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RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis

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RESPIRE 2 supports ciprofloxacin DPI clinical benefits in bronchiectasis, but did not reach statistical significance http://ow.ly/es9E30gNhos

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ABSTRACT   We evaluated the efficacy and safety of ciprofloxacin dry powder for inhalation (DPI) in patients with non-cystic fibrosis bronchiectasis, two or more exacerbations in the previous year and predefined sputum bacteria.

Patients were randomised 2:1 to twice-daily ciprofloxacin DPI 32.5 mg or placebo in 14- or 28-day on/off treatment cycles for 48 weeks. Primary end-points were time to first exacerbation and frequency of exacerbations. Enrolling countries and α level split (0.049 and 0.001 for 14- and 28-day cycles, respectively) differed from RESPIRE 1.

Patients were randomised to ciprofloxacin DPI (14 days on/off (n=176) or 28 days on/off (n=171)) or placebo (14 days on/off (n=88) or 28 days on/off (n=86)). The exacerbation rate was low across treatment arms (mean±SD 0.6±0.9). Active treatment showed trends to prolonged time to first exacerbation (ciprofloxacin DPI 14 days on/off: hazard ratio 0.87, 95.1% CI 0.62–1.21; p=0.3965; ciprofloxacin DPI 28 days on/off: hazard ratio 0.71, 99.9% CI 0.39–1.27; p=0.0511) and reduced frequency of exacerbations (ciprofloxacin DPI 14 days on/off: incidence rate ratio 0.83, 95.1% CI 0.59–1.17; p=0.2862; ciprofloxacin DPI 28 days on/off: incidence rate ratio 0.55, 99.9% CI 0.30–1.02; p=0.0014), although neither achieved statistical significance. Ciprofloxacin DPI was well tolerated.

Trends towards clinical benefit were seen with ciprofloxacin DPI, but primary end-points were not met.

Introduction

Non-cystic fibrosis bronchiectasis (NCFB) is a heterogeneous disease with a range of underlying aetiologies across geographical regions and a variable clinical course [1]. Patients with NCFB are subject to a vicious cycle of inflammation, poor mucus clearance and recurrent infection [2, 3]. This cycle manifests as a chronic cough, sputum production, airway damage and exacerbations, with the severity and impact of each exacerbation varying from patient to patient, and is responsible for progressive lung damage [2, 4].

Exacerbations of bronchiectasis are characterised by a debilitating increase in symptoms and are associated with poorer health outcomes, including reduced quality of life, depression, anxiety and increased mortality [5–7]. Reducing the frequency of exacerbations is therefore an important treatment goal; however, there are currently no antibiotic therapies licensed for this.

The RESPIRE programme consisted of two trials of the same overall design, as required by regulatory agencies. The objective of both studies was to assess the efficacy and safety of 14- and 28-day on/off regimens of ciprofloxacin dry powder for inhalation (DPI) in prolonging time to first exacerbation and reducing frequency of exacerbations in patients with NCFB. The RESPIRE 1 trial demonstrated that treatment with a 14-day on/off cycle of ciprofloxacin DPI significantly reduced frequency of exacerbations and prolonged time to first exacerbation in patients with NCFB. The 28-day ciprofloxacin DPI arm of RESPIRE 1 had trends towards clinical benefit, but failed to reach statistical significance [8]. Here, we report the results of the phase III RESPIRE 2 trial (ClinicalTrials.gov identifier NCT02106832). The main differences between RESPIRE 1 and 2 were a change in the recruiting countries (RESPIRE 2 drew more patients from Asia and Eastern Europe than RESPIRE 1) and specific alterations to the statistical plan, as described in the following sections.

Methods

Study design and treatment

The RESPIRE trials had the same overall methodology, which has been reported previously [9]. Two interventions were studied over 48 weeks: ciprofloxacin DPI 32.5 mg twice daily 14 days on/off (12 cycles) and ciprofloxacin DPI 32.5 mg twice daily 28 days on/off (6 cycles). There was an 8-week off-treatment follow-up period.

Study population

Patients with a primary diagnosis of NCFB (idiopathic or post-infectious aetiology) and stable disease were enrolled. Key inclusion criteria were: at least two exacerbations in the previous 12 months and a positive sputum culture at screening for at least one of seven pre-specified pathogens (*Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Stenotrophomonas maltophilia* or *Burkholderia cepacia*). Patients with active allergic bronchopulmonary aspergillosis, active or actively treated nontuberculous mycobacterial lung infection or tuberculosis, a primary diagnosis of chronic obstructive pulmonary disease (COPD), or documented chronic asthma were excluded. Randomisation was stratified by geographical region, pre-therapy positive culture for *P. aeruginosa* and chronic macrolide use.

End-points

Two different hierarchical statistical analysis approaches were developed with different regulatory authorities. The primary end-point for the US Food and Drug Administration (FDA) was time to first exacerbation within 48 weeks after start of treatment (ciprofloxacin DPI *versus* pooled placebo). For the European Medicines Agency (EMA)/other agencies, such as the China State Drug Administration, the primary end-point was frequency of exacerbations during the 48-week study (ciprofloxacin DPI *versus* matching placebo). The pooled placebo group refers to all patients from the 14- and 28-day on/off placebo arms; matching placebo refers to ciprofloxacin DPI 14 days on/off compared with placebo 14 days on/off and ciprofloxacin DPI 28 days on/off compared with placebo 28 days on/off [4]. For the primary end-points, exacerbations had to meet three criteria: 1) worsening of at least three signs or symptoms (dyspnoea, wheezing, cough, 24-h sputum volume or sputum purulence) beyond normal day-to-day variations for at least 2 consecutive days, 2) fever (body temperature >38.0°C) or malaise/fatigue and 3) systemic antibiotic treatment ("primary end-point definition"). Pre-defined subgroups and safety end-points are described in supplementary sections S1 and S2. Secondary end-points have been detailed previously [8, 9]. A secondary end-point of particular interest was exacerbation rate according to a less stringent definition, *i.e.* a respiratory event with worsening of at least one of the aforementioned signs or symptoms and systemic antibiotic use.

