Carer activity – leisure	5	0.00 (0.00)	0 (0–0)
Carer activity – housework	5	0.20 (0.45)	0 (0–0)
Carer activity – voluntary	5	0.00 (0.00)	0 (0–0)
Carer activity – other	5	0.60 (0.55)	1 (0–1)
Employment status			
Full-time	24	0.17 (0.38)	0 (0–0)
Part-time	24	0.12 (0.34)	0 (0–0)
Student	24	0.00 (0.00)	0 (0–0)
Retired	24	0.67 (0.48)	1 (0–1)
Housework	24	0.00 (0.00)	0 (0–0)

TABLE 22 Summary of time and travel data (continued)

	N	Mean (SD)	Median (IQR)
Caring	24	0.00 (0.00)	0 (0–0)
Unemployed – not seeking work	24	0.00 (0.00)	0 (0–0)
Unemployed – actively seeking work	24	0.00 (0.00)	0 (0–0)
Other	24	0.04 (0.20)	0 (0–0)
Household income			
< £6000	19	0.00 (0.00)	0 (0–0)
£6001–10,000	19	0.05 (0.23)	0 (0–1)
£10,001–15,000	19	0.16 (0.37)	0 (0–0)
£15,001–20,000	19	0.11 (0.32)	0 (0–0)
£20,001–30,000	19	0.05 (0.23)	0 (0–0)
£30,001–35,000	19	0.21 (0.42)	0 (0–0)
≥ £35,001	19	0.11 (0.32)	0 (0–0)

GP, general practitioner; *N*, number of participants.

TABLE 23 Summary of the HCUQ completeness at each time point

	Dual therapy (LAMA/LABA) (*N* = 14)	Triple therapy (ICS/LAMA/LABA) (*N* = 12)	Placebo (*N* = 7)
Baseline			
Complete	14 (100%)	12 (100%)	7 (100%)
Missing	0 (0%)	0 (0%)	0 (0%)
1 month			
Complete	14 (100%)	12 (100%)	7 (100%)
Missing	0 (0%)	0 (0%)	0 (0%)
6 months			
Complete	14 (100%)	11 (92%)	6 (86%)
Missing	0 (0%)	1 (8%)	1 (14%)
12 months			
Complete	13 (93%)	11 (92%)	6 (86%)
Missing	1 (7%)	1 (8%)	1 (14%)

N, number of participants.

TABLE 24 Summary of the EQ-5D-5L questionnaire completeness at each time point

	Dual therapy (LAMA/LABA) (*N* = 14)	Triple therapy (ICS/LAMA/LABA) (*N* = 12)	Placebo (*N* = 7)
Baseline			
Complete	14 (100%)	12 (100%)	7 (100%)
Missing	0 (0%)	0 (0%)	0 (0%)
1 month			
Complete	14 (100%)	12 (100%)	7 (100%)
Missing	0 (0%)	0 (0%)	0 (0%)
6 months			
Complete	14 (100%)	11 (92%)	6 (86%)
Missing	0 (0%)	1 (8%)	1 (14%)
12 months			
Complete	13 (93%)	11 (92%)	6 (86%)
Missing	1 (7%)	1 (8%)	1 (14%)

N, number of participants.

TABLE 25 Average total self-reported resource use over 12 months

	All (*N* = 30)		Dual therapy (LAMA/LABA) (*N* = 13)		Triple therapy (ICS/LAMA/LABA) (*N* = 11)		Placebo (*N* = 6)	
Resource	***N***	**Mean (SD)**	***N***	**Mean (SD)**	***N***	**Mean (SD)**	***N***	**Mean (SD)**
Inpatient stay	30	0.20 (0.55)[a]	13	0.23 (0.60)	11	0.27 (0.65)	6	0.00 (0.00)
No. of nights	30	3.67 (10.59)[a]	13	4.38 (11.03)	11	4.82 (13.01)	6	0.00 (0.00)
A&E	30	0.27 (0.53)	13	0.38 (0.65)	11	0.09 (0.30)	6	0.33 (0.52)
No. of visits	30	0.30 (0.60)	13	0.46 (0.78)	11	0.09 (0.30)	6	0.33 (0.52)
Outpatient appt.	30	1.43 (1.04)	13	1.31 (1.03)	11	1.45 (1.13)	6	1.67 (1.03)
No. of appts.	29	3.48 (3.83)	12	2.67 (3.28)	11	3.36 (3.88)	6	5.33 (4.76)
Phone hospital	29	0.83 (0.80)	12	0.83 (0.83)	11	0.82 (0.87)	6	0.83 (0.75)
No. of calls	29	1.41 (1.72)	12	1.50 (1.83)	11	1.45 (1.97)	6	1.17 (1.17)
Walk-in centre visits	30	0.10 (0.31)	13	0.08 (0.28)	11	0.09 (0.30)	6	0.17 (0.41)
No. of visits	30	0.13 (0.43)	13	0.08 (0.28)	11	0.09 (0.30)	6	0.33 (0.82)
Face-to-face consultation with a healthcare professional	29	1.55 (1.02)	12	1.58 (1.08)	11	1.36 (0.92)	6	1.83 (1.17)
GP	28	1.17 (0.90)	12	1.08 (1.00)	11	1.09 (0.83)	5	1.60 (0.89)
No. of visits	27	1.96 (1.83)	12	1.58 (1.62)	11	1.91 (1.64)	4	3.25 (2.75)
Practice nurse	28	0.68 (0.77)	12	0.67 (0.78)	11	0.64 (0.81)	5	0.80 (0.84)
No. of visits	27	1.22 (1.65)	12	1.25 (1.82)	11	1.00 (1.41)	4	1.75 (2.06)

