RESPIRE 1 Supplementary material

Section S1 Pre-defined subgroups for efficacy analyses

- The following subgroups were pre-defined for analysis:
    - Patients with and those without positive baseline culture of *Pseudomonas aeruginosa*
    - Patients with an FEV1 <50% and those with an FEV1 ≥50% of predicted at baseline
    - Patients with and those without a hospitalisation due to reported exacerbation in the previous year or more than two reported exacerbations requiring systemic antibiotic treatment in the previous year
    - Patients with and those without positive repeat culture (at least one organism in common) before start of study treatment (i.e. based on the central lab result at screening and randomisation visit)
    - Patients with and those without chronic macrolide use
    - Patients with and those without a ciprofloxacin-resistant pathogen based on systemic breakpoints at baseline (see online supplementary section S2).

Section S2 Safety end-points

- All adverse events were classified using Medical Dictionary for Regulatory Activities (MedDRA Version 18.1). The results were summarised, at a minimum, on the level of system organ class and preferred term. Data were also summarised according to intensity and investigator's causality assessment.
- Minimal inhibitory concentrations (MICs) of sputum isolates were tested against ciprofloxacin. Elevated (resistant) MICs were classified as follows based on Clinical and Laboratory Standards Institute breakpoints:[1]
    - *Haemophilus influenzae*: ≥2 µg/mL
    - *Moraxella catarrhalis*: ≥2 µg/mL
    - *Pseudomonas aeruginosa*: ≥4 µg/mL
    - *Staphylococcus aureus*: ≥4 µg/mL
    - *Streptococcus pneumoniae*: ≥4 µg/mL
    - *Burkholderia cepacia*: ≥4 µg/mL
    - *Stenotrophomonas maltophilia*: ≥4 µg/mL

[1]Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 2016

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TABLE S1 Randomisation by country

Country	Total N=416
Israel	53 (12.7)
Australia	52 (12.5)
New Zealand	51 (12.3)
Spain	49 (11.8)
Germany	47 (11.3)
United States	44 (10.6)
Japan	33 (7.9)
United Kingdom	27 (6.5)
Italy	21 (5.0)
Latvia	16 (3.8)
France	14 (3.4)
Argentina	6 (1.4)
Slovakia	2 (0.5)
Denmark	1 (0.2)

Data are presented as n (%).

TABLE S2 Pre-specified pathogens isolated at baseline

Species	Ciprofloxacin DPI 14-days on/off n=137	Placebo 14-days on/off n=68	Ciprofloxacin DPI 28-days on/off n=141	Placebo 28-days on/off n=70	Pooled placebo n=138	Total N=416
P. aeruginosa	83 (60.6)	41 (60.3)	83 (58.9)	45 (64.3)	86 (62.3)	252 (60.6)
H. influenzae	34 (24.8)	21 (30.9)	34 (24.1)	21 (30.0)	42 (30.4)	110 (26.4)
S. aureus	26 (19.0)	12 (17.6)	34 (24.1)	17 (24.3)	29 (21.0)	89 (21.4)
S. pneumoniae	11 (8.0)	8 (11.8)	11 (7.8)	4 (5.7)	12 (8.7)	34 (8.2)
M. catarrhalis	7 (5.1)	3 (4.4)	9 (6.4)	6 (8.6)	9 (6.5)	25 (6.0)
S. maltophilia	9 (6.6)	0 (0)	2 (1.4)	0 (0)	0 (0)	11 (2.6)
B. cepacia	0	0	0	0	0	0

Data are presented as n (%). Pathogens were isolated at screening, and/or Day 1. Patients could have more than one pathogen. DPI: dry powder for inhalation.

