RESPIRE 2 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 19.0). The results were summarised as a minimum based on system organ class and preferred term. Data were also summarised by intensity and causality according to the investigator's assessment.
- Minimal inhibitory concentrations (MICs) of sputum isolates tested against ciprofloxacin. Elevated (resistant) MICs were classified based on Clinical and Laboratory Standards Institute breakpoints as follows:[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

Section S3 Differences in statistical analysis plan for RESPIRE 2 *versus* RESPIRE 1

The analysis of the first secondary efficacy end-point according to the Food and Drug Administration (FDA) analysis plan “frequency of exacerbation events (stringent definition)” was changed so that no explicit extrapolations were performed for patients not completing the 48-week period. Instead, the same model as for the primary efficacy end-point according to the EMA/other analysis plan was used (i.e. patients’ time in study as an offset variable).

A weighted Bonferroni adjustment using alpha=0.049 for the 14 days on/off regimen and alpha=0.001 for the 28 days on/off regimen was applied. By prospectively adjusting the alpha level (an amendment to the statistical analysis plan approved by regulatory bodies), the power to detect a statistically significant difference in the 14-days arm was increased. Concurrently, the power in the 28-day arm was decreased.

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TABLE S1 Randomisation by country

Country	Patients
	N=521
Russia	60 (11.5)
Bulgaria	54 (10.4)
Latvia	45 (8.6)
Poland	39 (7.5)
South Korea	34 (6.5)
China	33 (6.3)
Serbia	33 (6.3)
Romania	32 (6.1)
Turkey	30 (5.8)
Australia	21 (4.0)
Germany	19 (3.6)
The Netherlands	19 (3.6)
United States	16 (3.1)
Portugal	14 (2.7)
Argentina	13 (2.5)
Thailand	13 (2.5)
Philippines	10 (1.9)
Hong Kong	9 (1.7)
Taiwan	9 (1.7)
Lithuania	6 (1.2)
Brazil	5 (1.0)
Czech Republic	4 (0.8)
South Africa	2 (0.4)
Austria	1 (0.2)

Data are presented as n (%).

TABLE S2 Pre-specified pathogens isolated at baseline

Species	Ciprofloxacin DPI 14-days on/off n=176	Placebo 14-days on/off n=88	Ciprofloxacin DPI 28-days on/off n=171	Placebo 28-days on/off n=86	Pooled placebo n=174	Total N=521
P. aeruginosa	107 (60.8)	55 (62.5)	99 (58.2)	54 (63.5)	109 (63.0)	315 (60.7)
S. aureus	43 (24.4)	26 (29.5)	42 (24.7)	21 (24.7)	47 (27.2)	132 (25.4)
H. influenzae	25 (14.2)	12 (13.6)	38 (22.4)	15 (17.6)	27 (15.6)	90 (17.3)
S. pneumoniae	11 (6.3)	3 (3.4)	14 (8.2)	7 (8.2)	10 (5.8)	35 (6.7)
M. catarrhalis	11 (6.3)	6 (6.8)	8 (4.7)	5 (5.9)	11 (6.4)	30 (5.8)
S. maltophilia	8 (4.5)	1 (1.1)	7 (4.1)	4 (4.7)	5 (2.9)	20 (3.9)
B. cepacia	0	2 (2.3)	1 (0.6)	1 (1.2)	3 (1.7)	4 (0.8)

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

TABLE S3 Concomitant respiratory medications at baseline

	Ciprofloxacin DPI 14-days on/off n=176	Placebo 14-days on/off n=88	Ciprofloxacin DPI 28-days on/off n=171	Placebo 28-days on/off n=86
Any respiratory medication	113 (64.2)	61 (69.3)	129 (75.4)	51 (59.3)
Mucolytics	47 (26.7)	18 (20.5)	48 (28.1)	20 (23.3)
Bronchodilators[#]	72 (40.9)	44 (50.0)	85 (49.7)	33 (38.4)
Inhaled corticosteroids[†]	57 (32.4)	28 (31.8)	72 (42.1)	25 (29.1)
Low-dose systemic corticosteroids	0 (0)	2 (2.3)	2 (1.2)	1 (1.2)
Long-term oral macrolides	11 (6.3)	7 (8.0)	14 (8.2)	8 (9.3)
Theophylline	14 (8.0)	6 (6.8)	17 (9.9)	5 (5.8)
Other respiratory medications	1 (0.6)	0	2 (1.2)	1 (1.2)

