Aksamit T, Bandel T-J, Criollo M, De Soyza A, Elborn JS, Operschall E, Polverino E, Roth K, Winthrop KL, Wilson R.

The RESPIRE trials: Two phase III, randomized, multicentre, placebo-controlled trials of Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) in non-cystic fibrosis bronchiectasis.

Contemporary Clinical Trials 2017, 58, 78-85.

Copyright:
© 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/BY/4.0/).

DOI link to article:
https://doi.org/10.1016/j.cct.2017.05.007

Date deposited:
19/06/2017

This work is licensed under a Creative Commons Attribution 4.0 International License

Newcastle University ePrints - eprint.ncl.ac.uk
The RESPIRE trials: Two phase III, randomized, multicentre, placebo-controlled trials of Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) in non-cystic fibrosis bronchiectasis

Timothy Aksamit, Tiemo-Joerg Bandel, Margarita Criollo, Anthony De Soyza, J. Stuart Elborn, Elisabeth Opschersall, Eva Polverino, Katrin Roth, Kevin L. Winthrop, Robert Wilson

a Mayo Clinic, Pulmonary Disease and Critical Care Medicine, Rochester, MN, USA
b Bayer Pharma AG, Wuppertal, Germany
c Bayer Inc., Mississauga, Ontario, Canada
d Newcastle University and Freeman Hospital, Newcastle upon Tyne, UK
e Host Defence Unit, Royal Brompton Hospital, London, UK
f Bayer Pharma AG, Berlin, Germany

ABSTRACT

The primary goals of long-term disease management in non-cystic fibrosis bronchiectasis (NCFB) are to reduce the number of exacerbations, and improve quality of life. However, currently no therapies are licensed for this. Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) has potential to be the first long-term intermittent therapy approved to reduce exacerbations in NCFB patients.

The RESPIRE programme consists of two international phase III prospective, parallel-group, randomized, double-blinded, multicentre, placebo-controlled trials of the same design. Adult patients with idiopathic or post-infectious NCFB, a history of ≥ 2 exacerbations in the previous 12 months, and positive sputum culture for one of seven pre-specified pathogens, undergo stratified randomization 2:1 to receive twice-daily Ciprofloxacin DPI 32.5 mg or placebo using a pocket-sized inhaler in one of two regimens: 28 days on/off treatment or 14 days on/off treatment. The treatment period is 48 weeks plus an 8-week follow-up after the last dose. The primary efficacy endpoints are time to first exacerbation after treatment initiation and frequency of exacerbations using a stringent definition of exacerbation. Secondary endpoints, including frequency of events using different exacerbation definitions, microbiology, quality of life and lung function will also be evaluated.

The RESPIRE trials will determine the efficacy and safety of Ciprofloxacin DPI. The strict entry criteria and stratified randomization, the inclusion of two treatment regimens and a stringent definition of exacerbation should clarify the patient population best positioned to benefit from long-term inhaled antibiotic therapy. Additionally RESPIRE will increase understanding of NCFB treatment and could lead to an important new therapy for sufferers.

Trial registration: The RESPIRE trials are registered in ClinicalTrials.gov, ID number NCT01764841 (RESPIRE 1; date of registration January 8, 2013) and NCT02106832 (RESPIRE 2; date of registration April 4, 2014).

Abbreviations: CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; DPI, dry powder for inhalation; EOS, end of study; EOT, end of treatment; FAS, full analysis set; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MIC, minimum inhibitory concentration; NCFB, non-cystic fibrosis bronchiectasis; NTM, non-tuberculous mycobacteria; QOL-B, Quality of Life-Bronchiectasis; SGRQ, St George’s Respiratory Questionnaire

E-mail addresses: Aksamit.Timothy@mayo.edu (T. Aksamit), tiemo-joerg.bandel@bayer.com (T.-J. Bandel), mcriollo@rogers.com (M. Criollo), anthony.de-soyza@ncl.ac.uk (A. De Soyza), j.elborn@imperial.ac.uk (J.S. Elborn), elisabeth.opschersall@bayer.com (E. Opschersall), eva.polverino@vhir.org (E. Polverino), katrin.roth@bayer.com (K. Roth), Winthrop@ohsu.edu (K.L. Winthrop), r.wilson@rbht.nhs.uk (R. Wilson).

http://dx.doi.org/10.1016/j.cct.2017.05.007
Received 4 January 2017; Received in revised form 2 May 2017; Accepted 7 May 2017
Available online 08 May 2017
1551-7144/ © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
1. Background

Non-cystic fibrosis bronchiectasis (NCFB) is a chronic respiratory disease, characterized by abnormal dilation of the bronchi leading to a cycle of inflammation and infection and reduced quality of life [1–5]. NCFB is associated with significant morbidity, and mortality of up to twofold higher than in the general population [6–8]. Frequent exacerbations are associated with a lower quality of life [9], future exacerbations, increased morbidity and mortality [10,11], and are likely linked to disease progression [12]. Mean exacerbation rates of 1.0 to 2.6 per year have been reported [10,13–15] and nearly 50% of patients, in at least one series, experience two or more exacerbations per year [16].