TABLE S3 Concomitant respiratory medications at baseline

	Ciprofloxacin DPI 14-days on/off	Placebo 14-days on/off	Ciprofloxacin DPI 28-days on/off	Placebo 28-days on/off
	n=137	n=68	n=141	n=70
Any respiratory medication	113 (82.5)	52 (76.5)	114 (80.9)	56 (80.0)
Mucolytics	27 (19.7)	13 (19.1)	26 (18.4)	10 (14.3)
Bronchodilators#	89 (65.0)	41 (60.3)	84 (59.6)	39 (55.7)
Inhaled corticosteroids	53 (38.7)	21 (30.9)	54 (38.3)	25 (35.7)
Low-dose systemic corticosteroids	4 (2.9)	0	6 (4.3)	1 (1.4)
Long-term oral macrolides	24 (17.5)	8 (11.8)	22 (15.6)	12 (17.1)
Theophylline	5 (3.6)	1 (1.5)	3 (2.1)	0
Other respiratory medication	0	0	2 (1.4)	2 (2.9)

Note: patients could be treated with more than one therapy at screening/baseline. Data are presented as n (%). #: bronchodilators include: long acting β-agonist bronchodilators, short acting β-agonist bronchodilators, long-acting anticholinergic bronchodilators and short-acting anticholinergic bronchodilators. DPI; dry powder for inhalation.

TABLE S4 Serious treatment-emergent (TE) adverse events (AEs) and deaths

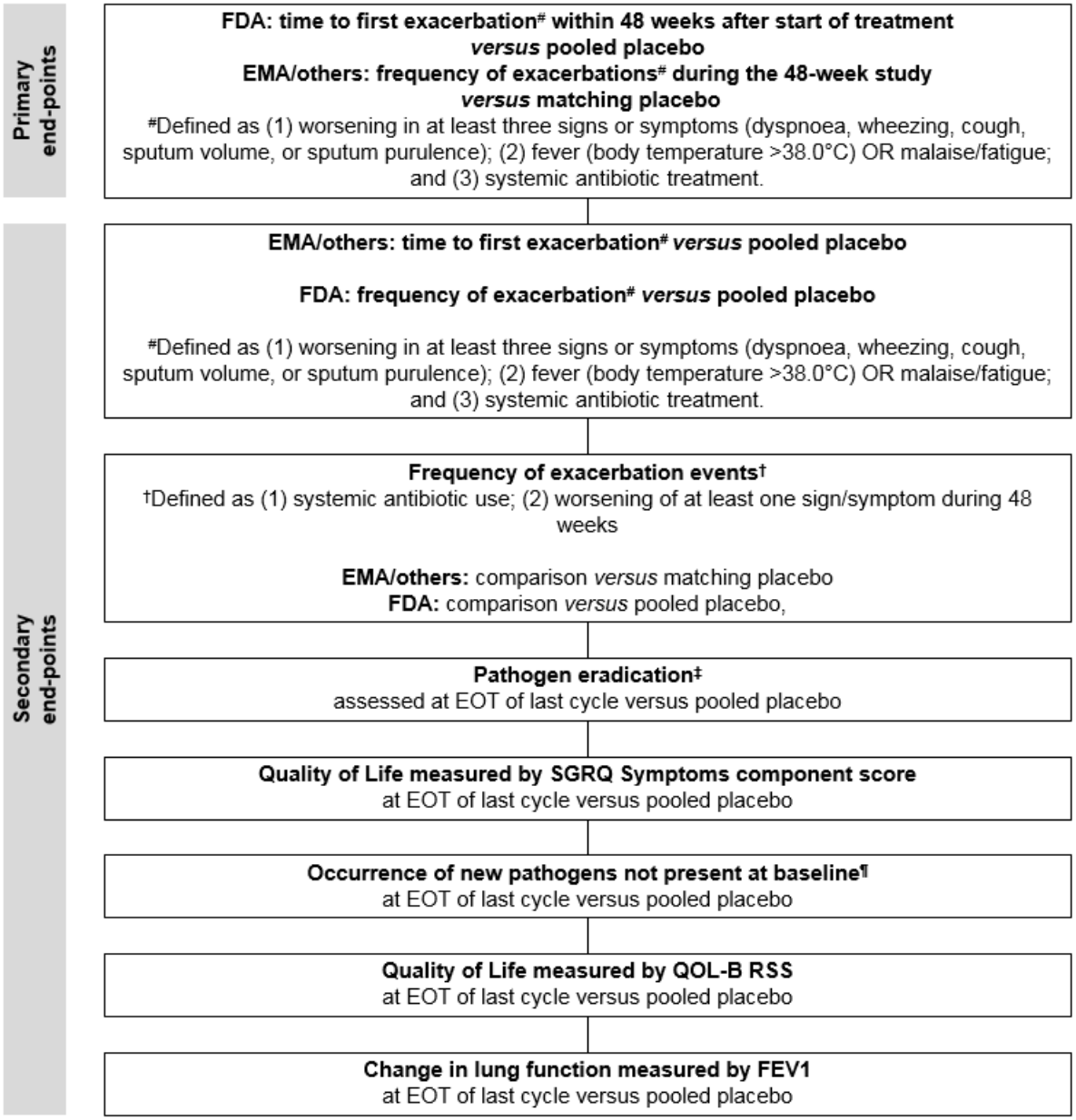