Patients could be treated with more than one therapy at baseline. Data are presented as n (%). DPI: dry powder for inhalation; [#]: bronchodilators include: long-acting β-agonists, short-acting β-agonists, combination bronchodilators (long-acting), combination bronchodilators (short-acting), long-acting anticholinergic bronchodilators and short-acting anticholinergic bronchodilators; [†]: inhaled corticosteroids include: inhaled corticosteroids and combined corticosteroids and long-acting β-agonists.

TABLE S4 Serious treatment-emergent adverse events and deaths

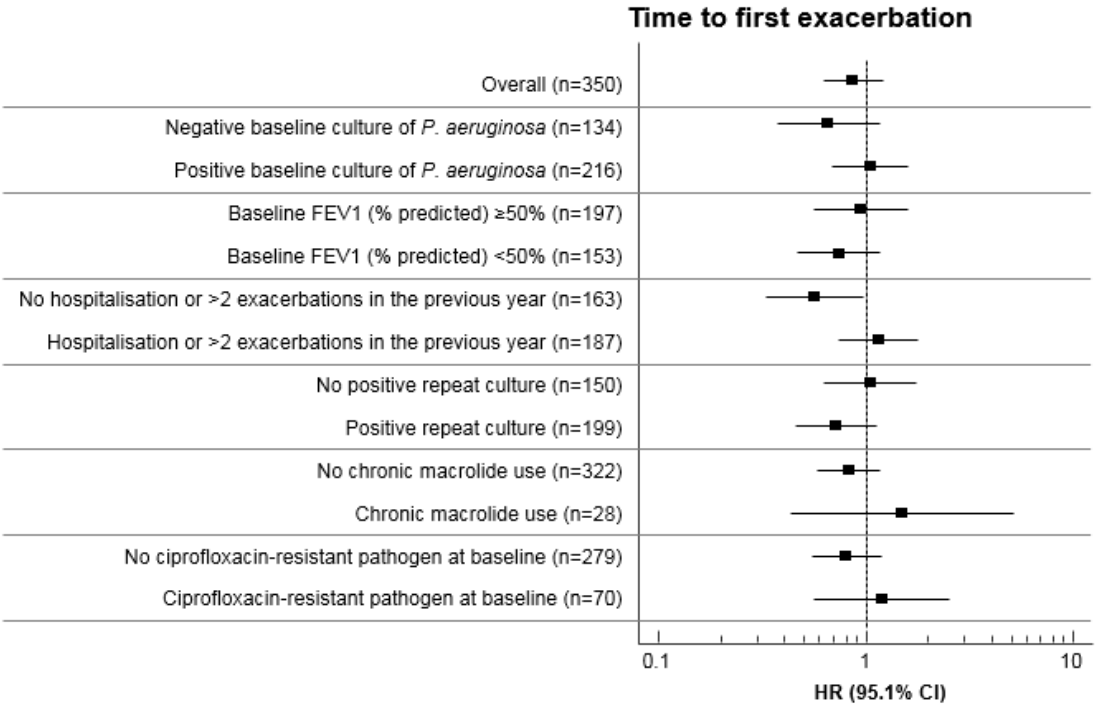
Preferred term	Ciprofloxacin DPI		Pooled placebo
	14-days on/off n=174[#]	28-days on/off n=171	n=174
Any serious TE adverse event	45 (25.9)	28 (16.4)	41 (23.6)
Respiratory, thoracic and mediastinal disorders	30 (17.2)	19 (11.1)	26 (14.9)
Bronchiectasis exacerbations	24 (13.8)	17 (9.9)	21 (12.1)
Haemoptysis	3 (1.7)	2 (1.2)	4 (2.3)
Chronic obstructive pulmonary disease	3 (1.7)	0	1 (0.6)
Infections and infestations	5 (2.9)	5 (2.9)	9 (5.2)
Pneumonia	2 (1.1)	3 (1.8)	2 (1.1)
Infective exacerbation of bronchiectasis	3 (1.7)	0	2 (1.1)
Gastrointestinal disorders	3 (1.7)	2 (1.2)	2 (1.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (1.1)	1 (0.6)	3 (1.7)
Musculoskeletal and connective tissue disorders	2 (1.1)	0	2 (1.1)
Nervous system disorders	1 (0.6)	2 (1.2)	0
Cardiac disorders	0	2 (1.2)	0
Hepatobiliary disorders	1 (0.6)	0	1 (0.6)
Blood and lymphatic system disorders	0	0	1 (0.6)
Ear and labyrinth disorders	1 (0.6)	0	0
Eye disorders	0	0	1 (0.6)
Injury, poisoning and procedural complications	0	0	1 (0.6)
Metabolism and nutrition disorders	0	0	1 (0.6)
Pregnancy, puerperium and	0	1 (0.6)	0