Reducing the number and frequency of exacerbations is a primary aim of long-term disease management [1]. There are currently no licensed therapies to reduce acute exacerbations and treatment approaches are primarily derived from studies in cystic fibrosis (CF). Inhaled antibiotic trials in NCFB have had largely disappointing results; some therapies have not demonstrated significant impacts on exacerbation rate [13,17–19] while others have reported unanticipated pulmonary adverse events [20–22]. To date, only a small, open-label, randomized study of continuous nebulized gentamicin achieved its primary endpoint [23]. Long-term therapy with oral macrolides has also been shown to reduce exacerbations [24–26]; however, studies have differed in design and patient population. Consequently the appropriate target patient population, drug, dose and risk-benefit of long-term use remain unclear [27].

Despite the critical impact of exacerbations on patients, there is neither a current validated or universally accepted definition for exacerbation nor established criteria for assessing the severity of exacerbations. Identifying and documenting an exacerbation in patients with chronic presence of bacterial pathogens in sputum culture and fluctuating symptoms can also be challenging, particularly as many patients start rescue antibiotics promptly in response to symptoms potentially suggestive of the onset of an exacerbation. The definition of exacerbation varies between clinical studies and sometimes includes symptoms caused by respiratory viruses or other events antibacterial therapy is not appropriate. The RESPIRE studies use two definitions of exacerbation: a stringent definition, in order to reduce the impact of variability in clinical assessments on efficacy outcomes; and a comparatively ‘less stringent’ definition which will act as a confirmatory analysis and provide insight into the impact of exacerbation definition on clinical endpoints.

Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) is an inhaled antibiotic consisting of capsules containing 32.5 mg ciprofloxacin inhalation powder which is formulated using Novartis’ PulmoSphere™ technology. The drug is delivered by a pocket-sized inhaler (Fig. 1). Each capsule contains 32.5 mg ciprofloxacin inhalation powder. Patients administer Ciprofloxacin DPI twice daily; the dose can be delivered in one-to-two breaths. Dry powder inhalers have a short administration time, improved portability and require no intensive cleaning [28]; features that could potentially promote treatment adherence.

Ciprofloxacin DPI was developed to delay and reduce exacerbations and improve quality of life in NCFB patients with frequent exacerbations and evidence of respiratory pathogens. A phase II, randomized, double-blind, placebo-controlled study of Ciprofloxacin DPI 32.5 mg for 28 days in patients with NCFB was promising, with significant reductions in total sputum bacterial load at end-of-treatment and a favourable safety and tolerability profile [29].

Ciprofloxacin DPI aims to be the first long-term intermittent therapy approved in NCFB. This paper describes the unique study design of phase III RESPIRE programme for Ciprofloxacin DPI in NCFB, the largest trial programme yet conducted in this population.

2. Methods/design

2.1. Aims

The primary objectives of the RESPIRE studies are to evaluate the efficacy of Ciprofloxacin DPI in prolonging the time to first exacerbation and reducing the frequency of exacerbations with two treatment regimens (28 days on/off and 14 days on/off) in patients with NCFB using a stringent definition of exacerbation.

Secondary objectives of these studies are to evaluate microbiology, quality of life, and lung function, in patients with NCFB treated with Ciprofloxacin DPI or placebo.

2.2. Exacerbation definitions

The two primary endpoints of time to first and frequency of exacerbations use a stringent definition of exacerbation. For stringently defined events occurring during the study, three criteria are required to be met:

1) Worsening of at least three signs or symptoms (dyspnoea, wheezing, cough, 24-hour sputum volume or sputum purulence) for at least 2 consecutive days (beyond normal day-to-day variations)

2) Fever (body temperature > 38.0 °C) OR malaise/fatigue

3) Treatment with systemic antibiotic(s)

This stringent definition of exacerbation will also be used for the first secondary endpoints.

A comparatively less stringent definition of exacerbation will be used for second secondary endpoints (Table 1). For this definition only two criteria are required to be met:

1) Worsening of one or more signs or symptoms (dyspnoea, wheezing, cough, 24-hour sputum volume or sputum purulence)

2) Treatment with systemic antibiotic(s).