TABLE 25 Average total self-reported resource use over 12 months (continued)

	All (*N* = 30)		Dual therapy (LAMA/LABA) (*N* = 13)		Triple therapy (ICS/LAMA/LABA) (*N* = 11)		Placebo (*N* = 6)	
Resource	***N***	**Mean (SD)**	***N***	**Mean (SD)**	***N***	**Mean (SD)**	***N***	**Mean (SD)**
Other healthcare professional	28	0.32 (0.48)	12	0.42 (0.51)	11	0.18 (0.40)	5	0.40 (0.55)
No. of visits	28	0.64 (1.28)	12	0.92 (1.73)	11	0.27 (0.65)	5	0.80 (1.10)
Home consultation with a healthcare professional	29	0.21 (0.56)	12	0.25 (0.62)	11	0.00 (0.00)	6	0.50 (0.84)
GP	29	0.00 (0.00)	12	0.00 (0.00)	11	0.00 (0.00)	6	0.00 (0.00)
No. of visits	29	0.00 (0.00)	12	0.00 (0.00)	11	0.00 (0.00)	6	0.00 (0.00)
Practice nurse	29	0.10 (0.41)	12	0.17 (0.58)	11	0.00 (0.00)	6	0.17 (0.41)
No. of visits	29	0.38 (1.86)	12	0.83 (2.89)	11	0.00 (0.00)	6	0.17 (0.41)
Other healthcare professional	29	0.14 (0.35)	12	0.17 (0.39)	11	0.00 (0.00)	6	0.33 (0.52)
No. of visits	28	0.18 (0.77)	11	0.36 (1.21)	11	0.00 (0.00)	6	0.17 (0.41)
Telephone consultation with a healthcare professional	29	1.38 (0.90)	12	1.00 (0.74)	11	1.55 (0.82)	6	1.83 (1.17)
GP	29	0.86 (0.83)	12	0.67 (0.78)	11	1.00 (0.89)	6	1.00 (0.89)
No. of calls	29	1.52 (1.96)	12	1.42 (2.15)	11	1.64 (1.96)	6	1.50 (1.87)
Practice nurse	29	0.24 (0.69)	12	0.08 (0.29)	11	0.36 (0.92)	6	0.33 (0.82)
No. of calls	28	0.36 (1.22)	12	0.17 (0.58)	10	0.60 (1.90)	6	0.33 (0.82)
NHS call centre	29	0.03 (0.19)	12	0.00 (0.00)	11	0.09 (0.30)	6	0.00 (0.00)
No. of calls	29	0.03 (0.19)	12	0.00 (0.00)	11	0.09 (0.30)	6	0.00 (0.00)
Other healthcare professional	29	0.45 (0.57)	12	0.42 (0.51)	11	0.36 (0.50)	6	0.67 (0.82)
No. of calls	29	0.76 (1.24)	12	1.08 (1.73)	11	0.45 (0.69)	6	0.67 (0.82)
Days off paid work/usual activity	21	9.81 (19.86)	9	14.22 (29.41)	8	5.75 (7.42)	4	8.00 (9.38)

A&E, accident and emergency; Appt., appointment; *N*, number of participants; No., number.

a Interpretation: 20% of participants reported being admitted to hospital at least once during their 12-month follow-up. The average number of nights patients were admitted to hospital over 12 months was 3.67 nights.