Preferred MedDRA term	Ciprofloxacin DPI		Pooled placebo n=137[#]
	14-days on/off n=136[#]	28-days on/off n=141	
Any serious TE adverse event	23 (16.9)	28 (19.9)	32 (23.4)
Respiratory, thoracic, and mediastinal disorders	10 (7.4)	19 (13.5)	18 (13.1)
Bronchiectasis exacerbations	8 (5.9)	16 (11.3)	17 (12.4)
Haemoptysis	1 (0.7)	2 (1.4)	2 (1.5)
Infections and infestations	5 (3.7)	9 (6.4)	9 (6.6)
Infective exacerbation of bronchiectasis	1 (0.7)	2 (1.4)	1 (0.7)
Pneumonia	4 (2.9)	4 (2.8)	5 (3.6)
Cardiac disorders	3 (2.2)	2 (1.4)	3 (2.2)
Cardiac failure	1 (0.7)	0	2 (1.5)
Injury, poisoning and procedural complications	4 (2.9)	1 (0.7)	2 (1.5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7)	1 (0.7)	4 (2.9)
Nervous system disorders	1 (0.7)	1 (0.7)	3 (2.2)
Renal and urinary disorders	2 (1.5)	0	2 (1.5)
Vascular disorders	2 (1.5)	0	1 (0.7)
General disorders and administration site conditions	2 (1.5)	1 (0.7)	0
Eye disorders	1 (0.7)	1 (0.7)	0
Gastrointestinal disorders	0	0	2 (1.5)
Musculoskeletal and connective tissue disorders	0	1 (0.7)	1 (0.7)
Blood and lymphatic system disorders	0	0	1 (0.7)