Fig. 1. Ciprofloxacin DPI consisting of capsules containing ciprofloxacin inhalation powder and a pocket-sized inhaler.
2.3. Study design

The RESPIRE programme consists of two trials (RESPIRE 1 and RESPIRE 2) that are of the same design but which differ slightly in their analysis plans. Both trials are prospective, parallel-group, randomized, double-blinded, multicentre, placebo-controlled trials in which patients with NCFB are randomized 2:1 to receive long-term intermittent regimens of twice-daily Ciprofloxacin DPI 32.5 mg or matching placebo. Outpatient clinics in Australia/New Zealand, Asia, Europe, Middle East, South Africa, and North and South America are participating.

The two intermittent Ciprofloxacin DPI regimens being studied in both RESPIRE 1 and RESPIRE 2 are: cycles of 14 days on- and 14 days off-drug or 28 days on- and 28 days off-drug (Fig. 2). Each active treatment group has a parallel placebo arm.

The treatment period in the RESPIRE trials is 48 weeks, followed by 8 weeks of off-treatment follow-up after the last study drug dose. The screening visit (Visit 1) is conducted from days 0 to 28 prior to the first study drug administration at randomization (Visit 2). Throughout the study, clinical, bacteriological and laboratory examinations will be performed. For pathogens, the bacterial species cultured at screening and on randomization are combined to form the baseline. For all other measurements, the last non-missing data point before the start of treatment is considered baseline. Following the randomization visit, study visits or calls are conducted at regular intervals during the 48-week treatment period, depending on the treatment regimen. Each visit includes collection of a sputum sample (before inhalation of the study drug); assessment of vital signs, and respiratory signs and symptoms; pulmonary function tests; a physical examination; and review of concomitant therapy, adverse events and hospitalizations for exacerbations. The St George’s Respiratory Questionnaire (SGRQ) is completed at randomization, at end of on-treatment cycle 6 (14 day regimen) and cycle 3 (28 day regimen), end of treatment (EOT) and end of study (EOS). Quality of Life-Bronchiectasis (QoL-B) questionnaire data is collected a total of nine (28 day regimen) or ten (14 day regimen) times throughout the study, including time points at EOT and EOS. Nasal swabs, blood and sputum samples for inflammatory markers and samples for pharmacokinetic analyses are collected at baseline and periodically thereafter. Telephone calls from the study site are used to remind the patient of the start of a new treatment cycle; check treatment compliance and results of home pregnancy tests; as well as to review adverse events, hospitalizations and changes in concomitant therapy. The EOT visit takes place at the end of the on-treatment phase in the last treatment cycle. EOT assessments are also performed for patients who discontinued the study prematurely. The EOS visit occurs 8 weeks after the last dose for both the 14 days on/off and 28 days on/off regimen.

Documented approval from Independent Ethics Committees and Institutional Review Boards was obtained from all participating centres/countries before the start of the study, according to Good Clinical Practice and local laws and regulations. Written informed consent was obtained from all participants.

2.4. Intervention

Ciprofloxacin DPI and matched placebo are provided as capsules for inhalation. The dose is delivered by a pocket-sized, portable, breath-actuated, dry powder inhaler (T-326) supplied by Novartis, San Carlos, CA (Fig. 1). The contents of a capsule, containing 35.5 mg of cipro-
floxacina or placebo, are inhaled in one breath, or two breaths if needed, twice daily. On every treatment day, study drug administration by inhalation is performed once in the morning and once in the evening after completion of the patient’s regular bronchiectasis treatment.

2.5. Entry criteria

Inclusion and exclusion criteria for the RESPIRE trials are shown in Table 2. Briefly, the studies include adult patients with a confirmed diagnosis of post-infectious or idiopathic NCFB based on a computed tomography scan including two or more lobes. Patients are required to have forced expiratory volume in 1 s (FEV1) between ≥30% and <90% predicted, a history of ≥2 documented exacerbations in the past 12 months, and a positive sputum culture at screening for Pseudomonas aeruginosa or one of six other pre-specified pathogens (Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Stenotrophomonas maltophilia, Burkholderia cepacia) as confirmed by a central microbiology laboratory. It is important to note that the two exacerbations reported in the prior year are not required to meet the stringent definition of exacerbation used for the primary endpoints of the study. Patients with certain underlying diseases, including cystic fibrosis, potentially associated with bronchiectasis are excluded from the RESPIRE studies (Table 2).

2.6. Randomization and masking

Randomization and medication kit numbers are generated by Bayer’s Randomization Management. Drug dispensation is managed by an interactive voice response system and interactive web response system run by an external vendor. At the randomization visit (Visit 2), patients receive a unique randomization number that allows subsequent identification of their randomized treatment group allocation. Patients in the study are randomized 2:1 (Ciprofloxacina DPI:placebo) and stratified for randomization based on chronic macrolide use, positive P. aeruginosa sputum culture and geographic region.

The study is blinded for treatment assignment, but not for treatment regimen (i.e., 28 days on/off treatment regimen or 14 days on/off regimen), as the length of treatment cycles must be known to patients.