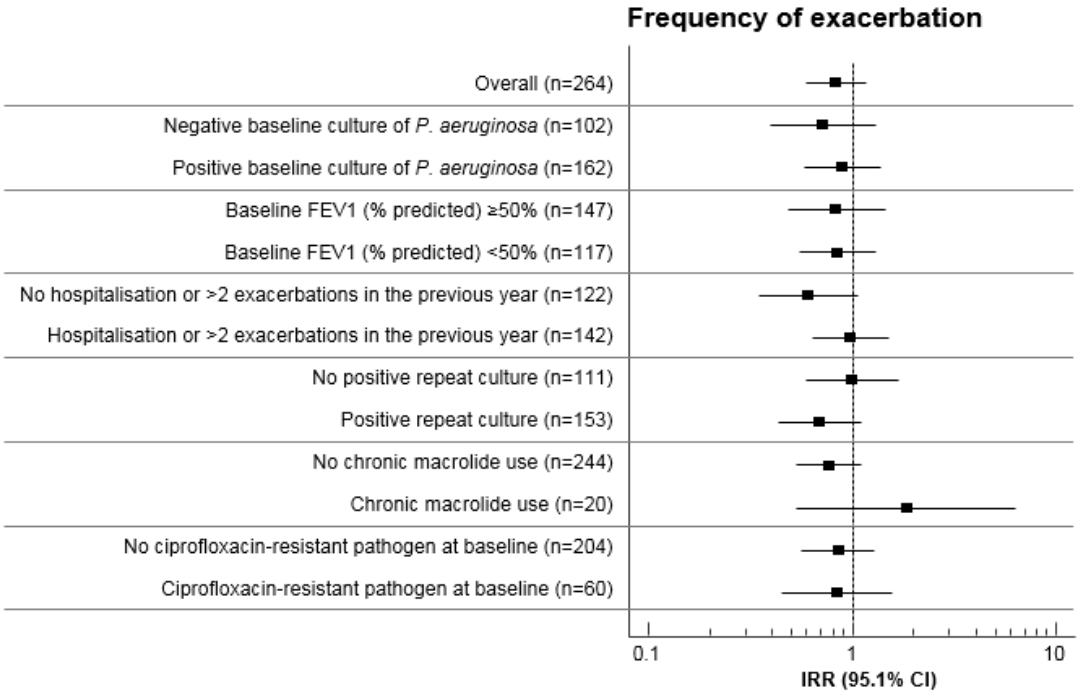
perinatal disorders			
Psychiatric disorders	1 (0.6)	0	0
Reproductive system and breast disorders	1 (0.6)	0	0
Vascular disorders	0	0	1 (0.6)
Any TE adverse event with outcome death	3 (1.7)	4 (2.3)	2 (1.1)
Bronchiectasis	1	2	2
Congestive cardiomyopathy	0	1	0
Cor pulmonale	0	1	0
Gastrointestinal haemorrhage	1	0	0
Oesopharyngeal carcinoma	1	0	0

[#]: two randomised subjects did not receive study medication (both in Ciprofloxacin DPI 14-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. DPI: dry powder for inhalation; MedDRA: Medical Dictionary for Regulatory Activities.TE: treatment emergent.