Hepatobiliary disorders	0	0	1 (0.7)
Immune system disorders	0	1 (0.7)	0
Investigations	0	1 (0.7)	0
Metabolism and nutrition disorders	1 (0.7)	0	0
Reproductive system and breast disorders	1 (0.7)	0	0
Any TE-AE with outcome death	1 (0.7)	2 (1.4)	3 (2.2)
Pneumonia	0	1 (0.7)	1 (0.7)
Aspiration pneumonia	1 (0.7)	0	0
Cor pulmonale	0	1 (0.7)	0
Pulmonary haemorrhage	0	0	1 (0.7)
Complications of transplant surgery	0	0	1 (0.7)

[#]: two randomised subjects did not receive study medication (one in Ciprofloxacin DPI 14-days on/off and one in placebo 28-days on/off). Data are presented as n (%). Serious TE adverse events are listed by MedDRA system organ class and by preferred term if more than one subject in any treatment group was affected. Subjects could experience more than one serious TE adverse event. DPI: dry powder for inhalation; MedDRA: Medical Dictionary for Regulatory Activities.

FIGURE S1 Ciprofloxacin DPI pocket-sized inhaler.

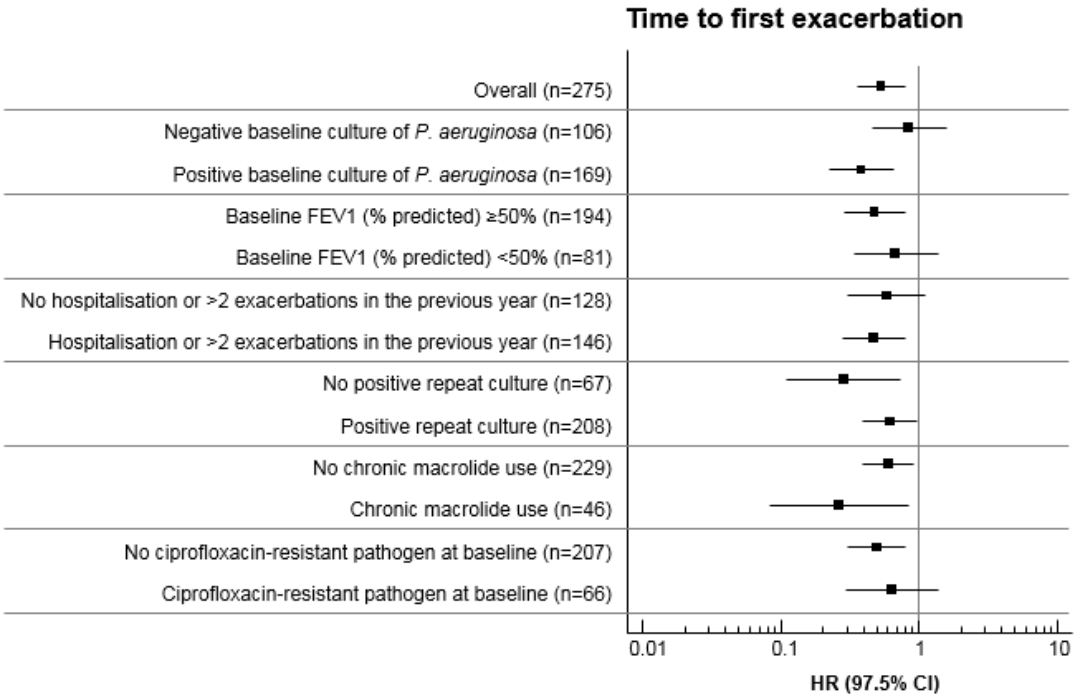
FIGURE S2 End-points according to hierarchical analysis plan.