Analyses

The statistical analysis plan for the RESPIRE programme has been described previously [9]. RESPIRE 2 followed the same analysis plan as for RESPIRE 1 with two exceptions. First, the primary analysis models

for the frequency of exacerbations end-point were harmonised between the FDA and EMA/others analyses with respect to the handling of treatment discontinuations. In the RESPIRE 1 FDA analysis, the frequency of exacerbations was extrapolated for patients not completing the 48-week period, whereas in RESPIRE 2 the patients' time in study was included as an offset variable in the FDA analysis as for the EMA/others analysis. Second, the significance levels (α level split) were amended before study end, based on experience gained from RESPIRE 1. In RESPIRE 1, a Bonferroni correction was used, resulting in a significance level of 0.025 for each treatment arm (14 and 28 days on/off). Following the statistical failure of the ciprofloxacin DPI 28-day on/off arm in RESPIRE 1, the α correction for RESPIRE 2 was prospectively amended to a weighted Bonferroni correction of 0.049 for the 14-day on/off arm and 0.001 for the 28-day on/off arm. The sponsoring company discussed this change before study end with the regulatory agencies who approved this change. Further details are given in supplementary section S3.

Results

Patients

A total of 521 patients from 24 countries were randomised to treatment (figure 1); the first patient visit was in April 2014 and the last visit was in October 2016. The highest enrolling countries were Russia (11.5%), Bulgaria (10.4%) and Latvia (8.6%) (supplementary table S1).

Patient demographics and baseline characteristics were balanced across groups (table 1). The majority of patients (58.0%) were female, the mean age was ~60 years and patients had a high likelihood of *P. aeruginosa* infection (60.7% of patients; see supplementary table S2 for additional pre-specified baseline pathogens). Lung function was generally poor, with >40% of patients having a forced expiratory volume in 1 s (FEV_1) % pred <50%. Approximately 30% of patients had a medical history of COPD and use of concomitant respiratory medications considered part of NCFB therapy was common (supplementary table S3).

442 patients (84.8%) completed the study and 79.5% of patients (414 out of 521) completed treatment. Patient compliance was high (mean >95% in all arms) (table 2).

Primary end-points

Both the 14- and 28-day ciprofloxacin DPI on/off arms increased the time to first exacerbation *versus* pooled placebo (figure 2). However, neither ciprofloxacin DPI treatment arm demonstrated a statistically significant difference compared with pooled placebo (ciprofloxacin DPI 14 days on/off: hazard ratio (HR) 0.87, 95.1% CI 0.62–1.21; p=0.3965 and ciprofloxacin DPI 28 days on/off: HR 0.71, 99.9% CI 0.39–1.27; p=0.0511) (table 3). The median time to first exacerbation was not estimable for any treatment arm due to the low exacerbation rates. Overall, 61.4% and 67.3% of patients treated with ciprofloxacin DPI 14 and 28 days on/off, respectively, did not experience an exacerbation matching the stringent definition, compared with 58.0% of patients in the pooled placebo arm.

Ciprofloxacin DPI 14 days on/off reduced the exacerbation incidence rate by 17% over 48 weeks (incidence rate ratio (IRR) 0.83, 95.1% CI 0.59–1.17; p=0.2862), while ciprofloxacin DPI 28 days on/off reduced the
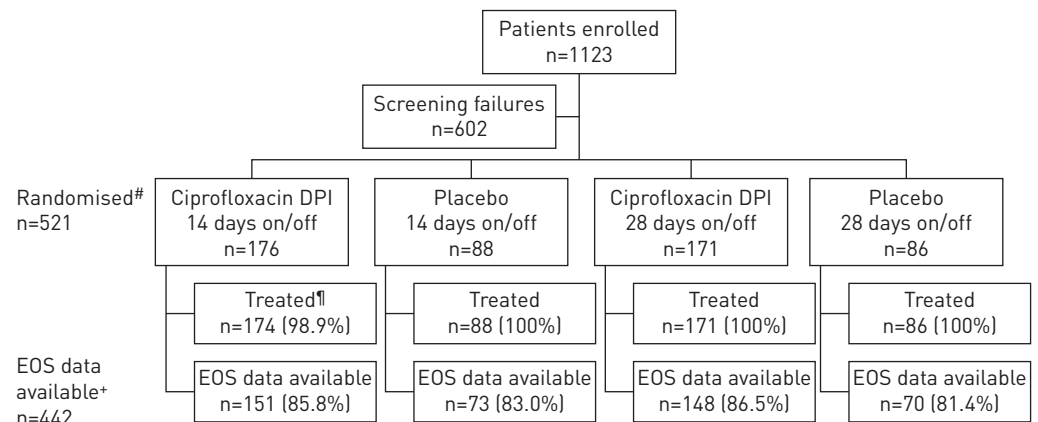

FIGURE 1 Patient disposition. DPI: dry powder for inhalation; EOS: end of study. [#]: randomisation stratified by geographical region, pre-therapy positive culture for *Pseudomonas aeruginosa* and chronic macrolide use; [¶]: patients randomised who received at least one treatment dose; [+]: patients with EOS data available include those who completed treatment and subsequent follow-up, or prematurely discontinued treatment but were followed further until the planned EOS (52/54 weeks), or prematurely discontinued treatment but completed the planned 8 weeks of follow-up.