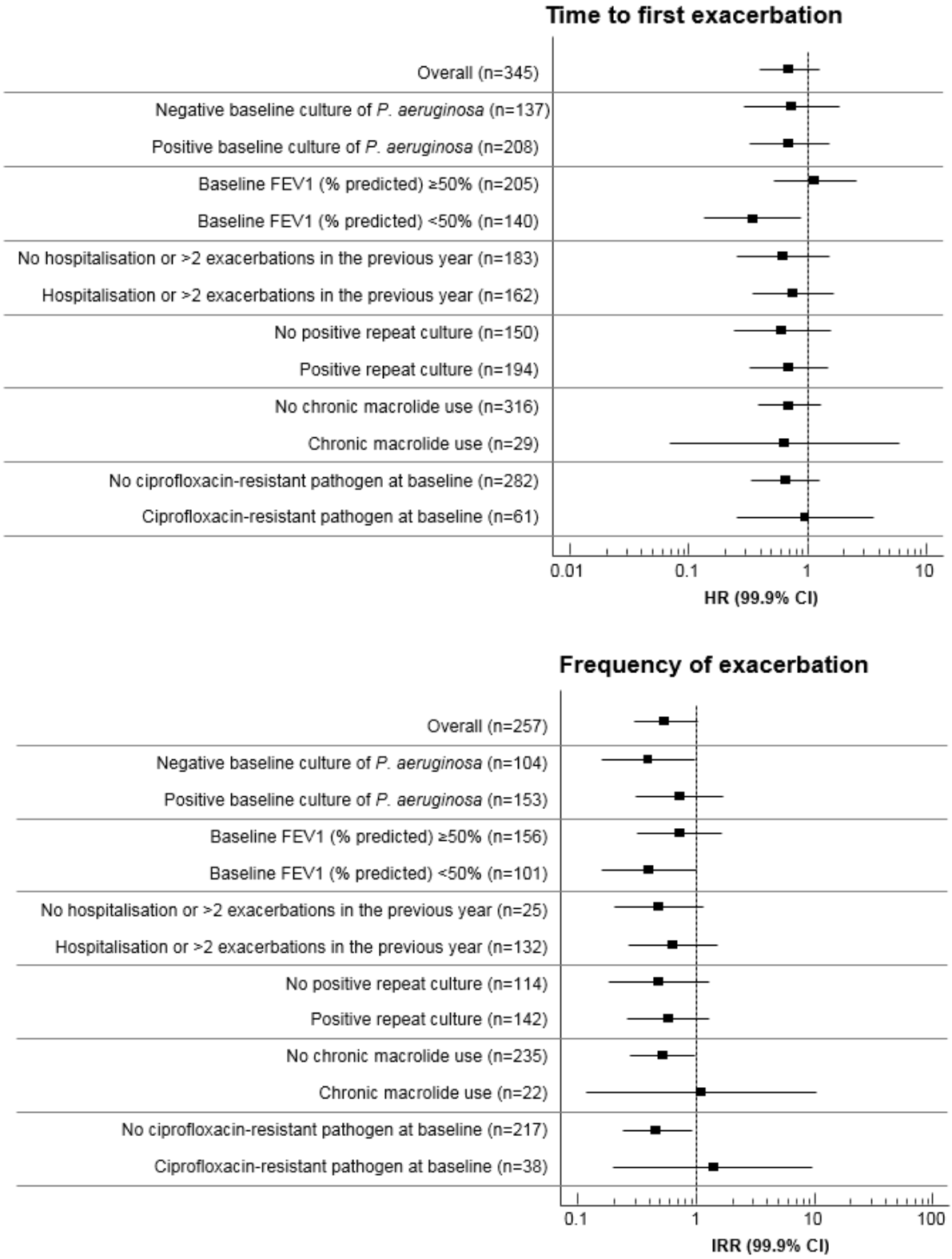
FIGURE S1 Efficacy of Ciprofloxacin DPI in pre-specified subgroups: a) Ciprofloxacin DPI 14-days on/off; b) Ciprofloxacin DPI 28-days on/off *vs* pooled (time to first exacerbation) or matching placebo (frequency of exacerbation).

a)





b)



CI: confidence interval; FEV1: forced expiratory volume in 1 second; HR: hazard ratio; IRR: incidence rate ratio.