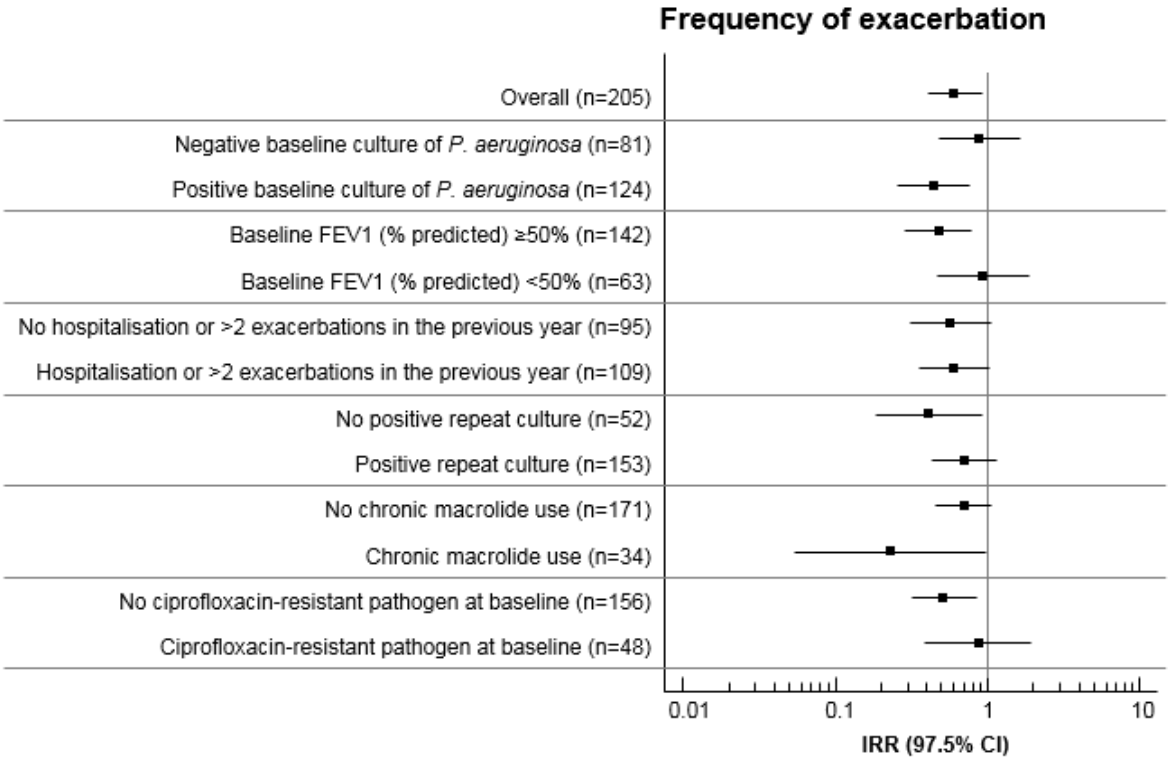


EMA: European Medicines Agency; EOT: end of treatment; FDA: Food and Drug Administration; FEV1: forced expiratory volume in 1 second; QOL-B RSS: Quality of Life-Bronchiectasis Respiratory Symptom Score; SGRQ: St. George's Respiratory Questionnaire; ‡Compared against baseline i.e. using all sputum samples collected at the screening and/or at the randomisation visit prior to first study drug inhalation. End of treatment is not EOT visit, but individual last treatment of last cycle Week 44/46. ¶Compared against baseline i.e. using all sputum samples collected at the screening and/or at the randomisation visit prior to first study drug inhalation.

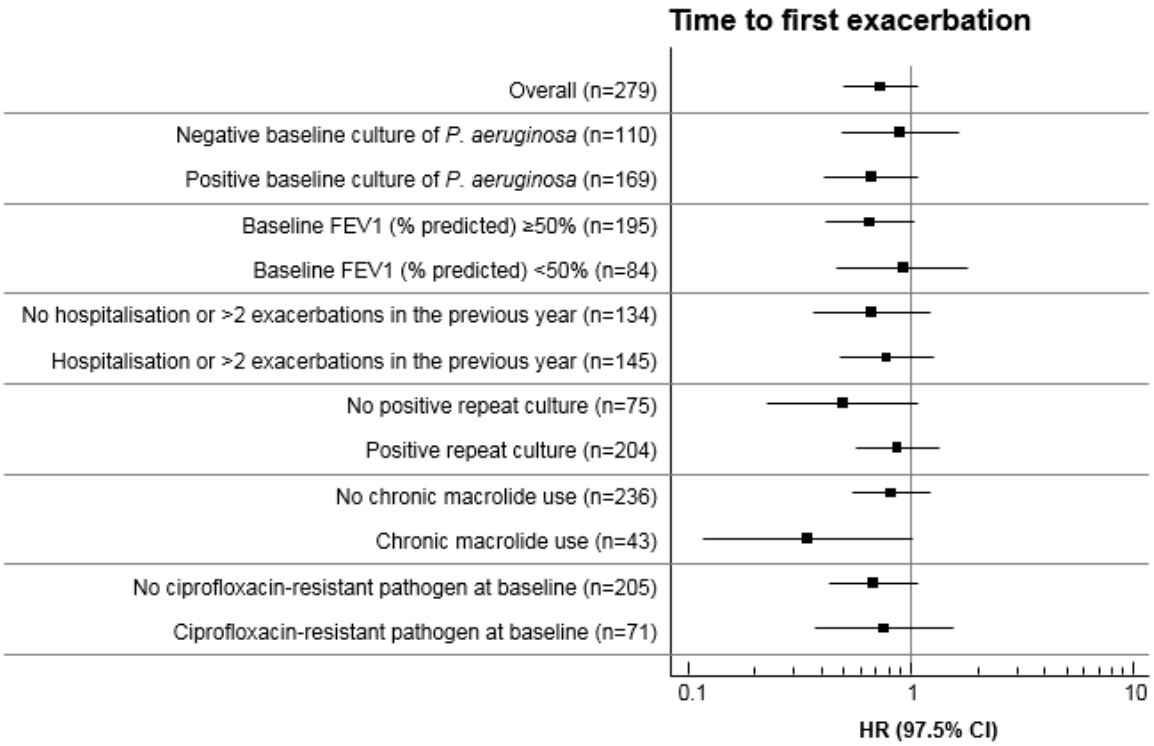
FIGURE S3 Efficacy of Ciprofloxacin DPI in pre-specified subgroups: a) Ciprofloxacin DPI 14-days on/off; b) Ciprofloxacin DPI 28-days on/off *versus* pooled (time to first exacerbation) or matching placebo (frequency of exacerbation).