Table 2
Key patient entry criteria for RESPIRE.

| Main inclusion criteria | Main exclusion criteria |
|-------------------------|-------------------------|
| Age ≥ 18 years.         | FEV1 < 30% or ≥90% predicted (post-bronchodilator). |
| Proven and documented diagnosis of idiopathic or post-infectious NCFB by computed tomography scan, including two or more lobes and dilated airways compatible with bronchiectasis at initial diagnosis. | Active allergic bronchopulmonary aspergillosis. |
| Positive culture from an adequate sputum sample at screening for: | Active and actively treated non-tuberculous mycobacterial infection or tuberculosis. |
| ○ Pseudomonas aeruginosa | Recent significant haemoptysis (≥300 mL or requiring blood transfusion) in the preceding 4 weeks before screening (and during the screening period). |
| ○ Haemophilus influenzae | Primary diagnosis of COPD. |
| ○ Moraxella catarrhalis | Known CF and/or documented chronic bronchial asthma. |
| ○ Staphylococcus aureus | Medical history of allergies to quinolones or fluoroquinolones. |
| ○ Streptococcus pneumoniae | | |
| ○ Stenotrophomonas maltophilia | | |
| ○ Burkholderia cepacia | | |
| History of ≥2 documented exacerbations in the past 12 months. | | |
| Stable pulmonary status as indicated by FEV1 ≥30% and <90% predicted. | | |
| Stable regimen of standard treatment with: | | |
| ○ bronchodilators, anticholinergics, inhaled corticosteroids or mucolytics, if used as chronic treatment for bronchiectasis, at least for the past 4 weeks prior to screening. | | |
| Patients on maintenance therapy with low-dose systemic corticosteroids should be receiving ≤10 mg/day prednisolone equivalent at least for the past 4 weeks before the screening visit. | | |
| ○ macrolides if used as chronic treatment for bronchiectasis for at least 6 months prior to screening. | | |
| Sputum production on the majority of days. | | |

CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; NCFB, non-cystic fibrosis bronchiectasis.
and investigators. When knowledge of the study drug is essential for the clinical management or welfare of the patient, the investigator may unblind a patient's treatment assignment.

2.7. Endpoints

2.7.1. Primary endpoints

Two different analysis plans have been agreed with two different regulatory organisations, i.e. the United States Food and Drug Administration (‘FDA’) and the European Medicines Agency and other ex-US agencies (‘EMA/others’) (Table 1). The primary endpoints agreed with authorities are:

1) Time to first exacerbation within 48 weeks after start of treatment (FDA)
2) Frequency of exacerbations during the 48-week study (EMA/others).

Time to first exacerbation (time from randomization until the visit at which the first qualifying exacerbation was recorded) will be evaluated against a pooled placebo group, and the frequency of exacerbations will be evaluated against matched placebo groups (i.e. Ciprofloxacin DPI 14 days on/off is compared to placebo 14 days on/off and Ciprofloxacin DPI 28 days on/off is compared to placebo 28 days on/off).

2.7.1.1. Exacerbations. Patients who experience worsening of respiratory signs and symptoms are required to attend an unscheduled visit with the investigator during which they provide a fresh sputum sample and undergo a physical examination to evaluate the signs and symptoms of exacerbations. Confirmed exacerbations are reported in the validated electronic system. For the primary endpoints, and first secondary endpoints, a stringent definition of exacerbation will be used (Table 1); exacerbations must fulfil all criteria to be deemed a qualifying event.

Study treatment may be temporarily interrupted during an acute exacerbation for the time of systemic antibiotic treatment. Thereafter, treatment with Ciprofloxacin DPI is to be continued according to the original treatment schedule.

2.7.2. Secondary endpoints

Table 1 presents a complete list of pre-specified secondary efficacy endpoints. Secondary endpoints will be evaluated by hierarchical testing in the order shown in Table 1 (e.g., once an endpoint does not meet the test for significance, all subsequent tests are no longer evaluated for statistically significant endpoint results, although they will be assessed for exploratory purposes).

Secondary endpoints involve further aspects that are important to the long-term management of NCFB patients. Microbial analyses (microbial re-identification and susceptibility testing) are performed by a central laboratory. Frequency of exacerbation events using a less stringent definition of exacerbation will be used as a confirmatory analysis and to provide insight into the impact of exacerbation definition on clinical endpoints.

2.7.3. Additional endpoints

Changes in spirometry values (FVC and FEV1/FVC) and inflammatory markers are being assessed as additional endpoints. A number of alternative definitions of exacerbation, addressing individual components of exacerbation definition such as fever and hospitalization, will also be evaluated for time to exacerbation and frequency of exacerbation assessments (Table 1).