TABLE 1 Patient demographics and baseline characteristics

	Ciprofloxacin DPI 14 days on/off	Placebo 14 days on/off	Ciprofloxacin DPI 28 days on/off	Placebo 28 days on/off	Pooled placebo	Total
Patients n	176	88	171	86	174	521
Female	96 (54.5)	62 (70.5)	92 (53.8)	52 (60.5)	114 (65.5)	302 (58.0)
Age years	60.4±13.7	60.4±15.0	59.3±14.2	60.6±13.7	60.5±14.3	60.1±14.0
Idiopathic aetiology	62 (35.2)	32 (36.4)	43 (25.1)	36 (41.9)	68 (39.1)	173 (33.2)
Region[#]						
Europe 1	64 (36.4)	32 (36.4)	65 (38.0)	32 (37.2)	64 (36.8)	193 (37.0)
Europe 2	54 (30.7)	27 (30.7)	54 (31.6)	28 (32.6)	55 (31.6)	163 (31.3)
Africa	0	0	2 (1.2)	0	2 (1.1)	2 (0.4)
Latin America	6 (3.4)	3 (3.4)	7 (4.1)	2 (2.3)	5 (2.9)	18 (3.5)
Asia	39 (22.2)	19 (21.6)	33 (19.3)	17 (19.8)	36 (20.7)	108 (20.7)
Australia	8 (4.5)	4 (4.5)	5 (2.9)	4 (4.7)	8 (4.6)	21 (4.0)
USA	5 (2.8)	3 (3.4)	5 (2.9)	3 (3.5)	6 (3.4)	16 (3.1)
Ethnicity						
White	133 (75.6)	68 (77.3)	135 (78.9)	67 (77.9)	135 (77.6)	403 (77.4)
Black/African	2 (1.1)	1 (1.1)	2 (1.2)	0	1 (0.6)	5 (1.0)
Asian	41 (23.3)	18 (20.5)	33 (19.3)	19 (22.1)	37 (21.3)	111 (21.3)
Multiple	0	1 (1.1)	1 (0.6)	0	1 (0.6)	2 (0.4)
FEV1 % pred	54.3±17.3	55.8±18.6	56.4±18.8	56.2±18.2	NC	55.5±18.2
FEV1 % pred <50%	78 (44.3)	39 (44.3)	65 (38.0)	36 (41.9)	75 (43.1)	218 (41.8)
SGRQ symptoms component score[¶]	61.26±19.54	63.47±19.48	60.75±20.61	58.56±19.17	NC	61.0±19.82
QoL-B RSS[¶]	52.17±18.49	48.67±17.72	50.14±19.07	53.95±16.00	NC	51.2±18.6
Exacerbations in prior 12 months	2.4±0.8	2.4±0.7	2.3±0.7	2.3±1.0	2.4±0.9	2.4±0.8
Three or more exacerbations in prior 12 months	42 (23.9)	22 (25.0)	35 (20.5)	16 (18.6)	38 (21.8)	115 (22.1)
Hospitalised for exacerbation in prior year	80 (45.5)	39 (44.3)	65 (38.0)	35 (40.7)	74 (42.5)	219 (42.0)
Long-term oral macrolides	11 (6.3)	7 (8.0)	14 (8.2)	8 (9.3)	15 (8.6)	40 (7.7)
History of COPD	50 (28.4)	31 (35.2)	39 (22.8)	28 (32.6)	59 (33.9)	148 (28.4)
Baseline *Pseudomonas aeruginosa*[+]	107 (60.8)	55 (62.5)	99 (58.2)	54 (63.5)	109 (63.0)	315 (60.7)

Data are presented as n (%) or mean±SD. DPI: dry powder for inhalation; FEV1: forced expiratory volume in 1 s; SGRQ: St George's Respiratory Questionnaire; QOL-B RSS: Quality of Life-Bronchiectasis respiratory symptoms domain score; COPD: chronic obstructive pulmonary disease; NC: not calculated. [#]: Europe 1: Austria, Czech Republic, Germany, Latvia, Lithuania, the Netherlands, Poland, Russia; Europe 2: Bulgaria, Portugal, Romania, Serbia, Turkey; Asia: China, Hong Kong, Philippines, South Korea, Taiwan, Thailand; Latin America: Argentina and Brazil; Africa: South Africa. [¶]: not available for Latvia, Philippines, Portugal, Romania, Serbia, Thailand or Turkey (177 subjects (34%) of the RESPIRE 2 population) due to the lack of a translated version; [+]: patients could have more than one species isolated.

exacerbation incidence rate by 45% (IRR 0.55, 99.9% CI 0.30–1.02; p=0.0014) (table 3). Neither arm reached the predefined statistical significance level (p=0.049 for the 14-day regimen and 0.001 for the 28-day regimen). Overall, the frequency of exacerbations in all arms was very low (figure 3). The overall mean±SD number of exacerbations was 0.6±0.9. Equivalent data for the treatment arms were 0.6±0.8 for ciprofloxacin DPI 14 days on/off compared with 0.7±1.0 in the matching placebo arm and 0.4±0.6 for ciprofloxacin DPI 28 days on/off *versus* 0.7±1.1 in the matching placebo arm.

Over 48 weeks, 61.4% of patients treated with ciprofloxacin DPI 14 days on/off compared with 67.3% of patients treated with ciprofloxacin DPI 28 days on/off and 58.0% of patients in the pooled placebo arm did not experience a protocol-defined exacerbation for the primary end-point.

Subgroup analyses
Exploratory analyses of the primary end-point in pre-specified subgroups did not reveal any differences in any of the subgroups for time to first exacerbation or frequency of exacerbations (supplementary figure S1).

Secondary end-points
Due to the hierarchical nature of the statistical analysis plan, formal significance testing could not be performed for secondary end-points because the primary end-points were not met. Exploratory analyses of

TABLE 2 Treatment compliance and duration[#]

	Ciprofloxacin DPI 14 days on/off	Placebo 14 days on/off	Ciprofloxacin DPI 28 days on/off	Placebo 28 days on/off
Patients n	176	88	171	86
Compliance %				
Mean±SD	96.2±8.2	96.2±9.9	95.8±10.8	96.3±8.9
Compliance ⩾80% n (%)	167 (94.9)	82 (93.2)	159 (93.0)	81 (94.2)
Treatment duration days				
Mean±SD	281.7±91.6	272.1±103.0	269.5±86.4	262.7±90.7
Median	322.0	322.0	308.0	307.0

DPI: dry powder for inhalation. [#]: compliance was determined after imputation of (partially) missing exposure dates as number of capsules taken/number of planned capsules. Treatment duration was assessed from first to last day of study drug intake irrespective of interruptions or off-cycles; the final off-cycle after the last dose was not included. The maximum treatment duration was 322 days for the 14-day on/off arm and 308 days for the 28-day on/off arm.

secondary end-points suggested that ciprofloxacin DPI treatment was associated with benefits, including a reduced frequency of exacerbations (defined according to the primary end-point) *versus* pooled placebo for the ciprofloxacin DPI 28-day on/off arm (figure 4).