TABLE 26 Unit costs

Resource	Unit cost (£)	Source
Inpatient stay	406	NHS reference costs – regular day or night admission[29]
A&E visit	242	NHS reference costs – emergency care[29]
Outpatient visit	203	NHS reference costs – outpatient procedures[29]
Hospital phone	20.70	PSSRU consultant medical.[30] Assumed to be a 9-minute call, same as a GP
Walk-in clinic	51	PSSRU.[30] Assumed to be the same as a GP consultation
GP visit	51	PSSRU[30]
Practice nurse visit	8.48	PSSRU.[30] Assumed to be a 9-minute and 42-second visit[41]
GP home visit	118.76	PSSRU.[30] Assumed to be a 23-minute and 15-second visit to include travel time[42]
Nurse home visit	53.74	NHS reference costs – nursing district nurse, adult, face to face[29]
GP phone call	15.33	PSSRU.[30] Telephone triage, GP-led
Nurse phone call	8.61	PSSRU.[30] Telephone triage, nurse-led
NHS 111	12.72	Turner *et al.*[43] Inflated to 2023[44]

A&E, Accident & Emergency; GP, general practitioner; PSSRU, Personal Social Services Research Unit.

TABLE 27 Average total primary and secondary care costs

	All (*N* = 30)		Dual therapy (LAMA/LABA) (*N* = 13)		Triple therapy (ICS/LAMA/LABA) (*N* = 11)		Placebo (*N* = 6)	
Resource	***N***	**Mean £ (SD)**	***N***	**Mean £ (SD)**	***N***	**Mean £ (SD)**	***N***	**Mean £ (SD)**
Inpatient costs	30	1499 (4301)	13	1780 (4477)	11	1956 (5284)	6	0 (0)
A&E costs	30	73 (144)	13	112 (188)	11	22 (73)	6	81 (125)
Outpatient costs	29	707 (778)	12	541 (667)	11	683 (788)	6	1083 (966)
Phone hospital costs	29	29 (36)	12	31 (38)	11	30 (41)	6	24 (24)
Total secondary care costs	**30**	**2273 (4776)**	**13**	**2420 (5011)**	**11**	**2691 (5875)**	**6**	**1187 (1080)**
Walk-in centre costs	30	7 (22)	13	4 (14)	11	5 (15)	6	17 (42)
GP costs	27	100 (93)	12	81 (83)	11	97 (84)	4	166 (140)
Practice nurse costs	27	10 (14)	12	11 (15)	11	8 (12)	4	15 (17)
GP home costs	29	0 (0)	12	0 (0)	11	0 (0)	6	0 (0)
Nurse home costs	29	20 (100)	12	45 (155)	11	0 (0)	6	9 (22)
GP phone costs	29	24 (30)	12	22 (33)	11	25 (30)	6	23 (29)
Nurse phone costs	28	3 (11)	12	1 (5)	10	5 (16)	6	3 (7)
NHS 111 costs	29	0.44 (2)	12	0 (0)	11	1 (4)	6	0 (0)
Total primary care costs	**30**	**174 (190)**	**13**	**171 (240)**	**11**	**166 (142)**	**6**	**195 (177)**
Total NHS costs	**30**	**2447 (4793)**	**13**	**2591 (5107)**	**11**	**2858 (5818)**	**6**	**1382 (1067)**

A&E, Accident & Emergency.

TABLE 28 Average total utility values and QALYs

	All (*N* = 33)		Dual therapy (LAMA/LABA) (*N* = 14)		Triple therapy (ICS/LAMA/LABA) (*N* = 12)		Placebo (*N* = 7)	
Resource	***N***	**Mean (SD)**	***N***	**Mean (SD)**	***N***	**Mean (SD)**	***N***	**Mean (SD)**
Baseline utility	33	0.725 (0.25)	14	0.675 (0.28)	12	0.768 (0.22)	7	0.750 (0.258)
1-month utility	33	0.705 (0.26)	14	0.625 (0.29)	12	0.788 (0.21)	7	0.723 (0.25)
6-month utility	31	0.707 (0.26)	14	0.642 (0.28)	11	0.775 (0.22)	6	0.734 (0.30)
12-month utility	30	0.742 (0.22)	13	0.660 (0.27)	11	0.826 (0.14)	6	0.750 (0.16)
QALYs	30	0.723 (0.24)	13	0.654 (0.27)	11	0.796 (0.19)	6	0.738 (0.25)

This synopsis should be referenced as follows:
Wilson N, Morton M, Homer T, Konkoth AB, Joyce R, Kershaw A, *et al.* A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis [published online ahead of print February 4 2026]. *Health Technol Assess* 2026. https://doi.org/10.3310/GGCC1111