2.7.4. Safety endpoints

Safety analyses include the occurrence of adverse events, the occurrence of inhalation-induced bronchospasm (decrease in FEV1 ≥ 15% [absolute value] following study drug administration), and changes in laboratory safety values. The presence of non-tuberculous mycobacteria (NTM) or Aspergillus as well as the presence of new or recurring pathogens and development of ciprofloxacin-resistant pathogenic bacterial isolates will also be analysed. Adverse events of special interest include bronchospasm, hemoptysis, hypersensitivity reaction and tendon disorder. RESPIRE 1 includes a safety analysis, performed by an independent Data Safety Monitoring Committee after at least 100 patients have completed day 168 of the clinical study. The safety assessment will evaluate all available data to that date in order to determine patient safety and to decide on continuation of the study.

2.8. Statistical analysis

2.8.1. Sample size

Sample size calculations are based on the primary efficacy variable of time to first protocol-defined exacerbation, using the stringent definition (Table 1). Assuming that Ciprofloxacin DPI prolongs median time to first exacerbation by 67%, a total of 200 first exacerbation events across all treatment arms are needed to show a prolongation in time to first exacerbation for at least one active regimen over pooled placebo with a study-wise power of 90% and a study-wise α of 0.05.

The required sample size has been determined based on blinded data, taking into account observed and expected exacerbation data. The expected proportion of patients with an event before EOT is estimated as well as the exponential drop-out rate and expected proportion of drop-outs. In addition, the expected proportion of patients prematurely discontinuing before an event is estimated. Recruitment is terminated when it could be expected that the required number of qualifying exacerbations, as defined within the study protocol, would be reached with the enrolled patients within the planned treatment period.

For the corresponding analysis of frequency of exacerbations within 48 weeks, the same assumptions as above are used; based on the sample size determined, the comparison of the single active arm versus matching placebo will have a power of at least 90%.

2.8.2. Efficacy analyses

Efficacy variables will be evaluated in the full analysis set (FAS), defined as all randomized patients; the FAS is identical to the intent-to-treat population. Analyses in the per protocol population (all patients in the FAS with a compliance of ≥80% of planned capsules, and no protocol violations influencing treatment efficacy) will serve as supporting evidence. Both 14 day and 28 day regimens will be tested in parallel. Primary variables will be tested first, followed by secondary variables in hierarchical order as shown in Table 1. To protect the study-wise α-level of 0.05, the alpha level, which is two-sided, will be split between the tests for the two regimens. An individual study will be considered successful if the hypothesis for the primary endpoint can be rejected for at least one Ciprofloxacin DPI treatment regimen. As highlighted above, two different analysis plans were agreed with the regulatory authorities.

2.8.3. Primary endpoints

For the FDA primary endpoint of time to first exacerbation using a stringent definition of exacerbation, a Cox proportional hazards model will be used to test for differences between the Ciprofloxacin DPI groups and pooled placebo group. The independent variables will be treatment group, geographic region, baseline positive culture for P. aeruginosa and chronic macrolide use. A logrank test will also be performed as a sensitivity analysis.

For the EMA/others primary endpoint of frequency of exacerbations using a stringent definition of exacerbation, a Poisson regression with adjustment for over-/under-dispersion will be used to analyze the frequency of exacerbations over 48 weeks. The model will include treatment group, pre-therapy positive culture for P. aeruginosa, chronic
macrolide use, geographic region as covariates and time in study as offset. This endpoint will be tested against matched placebo.

2.8.4. Secondary endpoints

For the first secondary FDA endpoint of frequency of exacerbation events (using the stringent definition of exacerbation) the Ciprofloxacin DPI groups will be compared to pooled placebo using a Poisson regression. In RESPIRE 1, time in study will not be included in the model but rather the frequency of exacerbation events for patients who discontinued will be extrapolated. The extrapolation rate agreed with the regulatory authority is based on whether the patient had an exacerbation event while on study drug (in patients without an exacerbation event at time of withdrawal, the average event rate per day of all treatment groups is used; in patients with at least one exacerbation, the observed rate is linearly extrapolated to 48 weeks). In RESPIRE 2 on the other hand, time in study will be used as an offset.

For the EMA/others first secondary endpoint of time to first exacerbation (using the stringent definition of exacerbation) a Cox proportional hazards model will be used to test for differences between the Ciprofloxacin DPI groups and pooled placebo group. The independent variables will be treatment group, geographic region, baseline positive culture for *P. aeruginosa* and chronic macrolide use.