The mean±SD number of exacerbations reported using the less stringent definition was 0.7±1.0 for ciprofloxacin DPI 14 days on/off compared with 0.8±1.1 in the matching placebo arm and 0.5±0.8 for ciprofloxacin DPI 28 days on/off compared with 0.9±1.1 in the matching placebo arm.

Safety

Ciprofloxacin DPI was well tolerated, with lowest adverse event rates observed in the ciprofloxacin DPI 28-day on/off arm. A total of 349 out of 519 (67.2%) patients experienced an adverse event at any time after enrolment: 131 (75.3%) patients in the ciprofloxacin DPI 14-day on/off arm, 101 (59.1%) in the ciprofloxacin DPI 28-day on/off arm and 117 (67.2%) in the pooled placebo group.

Overall, 64.9% of patients experienced a treatment-emergent adverse event. Treatment-emergent musculoskeletal adverse events were infrequently reported. Tendon disorders were reported by two patients in each ciprofloxacin DPI treatment group (one tendon disorder and one trigger finger in the ciprofloxacin DPI 14-day on/off arm; discomfort and one ligament sprain in the ciprofloxacin DPI 28-day on/off arm) and zero patients in the placebo groups. Premature discontinuations due to treatment-emergent adverse events were uncommon and occurred with similar frequencies across treatment arms (table 4).

Serious treatment-emergent adverse events occurred in 22.0% of patients overall; rates were slightly lower in the ciprofloxacin DPI 28-day on/off arm compared with other arms. Respiratory disorders and infections/

TABLE 3 Primary end-points: time to first exacerbation and frequency of exacerbations[#] in patients treated with ciprofloxacin dry powder for inhalation (DPI) *versus* placebo over 48 weeks

Primary end-point	HR or IRR[¶] (95.1% or 99.9% CI[⁺])	p-value (Wald-type test)
Time to first exacerbation		
Ciprofloxacin DPI 14 days on/off *versus* pooled placebo	0.8662 (0.62–1.21)	0.3965
Ciprofloxacin DPI 28 days on/off *versus* pooled placebo	0.7062 (0.39–1.27)	0.0511
Frequency of exacerbations		
Ciprofloxacin DPI 14 days on/off *versus* matching placebo	0.8313 (0.59–1.17)	0.2862
Ciprofloxacin DPI 28 days on/off *versus* matching placebo	0.5493 (0.30–1.02)	0.0014

HR: hazard ratio; IRR: incidence rate ratio. [#]: for the primary end-points, an exacerbation (stringent definition) was required to meet three criteria: 1) worsening in at least three signs or symptoms (dyspnoea, wheezing, cough, 24-h sputum volume or sputum purulence) beyond normal day-to-day variation for at least 2 consecutive days, 2) fever (body temperature >38.0°C) or malaise/fatigue, and 3) systemic antibiotic treatment; [¶]: HRs were calculated for time to first exacerbation; IRRs were calculated for frequency of exacerbations; [⁺]: the confidence interval is 95.1% for comparisons of ciprofloxacin DPI 14 days on/off *versus* placebo and 99.9% for comparisons of ciprofloxacin DPI 28 days on/off *versus* placebo.
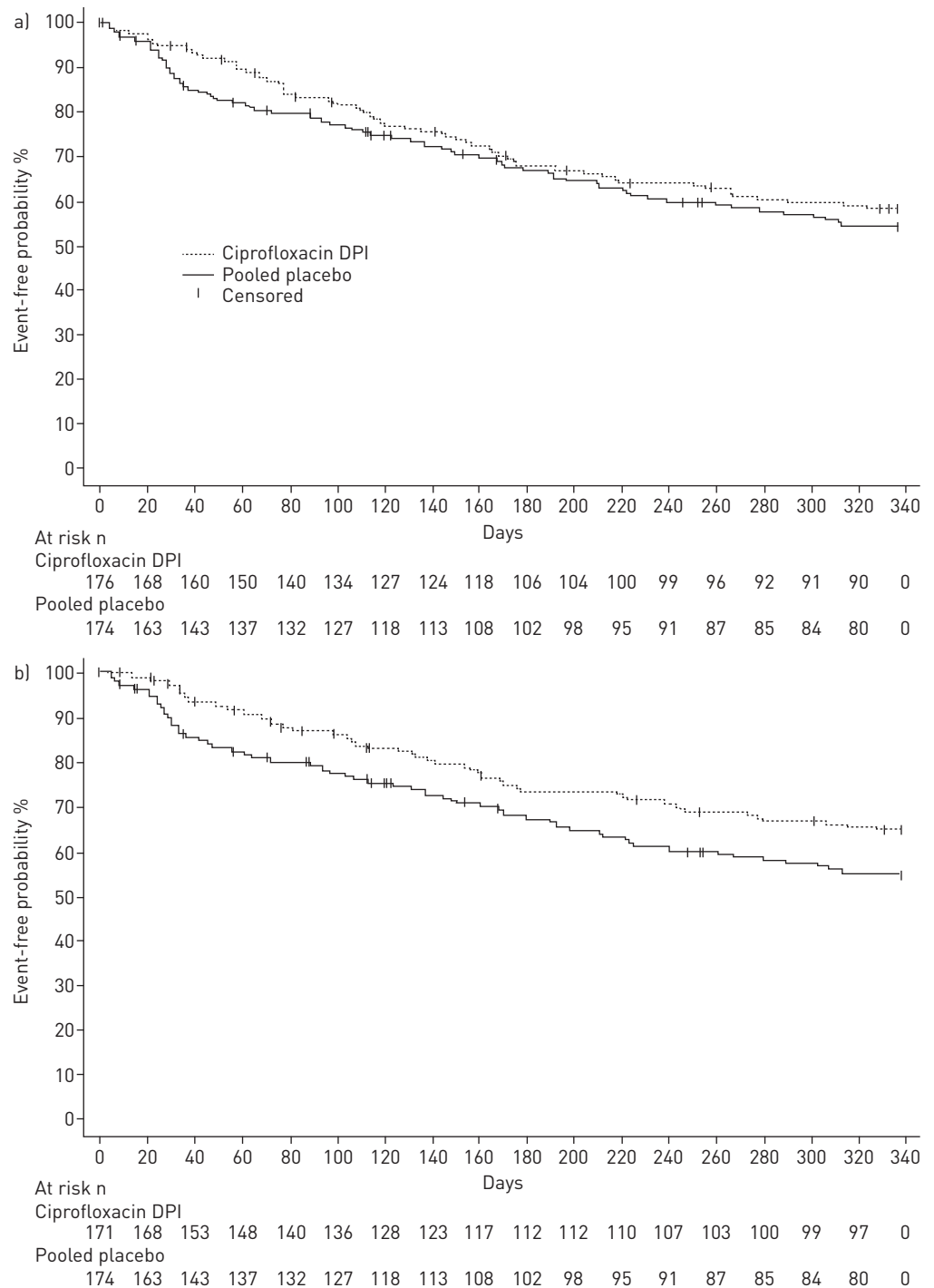
FIGURE 2 Time to first exacerbation for patients receiving ciprofloxacin dry powder for inhalation (DPI) a) 14 days on/off or placebo and b) 28 days on/off or placebo. For the primary end-point exacerbations were required to meet three criteria: 1) worsening in at least three signs or symptoms (dyspnoea, wheezing, cough, 24-h sputum volume or sputum purulence) beyond normal day-to-day variation for at least 2 consecutive days, 2) fever (body temperature >38.0°C) or malaise/fatigue, and 3) systemic antibiotic treatment.