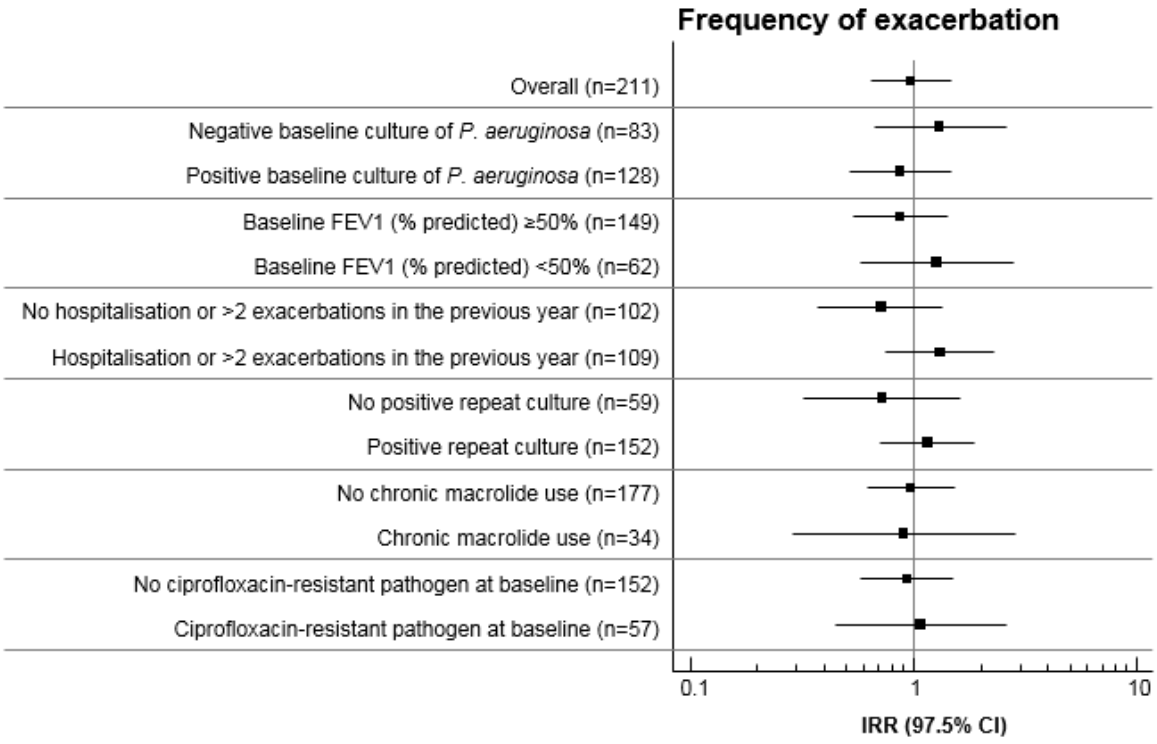
a)





b)





n=total number of patients (active therapy and pooled placebo or active and matching placebo). CI: confidence interval; FEV1: forced expiratory volume in 1 second; HR: hazard ratio; IRR: incidence rate ratio.