For both FDA and EMA/others second secondary endpoints of frequency of exacerbation events using the less stringent definition of exacerbation, a Poisson regression with adjustment for over-/under-dispersion will be used as described previously with the FDA analysis comparing to pooled placebo, and EMA/others analysis comparing to matched placebo. Treatment group, positive baseline culture for *P. aeruginosa* and geographic region and chronic macrolide use will be used as covariates. In the EMA/others analysis plan for RESPIRE 1 and 2, and in the FDA analysis plan for RESPIRE 2, time in study will be used as an offset. For the RESPIRE 1 FDA analysis of this endpoint, the frequency of exacerbation events for patients who discontinued will be extrapolated as for the primary endpoint.

Pathogen eradication (defined as a negative culture result at EOT for the pre-specified baseline pathogen(s)) and acquisition of new pathogens (defined as presence of any of the pre-specified organisms not cultured at baseline at EOT) will be analysed by a Cochran–Mantel–Haenszel test. This will be stratified by geographic region, pre-therapy positive culture for *P. aeruginosa* and chronic macrolide use and will compare each Ciprofloxacin DPI arm against pooled placebo.

Change from baseline to EOT in SGRQ symptoms component score, QoL-B respiratory symptoms domain and FEV1 will be analysed for Ciprofloxacin DPI versus pooled placebo using an analysis of covariance model (ANCOVA) with baseline score as covariate and the following factors: treatment group, baseline positive culture for *P. aeruginosa*, chronic macrolide use and geographic region. Additional sensitivity analyses with mixed-effect repeated measure models will also be performed.

Planned subgroup analyses will provide descriptive statistics and exploratory *P* values for patients with vs without positive baseline culture of *P. aeruginosa*; FEV1 < 50% of predicted at baseline; hospitalization due to exacerbation or > 2 exacerbations requiring systemic antibiotic treatment in the previous year; persistent pathogen culture (at least one organism in common at screening and randomization visit) before start of study treatment; chronic macrolide use; and ciprofloxacin resistant pathogen at baseline using Clinical Laboratory Standards Institute breakpoints for systemic treatment with ciprofloxacin.

2.8.5. Additional and safety endpoints

All other efficacy variables will be analysed descriptively using summary statistics or frequency tables as appropriate, no interaction model will be used.

Safety analyses will be performed in the safety population (which includes all randomized patients who received study medication).

Adverse events will be considered treatment-emergent if they first occurred at or after the first administration of study medication or worsened during the course of the study up to and including 30 days after the last administration of study medication. Incidence rates for adverse events will be coded by preferred term and system organ class, as per the most up-to-date version of the Medical Dictionary for Regulatory Activities. Adverse events will be summarized according to intensity (mild, moderate, severe) and causality by investigator's assessment; adverse events of special interest include bronchospasm and haemoptysis, amongst others mentioned previously.

3. Discussion

The RESPIRE trials are designed to evaluate whether intermittent, long-term therapy with Ciprofloxacin DPI is superior to placebo in prolonging the time to exacerbation and/or reducing the frequency of exacerbations over 48 weeks in patients with NCfB. Other studies of inhaled antibiotics in this patient population have had limited success in this respect, perhaps in part due to multiple aetiologies included and the heterogeneous nature of NCfB [5]. With the largest NCfB patient population ever studied in interventional trials, the RESPIRE programme has the potential to provide important insight into long-term treatment outcomes in patients with NCfB who have been treated with Ciprofloxacin DPI.

The RESPIRE trials have strict entry criteria in terms of NCfB disease: the patient population is limited to patients with one of two major aetiologies (post-infectious or idiopathic) and who experience frequent exacerbations (at least two documented in the previous 12 months). In particular, patients with a primary diagnosis of COPD are excluded, as these patients may have a different disease course and a variable response to therapy [30]. It is intended that the patient phenotype required by the RESPIRE trials will represent the two major aetiological groups reported in most case series. The strict entry criteria may also help to define the patient population who could be likely benefit the most from treatment with a long-term inhaled antibiotic therapy.

Stratification for chronic macrolide therapy will provide efficacy and safety data that are specific for patients who are being treated with long-term macrolides and those who are not. Data from a US cohort indicate that 14% of NCfB patients receive chronic macrolide therapy [31] and evidence for their use as long-term anti-inflammatory treatment is growing [32]. It is therefore, important to explore the use of investigational NCfB therapies in patients on long-term macrolide therapy.