infestations were the most common system organ classes reported for serious treatment-emergent adverse events (supplementary table S4). One serious treatment-emergent adverse event (atrial flutter) was considered drug related. This treatment-emergent adverse event occurred in a subject in the ciprofloxacin DPI 28-day on/off arm who had a history of ischaemic heart disease. This patient also experienced severe fatal congestive cardiomyopathy, which was reported in parallel but was not considered to be drug related.

Nine treatment-emergent deaths were reported during the study (three (1.7%) in the ciprofloxacin DPI 14-day on/off arm, four (2.3%) in the ciprofloxacin DPI 28-day on/off arm and two (1.1%) in the pooled placebo group), but no fatalities were considered to be drug related and deaths were consistent with morbidities common to the patient population being studied (supplementary table S4).

Changes in ciprofloxacin minimal inhibitory concentrations

At baseline, 98 out of 521 (18.8%) patients had a pathogen with an elevated minimal inhibitory concentration (MIC) for ciprofloxacin (defined as resistant based on systemic ciprofloxacin breakpoints as specified in supplementary section S2) isolated from their sputum. The number of patients with the development of at least one isolate from sputum with an elevated MIC from pre-treatment to any time point during the study was 37 out of 176 (21.0%) for ciprofloxacin DPI 14 days on/off, 28 out of 170 (16.5%) for ciprofloxacin DPI 28 days on/off and 17 out of 173 (9.8%) for pooled placebo. At the end-of-study (EOS) visit that occurred 8 weeks after the end of treatment, pathogens with elevated MICs were isolated from 26 patients (5%) (ciprofloxacin DPI 14 days on/off 12 out of 176 (6.8%), ciprofloxacin DPI 28 days on/off 10 out of 171 (5.8%) and pooled placebo four out of 174 (2.3%)) who had susceptible bacteria at baseline. During the study, elevated MICs were more common in patients receiving active therapy. The percentage of patients with at least one isolate from sputum with an elevated MIC at any time point including baseline and EOS was 52.3% for ciprofloxacin DPI 14 days on/off, 39.8% for ciprofloxacin DPI 28 days on/off and 29.3% for pooled placebo.
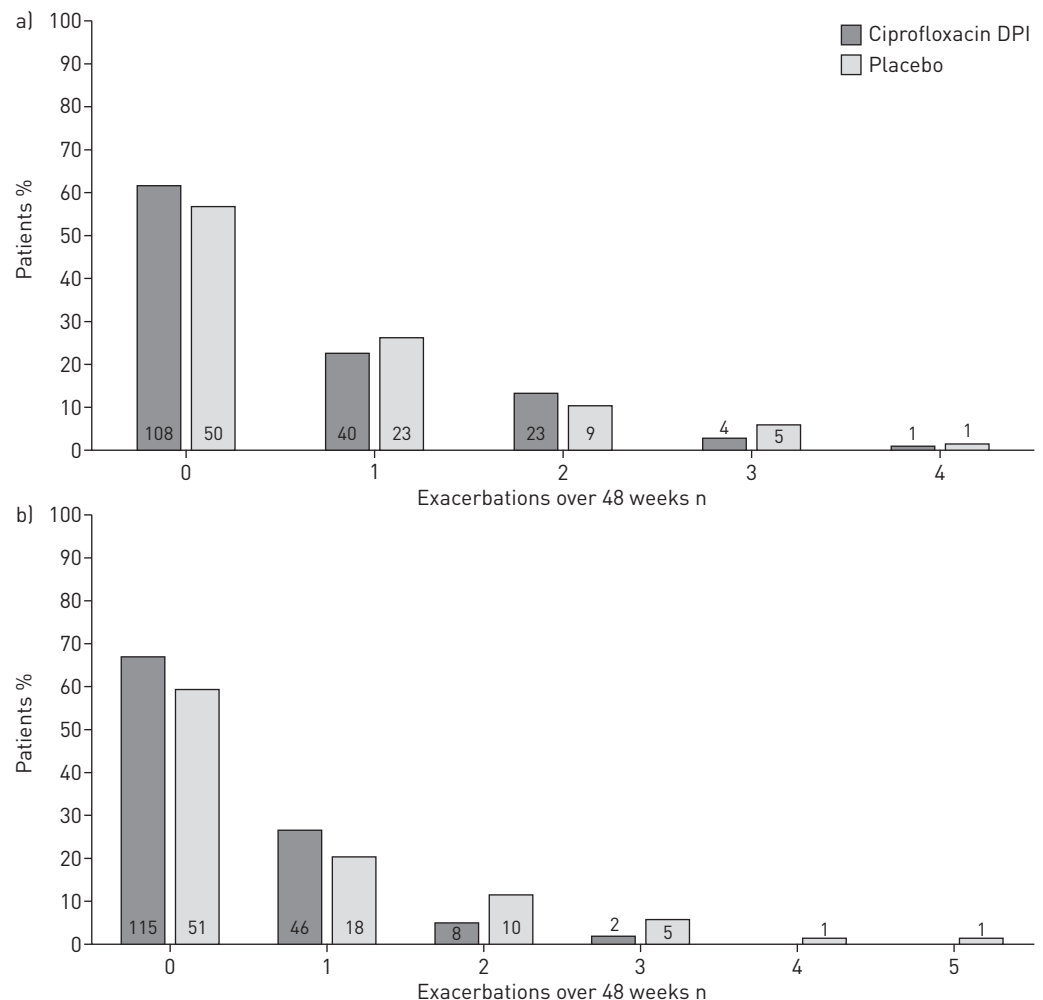

FIGURE 3 Descriptive frequency of exacerbations over 48 weeks for patients receiving ciprofloxacin dry powder for inhalation (DPI) a) 14 days on/off or matching placebo and b) 28 days on/off or matching placebo. Numbers within or above bars indicate number of patients. For the primary end-point exacerbations were required to meet three criteria: 1) worsening in at least three signs or symptoms (dyspnoea, wheezing, cough, 24-h sputum volume or sputum purulence) beyond normal day-to-day variation for at least 2 consecutive days, 2) fever (body temperature >38.0°C) or malaise/fatigue, and 3) systemic antibiotic treatment.

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a)

FDA analysis *vs* PPL

EMA/others analyses *vs* MPL
or PPL as indicated

b)

FDA analysis *vs* PPL

EMA/others analyses *vs* MPL
or PPL as indicated

Primary end-points

Time to first exacerbation#
HR 0.87 (CI 0.62–1.21)
p=0.3965

Frequency of exacerbations# *vs* MPL
IRR 0.83 (CI 0.59–1.17)
p=0.2862

Time to first exacerbation#
HR 0.71 (CI 0.39–1.27)
p=0.0511

Frequency of exacerbations# *vs* MPL
IRR 0.55 (CI 0.30–1.02)
p=0.0014

Secondary end-points

Frequency of exacerbations#
IRR 0.81 (CI 0.61–1.08)
p=0.1471

Time to first exacerbation# *vs* PPL
HR 0.87 (CI 0.62–1.21)
p=0.3965

Frequency of exacerbations#
IRR 0.56 (CI 0.33–0.95)
p=0.0003

Time to first exacerbation# *vs* PPL
HR 0.71 (CI 0.39–1.27)
p=0.0511

Frequency of exacerbations
(less stringent definition¶)
IRR 0.84 (CI 0.64–1.09)
p=0.1811

Frequency of exacerbations
(less stringent definition¶) *vs* MPL
IRR 0.86 (CI 0.62–1.18)
p=0.3415

Frequency of exacerbations
(less stringent definition¶)
IRR 0.63 (CI 0.39–1.01)
p=0.0014

Frequency of exacerbations
(less stringent definition¶) *vs* MPL
IRR 0.61 (CI 0.35–1.07)
p=0.0041

Eradication of pre-specified baseline
pathogens+ at EOT
OR 1.34 (CI 0.76–2.38)
p=0.3162

Eradication of pre-specified baseline
pathogens+ at EOT *vs* PPL
OR 1.34 (CI 0.76–2.38)
p=0.3162

Eradication of pre-specified baseline
pathogens+ at EOT
OR 1.16 (CI 0.46–2.97)
p=0.6019

Eradication of pre-specified baseline
pathogens+ at EOT *vs* PPL
OR 1.16 (CI 0.46–2.97)
p=0.6019

Change from baseline to EOT in SGRQ
symptoms component score
Adjusted difference −1.40 (CI −5.94–3.15)
p=0.5446

Change from baseline to EOT in SGRQ
symptoms component score *vs* PPL
Adjusted difference −1.40 (CI −5.94–3.15)
p=0.5446

Change from baseline to EOT in SGRQ
symptoms component score
Adjusted difference −1.44 (CI −9.06–6.17)
p=0.5302

Change from baseline to EOT in SGRQ
symptoms component score *vs* PPL
Adjusted difference −1.44 (CI −9.06–6.17)
p=0.5302

Occurrence of new pathogens+ not present
at baseline
OR 0.29 (CI 0.12–0.75)
p=0.0072

Occurrence of new pathogens+ not present
at baseline *vs* PPL
OR 0.29 (CI 0.12–0.75)
p=0.0072

Occurrence of new pathogens+ not present
at baseline
OR 0.41 (CI 0.09–1.96)
p=0.0534

Occurrence of new pathogens+ not present
at baseline *vs* PPL
OR 0.41 (CI 0.09–1.96)
p=0.0534

Change from baseline to EOT
in QOL-B RSS
Adjusted difference 2.22 (CI −2.23–6.67)
p=0.3247

Change from baseline to EOT
in QOL-B RSS *vs* PPL
Adjusted difference 2.22 (CI −2.23–6.67)
p=0.3247

Change from baseline to EOT
in QOL-B RSS
Adjusted difference 2.75 (CI −4.92–10.42)
p=0.2340

Change from baseline to EOT
in QOL-B RSS *vs* PPL
Adjusted difference 2.75 (CI −4.92–10.42)
p=0.2340

Change from baseline to EOT
in FEV_1 (post-bronchodilator)
Adjusted difference −0.04 (CI −0.11–0.03)
p=0.2657

Change from baseline to EOT
in FEV_1 (post-bronchodilator) *vs* PPL
Adjusted difference −0.04 (CI −0.11–0.03)
p=0.2657

Change from baseline to EOT
in FEV_1 (post-bronchodilator)
Adjusted difference 0.04 (CI −0.08–0.16)
p=0.3100