The RESPIRE trials are unique in their inclusion of patients with seven different Gram-positive and Gram-negative pathogens. The majority of NCfB patients are chronically colonized (~72%); commonly with *P. aeruginosa* and *H. influenzae* [11]. While *P. aeruginosa* is associated with a worse clinical course in NCfB patients with frequent exacerbations over 48 weeks in patients with NCfB. The RESPIRE trials are designed to evaluate whether intermittent, long-term therapy with Ciprofloxacin DPI is superior to placebo in prolonging the time to exacerbation and/or reducing the frequency of exacerbations over 48 weeks in patients with NCfB. Other studies of inhaled antibiotics in this patient population have had limited success in this respect, perhaps in part due to multiple aetiologies included and the heterogeneous nature of NCfB [5]. With the largest NCfB patient population ever studied in interventional trials, the RESPIRE programme has the potential to provide important insight into long-term treatment outcomes in patients with NCfB who have been treated with Ciprofloxacin DPI. The RESPIRE trials have strict entry criteria in terms of NCfB disease: the patient population is limited to patients with one of two major aetiologies (post-infectious or idiopathic) and who experience frequent exacerbations (at least two documented in the previous 12 months). In particular, patients with a primary diagnosis of COPD are excluded, as these patients may have a different disease course and a variable response to therapy [30]. It is intended that the patient phenotype required by the RESPIRE trials will represent the two major aetiological groups reported in most case series. The strict entry criteria may also help to define the patient population who could be likely benefit the most from treatment with a long-term inhaled antibiotic therapy.

Stratification for chronic macrolide therapy will provide efficacy and safety data that are specific for patients who are being treated with long-term macrolides and those who are not. Data from a US cohort indicate that 14% of NCfB patients receive chronic macrolide therapy [31] and evidence for their use as long-term anti-inflammatory treatment is growing [32]. It is therefore, important to explore the use of investigational NCfB therapies in patients on long-term macrolide therapy.

The RESPIRE trials are unique in their inclusion of patients with seven different Gram-positive and Gram-negative pathogens. The majority of NCfB patients are chronically colonized (~72%); commonly with *P. aeruginosa* and *H. influenzae* [11]. While *P. aeruginosa* is associated with a worse clinical course in NCfB compared with other bacteria [7,14,33-35] pathogens such as *Moraxella catarrhalis* and *Staphylococcus aureus* often colonize NCfB patients and may also be associated with poorer outcomes [11]. In addition, bacterial load has been correlated to number of exacerbations [36] and it is therefore important to determine the impact of inhaled antibiotic therapy on bacterial burden in the lungs of bronchiectasis patients. Ciprofloxacin DPI showed efficacy at reducing bacterial burden in a phase II study and a trend towards fewer exacerbations [29]; these data seem to suggest that the microbiological efficacy of Ciprofloxacin DPI has an impact on its clinical efficacy. By including seven different pathogens, the RESPIRE studies could provide insight into this aspect of treatment as well as help to ensure that the trial cohort is representative of the overall population of NCfB patients with frequent exacerbations [36–38]. Stratification by positive baseline *P. aeruginosa* culture will also allow exploration of whether all patients benefit from Ciprofloxacin DPI or if benefits are dependent on the presence or absence of this.
The impact of Ciprofloxacin DPI on bacterial resistance is an equally important consideration as inhaled antibiotics are likely to have different impacts on microbial elimination and resistance compared to systemic antibiotics, owing to the high local concentrations and low systemic exposure [39]. The duration of the RESPIRE trials (approximately 1-year) should provide an adequate duration for an exploration of efficacy, safety and microbial susceptibility data relevant to long-term therapy.

Another key, unique feature of the RESPIRE programme is the investigation of both a 14-day and 28-day on/off treatment regimen. On/off dosing was originally chosen for inhaled tobramycin in CF to maximize benefits while reducing the emergence of resistance [40] and indeed, early studies of aerosolized tobramycin in patients with CF, demonstrated improvements in spirometry assessments of lung function peaked at 4 weeks [41–42]. However, the CF-based rationale for a 28-day cycle may not apply in NCFB, and indeed there is no evidence for the appropriate cycle duration in these patients. In phase II studies of Ciprofloxacin DPI in CF and NCFB patients, peak reductions in bacterial load were observed between days 8–15 [29,43]. These data imply that a 14 days treatment regimen may be beneficial to maximize the anti-microbial effect while minimizing the recovery time for surviving bacterial colonization in this patient population. The testing of two different intermittent regimens in the RESPIRE trials should therefore allow evaluation of NCFB-specific dosing strategies and may enhance understanding of the effect of antibiotic cycles on treatment outcomes.

The lack of a validated and well accepted definition of exacerbation is an important issue in the management NCFB. Identifying and documenting exacerbations in this patient population is challenging and the varying definitions used by individual centres and trials can make the comparison of research and results difficult. By using a stringent definition of exacerbation in the RESPIRE trials the impact of variability between clinical assessments should be reduced. Furthermore, the application of a more stringent, but possibly less sensitive, definition will likely reduce the number of protocol-defined exacerbations observed during the trial, but will hopefully also limit these events to bacterial exacerbations that could potentially be reduced by antibiotic therapy. Secondary endpoints, using a comparatively less stringent definition of exacerbation will serve as confirmatory analyses. Additional, descriptive assessments involving other definitions of exacerbation should allow further insight into the most clinically relevant criteria for defining exacerbations in patients with NCFB.