Change from baseline to EOT
in FEV_1 (post-bronchodilator) *vs* PPL
Adjusted difference 0.04 (CI −0.08–0.16)
p=0.3100

FIGURE 4 Results for ciprofloxacin dry powder for inhalation (DPI) in US Food and Drug Administration (FDA) and European Medicines Agency (EMA)/other agencies hierarchical analyses for ciprofloxacin DPI a) 14 days on/off and b) 28 days on/off *versus* pooled placebo (PPL) or matching placebo (MPL). HR: hazard ratio; IRR: incidence rate ratio; EOT: end of treatment; SGRQ: St George's Respiratory Questionnaire; QOL-B RSS: Quality of Life-Bronchiectasis respiratory symptoms domain score; FEV_1: forced expiratory volume in 1 s. #: the primary (stringent) definition of exacerbation was a respiratory event that met three separate criteria: 1) worsening in at least three signs or symptoms (dyspnoea, wheezing, cough, 24-h sputum volume or sputum purulence) beyond normal day-to-day variation for at least 2 consecutive days, 2) fever (body temperature >38.0°C) or malaise/fatigue, and 3) systemic antibiotic treatment; ¶: the less stringent definition of exacerbation was a respiratory event with worsening of at least one of the aforementioned signs or symptoms and systemic antibiotic use; +: *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Stenotrophomonas maltophilia* or *Burkholderia cepacia* (eradication of pathogens was defined as a negative culture result at EOT for all pre-specified pathogens in a subject with a positive baseline culture for at least one pre-specified pathogen; occurrence of a new pathogen was defined as a positive culture for at least one pre-specified pathogen at EOT in a subject who did not have a positive culture for that pathogen at baseline). Dashed lines indicate statistical significance was not reached. The α level for end-points was 0.049 for the 14-day arm and 0.001 for the 28-day arm. The confidence interval is 95.1% for comparisons of ciprofloxacin DPI 14 days on/off *versus* placebo and 99.9% for comparisons of ciprofloxacin DPI 28 days on/off *versus* placebo.

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TABLE 4 Treatment-emergent adverse events (TE-AEs)[#] (MedDRA classifications)

	Ciprofloxacin DPI		Pooled placebo	Total
	14 days on/off	28 days on/off		
Patients	174[¶]	171	174	519[¶]
Any TE-AE	127 (73.0)	94 (55.0)	116 (66.7)	337 (64.9)
Any drug-related TE-AE	28 (16.1)	19 (11.1)	24 (13.8)	71 (13.7)
TE-AE with outcome death	3 (1.7)	4 (2.3)	2 (1.1)	9 (1.7)
Discontinuation due to TE-AE	10 (5.7)	6 (3.5)	10 (5.7)	26 (5.0)
Any serious TE-AE	45 (25.9)	28 (16.4)	41 (23.6)	114 (22.0)
Any drug-related serious TE-AE	0	1 (0.6)	0	1 (0.2)
TE-AE reported in at least 5% of patients in any group				
Respiratory, thoracic and mediastinal disorders	70 (40.2)	42 (24.6)	68 (39.1)	180 (34.7)
Bronchiectasis	24 (13.8)	17 (9.9)	21 (12.1)	62 (11.9)
Haemoptysis	17 (9.8)	12 (7.0)	22 (12.6)	51 (9.8)
Cough	7 (4.0)	5 (2.9)	11 (6.3)	23 (4.4)
Bronchospasm	7 (4.0)	3 (1.8)	9 (5.2)	19 (3.7)
Dyspnoea	10 (5.7)	4 (2.3)	3 (1.7)	17 (3.3)
Infections and infestations	49 (28.2)	45 (26.3)	43 (24.7)	137 (26.4)
Nasopharyngitis	16 (9.2)	10 (5.8)	14 (8.0)	40 (7.7)
Upper respiratory tract infections	8 (4.6)	10 (5.8)	5 (2.9)	23 (4.4)
Gastrointestinal disorders	29 (16.7)	22 (12.9)	26 (14.9)	77 (14.8)
Nervous system disorders	25 (14.4)	26 (15.2)	12 (6.9)	63 (12.1)
Headache	10 (5.7)	10 (5.8)	5 (2.9)	25 (4.8)
Dysgeusia	8 (4.6)	9 (5.3)	2 (1.1)	19 (3.7)
General disorders and administration site conditions	14 (8.0)	14 (8.2)	13 (7.5)	41 (7.9)
Musculoskeletal and connective tissue disorders	18 (10.3)	12 (7.0)	10 (5.7)	40 (7.7)
Skin and subcutaneous tissue disorders	12 (6.9)	8 (4.7)	11 (6.3)	31 (6.0)
Investigations	13 (7.5)	6 (3.5)	10 (5.7)	29 (5.6)
Metabolism and nutrition disorders	11 (6.3)	5 (2.9)	8 (4.6)	24 (4.6)
Vascular disorders	9 (5.2)	5 (2.9)	6 (3.4)	20 (3.9)

Data are presented as n or n (%). MedDRA: Medical Dictionary for Regulatory Activities; DPI: dry powder for inhalation. [#]: defined as those that first occurred or worsened during the study from the first administration of study medication (ciprofloxacin DPI or placebo) until 30 days after administration of the last dose of study medication; [¶]: two randomised subjects did not receive study medication (both in ciprofloxacin DPI 14 days on/off).

Discussion

The RESPIRE 2 trial constitutes the second trial in the RESPIRE programme. RESPIRE 1 demonstrated a significant treatment effect for the ciprofloxacin DPI 14-day on/off treatment regimen and a trend towards improved outcomes in the ciprofloxacin DPI 28-day on/off arm [8]. In RESPIRE 2, end-points favoured ciprofloxacin DPI over placebo, but the positive efficacy signals did not translate into statistical significance for either active treatment arm. The observed positive trends in RESPIRE 2 were generally more pronounced in the ciprofloxacin DPI 28-day on/off arm than in the 14-day on/off arm. However, due to the pre-specified significance level of 0.001 for the ciprofloxacin DPI 28-day on/off arm, differences from placebo did not achieve statistical significance.

Exacerbation rates in RESPIRE 2 were much lower than expected and lower than those observed in RESPIRE 1. In RESPIRE 2, 62.2% of patients did not experience an exacerbation according to the primary definition (defined by three signs or symptoms), which was notably higher than the 52% of patients in RESPIRE 1 with no exacerbations [8]. As the study entry criteria were chosen to enrich the population of "frequent exacerbators", requiring two or more documented exacerbations in the previous year, the low exacerbation rates that occurred during the trial were unexpected. For both trials, a stringent definition of exacerbation was used for primary end-point evaluations [9]. This definition was not, however, applied for the entry criteria. As each patient experiences their disease differently [10] and as patients are often educated to take antibiotic treatment when symptoms increase, it is likely that the prior exacerbations did not meet the stringent definition used during the trial. A proposed standardised definition of an exacerbation has recently been published [11]; this may be of benefit in future clinical trials to reduce heterogeneity.

Understanding the low exacerbation rates observed in both active and placebo arms of RESPIRE 2, and the differences in exacerbation rates between RESPIRE 1 and 2, requires examination of a number of factors,

including patient characteristics and geography. Baseline demographics varied somewhat between RESPIRE 1 and RESPIRE 2, despite their identical inclusion and exclusion criteria. As patient phenotype is known to affect prognosis [10], it is possible that the differing patient profiles led to different clinical outcomes. Patients in RESPIRE 2 were generally younger (mean age 60.1 *versus* 64.7 years) and more likely to have had only two exacerbations in the last year (78% *versus* 55%) than patients in RESPIRE 1 [8]; two episodes was the minimum frequency of exacerbations required to enter the study. RESPIRE 2 patients had poorer lung function as indicated by the proportion of patients with FEV_1 % pred <50% (41.8% *versus* 30.0%) and more respiratory symptoms as assessed by the St George's Respiratory Questionnaire symptoms component score (mean 61.0 *versus* 56.8) [8].

Although a primary diagnosis of COPD was an exclusion criterion, 28% of patients in RESPIRE 2 had a history of COPD *versus* 16% in RESPIRE 1, suggesting that more patients in RESPIRE 2 had an overlapping diagnosis of bronchiectasis/COPD. This is supported by the greater theophylline use in RESPIRE 2 (8.1%) *versus* RESPIRE 1 (2.2%). The precise nature of the relationship between COPD and bronchiectasis remains to be established. Optimal treatment of these patients is poorly understood and may differ from therapies recommended for either condition alone [12]. Excluding patients with an overlapping bronchiectasis/COPD diagnosis may result in more homogeneous NCFB patient populations in clinical trials. Patients in RESPIRE 2 had indicators of more severe airflow obstruction, but bronchiectasis severity could not be fully evaluated because computed tomography scans were not assessed at baseline. Not all parameters included in bronchiectasis severity indices were collected at baseline, as details for these had not been published when the RESPIRE studies were being designed [7, 13].

RESPIRE 1 and 2 also differed in the geographical regions that were represented, with RESPIRE 2 enrolling more patients from Asia and Eastern Europe. The variability in clinical practice could have potentially impacted the determination of exacerbations and treatment prior to enrolment. Specialist care for individuals with bronchiectasis is well developed, and research interest is relatively intense in Western Europe, the USA and Australia, which has led to the development of treatment guidelines and national standards [14–16]. European guidelines have only recently been published [17] and similar initiatives have been less common in other areas of the world [1]. This may have led to different disease management practices prior to enrolment. For example, patients in RESPIRE 2 were less likely to be treated with standard respiratory medications (67.9% *versus* 80.5%) or long-term macrolide treatment (7.7% *versus* 15.9%) than those in RESPIRE 1 [8]. This might reflect individual country practices or could be explained by different patient phenotypes. Reducing the heterogeneity of patient populations, in terms of phenotypic differences and standards of care prior to enrolment, is an important consideration for future trials.

Any comparison of the outcomes of RESPIRE 1 and 2 should take into consideration the change in extrapolation method and significance levels. Based on experience gained in RESPIRE 1, significance levels were amended by the sponsor with agreement from regulatory authorities to maximise the likelihood of achieving a significant result in the ciprofloxacin DPI 14-day on/off arm. If the α adjustment applied in RESPIRE 1 (p=0.025) had been used in RESPIRE 2, the ciprofloxacin DPI 28-day on/off arm would have met the primary end-point for the EMA/others analysis of frequency of exacerbations (IRR 0.55, 99.9% CI 0.30–1.02; p=0.0014). The FDA primary end-point, however, would not have been statistically significant nor would results in the ciprofloxacin DPI 14-day on/off arm have been affected.

As observed in RESPIRE 1, ciprofloxacin DPI was well tolerated. The number of study-drug-related treatment-emergent adverse events was markedly lower in RESPIRE 2 than RESPIRE 1 (13.7% *versus* 25.1%) [8]. Differences were largely due to lower numbers of respiratory treatment-emergent adverse events; contributory factors may include a lower rate of exacerbations in RESPIRE 2 or a higher threshold for diagnosis of these adverse events in centres involved in RESPIRE 2 *versus* RESPIRE 1. Trial discontinuation rates were low (5% due to treatment-emergent adverse events) and comparable across treatment arms. Together with data from RESPIRE 1, these findings support a favourable safety profile for ciprofloxacin DPI.

The limitations of the RESPIRE programme study design have been discussed previously [8]. RESPIRE 2 additionally highlighted the impact of low exacerbation rates on efficacy outcomes. Future NCFB trials should consider using a more stringent definition for prior exacerbations as an inclusion criterion and collecting data needed to calculate bronchiectasis severity based on published severity assessment tools [7, 13].

In conclusion, despite efficacy signals showing trends towards clinical benefits and excellent tolerability in the RESPIRE 2 study, neither the 14- or 28-day on/off ciprofloxacin DPI arms met the primary end-points of increasing time to first exacerbation or reducing frequency of exacerbations. The RESPIRE clinical trial programme thus encapsulates both the promise and difficulties of documenting a statistically significant impact on exacerbations in NCFB patients, and substantially contributes to the body of knowledge on the optimal design of clinical trials.

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