It is intended that the unique aspects of the RESPIRE programme described above will lead to advances in the understanding and treatment of NCFB, including optimal treatment regimen, and provide an important new therapy to improve the lives of NCFB patients who experience frequent exacerbations and have evidence of respiratory pathogens including but not limited to, P. aeruginosa.

Declarations

Ethics approval and consent to participate

Approval of Independent Ethics Committees and Institutional Review Boards was obtained from all participating centres/countries prior to commencement of the studies. Written informed consent was obtained from all participants at screening visit.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

TJB, MC, EO, KR are employees of Bayer. TA has participated in clinical trials sponsored by Bayer, Aradigm/Grifols, Inamed, and Gilead but has not received personal or research support. All funding has been directly made to the Mayo Foundation for Medical Research and Education. ADS has received fees from Almirall, AstraZeneca, Bayer, Chiesi, Forest Laboratories, GSK and Novartis for lectures and advisory board memberships and educational grant support from AstraZeneca, Gilead, Bayer, Forest Laboratories and Novartis for research into bronchiectasis. JSE has received consultancy fees from Bayer, Vertex, Gilead and Raptor. He holds grants with Novartis and Basilea. All payments are made to Queens University Belfast. EP has received fees for speeches or consultancies from Bayer, Pfizer, Novartis, Brahms, Polyphor, MPR, Glaxo-Smithkline and Menarini. KW has received fees for consultancy to Bayer. RW has received fees from Bayer for lectures and advisory board memberships.

Funding

The RESPIRE studies are sponsored by Bayer HealthCare AG (15625 and 15626), Germany which was involved in the design of the study and the decision to submit the manuscript for publication in collaboration with the authors.

Authors' contributions

All authors made substantial contributions to the conception and design of this manuscript. All were involved in drafting the manuscript and revising it critically for important intellectual content and have given final approval of the version to be published.

Acknowledgements

JSE, ADS and RW acknowledge the support of EMBARC and the Medical Research Council funded by BronchUK collaborative for peer support and advice in bronchiectasis. The authors would like to thank Ulrike Krahn for critically reviewing the manuscript. Manuscript support was provided by Hightfield Communication, Oxford, UK and Fusion MD, Montreal, Canada and funded by Bayer AG (15625 and 15626).

References

[1] M.C. Pasteur, D. Bilton, A.T. Hill, British Thoracic Society Bronchiectasis non-CF Guideline Group, British Thoracic Society guideline for non-CF bronchiectasis, Thorax 65 (Suppl. 1) (2010) 1–58.
[2] M.J. McDonnell, C. Ward, J.L. Lordan, R.M. Rutherford, Non-cystic fibrosis bronchiectasis, J. Med. 106 (2013) 709–715.
[3] P.J. McShane, E.T. Naureckas, G. Tino, M.E. Streek, Non-cystic fibrosis bronchiectasis, Am. J. Respir. Crit. Care Med. 188 (2013) 647–656.
[4] P.J. Cole, Inflammation: a two-edged sword – the model of bronchiectasis, Eur. J. Respir. Dis. Suppl. 147 (1986) 6–15.
[5] J.D. Chalmers, S. Aliberti, F. Blasi, Management of bronchiectasis in adults, Eur. Respir. J. 45 (2015) 1446–1462.
[6] J.H. Roberts, R. Hubbard, Trends in bronchiectasis mortality in England and Wales, Respir. Med. 104 (2010) 981–985.
[7] M.R. Leeberger, A.U. Wells, D.M. Hansell, N. Chinyanganya, A. Devaraj, M. Meister, et al., Mortality in bronchiectasis: a long-term study assessing the factors influencing survival, Eur. Respir. J. 34 (2009) 843–849.
[8] J.K. Quint, E.R. Millett, M. Joshi, V. Navaratnam, S.L. Thomas, J.R. Hurst, et al., Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study, Eur. Respir. J. 47 (2016) 186–193.
[9] C.B. Wilson, P.W. Jones, C.J. O’Leary, P.J. Cole, R. Wilson, Validation of the St. George’s Respiratory Questionnaire in bronchiectasis, Am. J. Respir. Crit. Care Med. 156 (1997) 536–541.
[10] P.C. Goeminne, H. Scheers, A. Decraene, S. Seyes, L.J. Dupont, Risk factors for morbidity and death in non-cystic fibrosis bronchiectasis: a retrospective cross-sectional analysis of CT diagnosed bronchiectatic patients, Respir. Res. 13 (2012) 21.
[11] J.D. Chalmers, P. Goeminne, S. Aliberti, M.J. McDonnell, S. Lonni, J. Davidson, et al., The Bronchiectasis Severity Index: An international derivation and validation
