FDA Briefing Document

Ciprofloxacin Dry Powder for Inhalation (DPI) Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

November 16, 2017

The committee will discuss New Drug Application (NDA) 209367 (ciprofloxacin dry powder for inhalation), submitted by Bayer Healthcare Pharmaceuticals, Inc., for the proposed indication of reduction of exacerbations in non-cystic fibrosis bronchiectasis (NCFB) adult patients (≥18 years of age) with respiratory bacterial pathogens. The Federal Register notice for this AMDAC is dated September 29, 2017.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought ciprofloxacin dry powder for inhalation (DPI) to this Advisory Committee to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

1 Introduction

This briefing document describes the review of safety and efficacy data for ciprofloxacin DPI, prepared by the FDA for the panel members of the Advisory Committee. We would like the committee to discuss whether the data are adequate to support safety and efficacy of ciprofloxacin DPI for reduction of exacerbations in non-cystic fibrosis bronchiectasis (NCFB) adult patients (≥18 years of age) with respiratory bacterial pathogens.

We are also interested in any other issues the committee considers relevant.

2 Background on Non-Cystic Fibrosis Bronchiectasis

Bronchiectasis is characterized by inflamed and easily collapsible airways and obstruction to airflow.[1] The diagnosis of bronchiectasis is established clinically on the basis of cough on most days with viscous sputum production, often one or more exacerbations per year, and radiographically by the presence of bronchial wall thickening and airway dilatation on chest CT scans.[2] In a review of 103 bronchiectasis patients, the following clinical symptoms were documented: cough (98%), daily sputum production (78%), dyspnea (62%), rhinosinusitis (73%), hemoptysis (27%), and recurrent pleurisy (20%).[3] Physical findings included crackles (75%) and wheezing (22%). In a study of 117 bronchiectasis patients, fatigue was noted in 43% and correlated with lower FEV_1.[4]

It is estimated that approximately 110,000 individuals have bronchiectasis in the U.S.[5] The prevalence of bronchiectasis increases with age with an 8 to 10-fold difference in prevalence after the age of 60 (300 to 500/100,000) as compared to ages <40 to 50 years (40 to 50/100,000).[5,6] Bronchiectasis is more common in women. From a pathophysiological perspective, induction of bronchiectasis requires: (1) an infectious or environmental pulmonary event, and (2) impaired drainage, airway obstruction, or a defect in host defense.[1] The resulting host response, immune effector cells (predominately neutrophils), neutrophil elastase, reactive oxygen intermediates, and inflammatory cytokines found in respiratory secretions create transmural inflammation, mucosal edema, cratering, ulceration, and neovascularization in the airways.[7,8] The result is permanent abnormal dilatation and destruction of the major bronchi and bronchiole walls.[1]

The extent of pulmonary involvement is typically characterized by high resolution CT. Severity has been assessed using health-related quality of life questionnaires and pulmonary function tests which typically show an obstructive pattern (reduced or normal forced vital capacity (FVC), low FEV_1, and low FEV_1/FVC).

Since bronchiectasis is a manifestation of scarring resulting from prior injury, infection, or ongoing problems with secretion clearance, treatment of the underlying disease is not typically possible. Treatment of acute exacerbations with antibacterial drugs transiently reduces the bacterial load and airway and systemic inflammatory mediators.[9] Acute bacterial exacerbations are typically heralded by increased sputum production that is

darker and more viscous and may also include malaise, dyspnea, pleuritic chest pain, and/or hemoptysis. Fever and chills are generally absent.[10] Viral infections may also play a role in acute exacerbations.[11] Colonizing flora in patients with bronchiectasis include: *H. influenzae*, *M. catarrhalis*, *S. aureus*, *P. aeruginosa* (especially mucoid types), and less frequently, *S. pneumoniae*.[12,13] The presence of *P. aeruginosa* in sputum has been associated with increased death, exacerbations, and hospital admissions.[14,15]

Studies of inhaled antibacterial drugs (tobramycin, gentamicin, aztreonam, and colistin) for the prevention of NCFB exacerbations have yielded mixed results and none are approved for this indication.[16-21]

Other therapies used include, but are not limited to: mucolytic agents, airway hydration, respiratory physiotherapy, as well as use of inhaled bronchodilators, anti-inflammatory medications, anti-gastroesophageal reflux therapies, lung resection surgery, and immunization. [22]

3 Ciprofloxacin Dry Powder for Inhalation (DPI) Product Information

Ciprofloxacin is a synthetic, fluorinated carboxyquinolone and has in vitro activity against both Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin results from inhibition of bacterial type II topoisomerases (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination.

The drug substance is ciprofloxacin (hydrated micronized). The drug product, ciprofloxacin DPI, is a dry powder for inhalation produced by PulmoSphere® technology (Novartis Pharmaceuticals) and supplied in hydroxypropyl methylcellulose (HPMC) capsules.

4 Ciprofloxacin DPI Clinical Development and Regulatory History

The Applicant's proposed indication for ciprofloxacin DPI is for reduction of exacerbations in NCFB adult patients (≥18 years of age) with respiratory bacterial pathogens. Of note, the primary endpoint for the Phase 3 trials was time to first exacerbation from start of study treatment. Frequency of exacerbations was considered a secondary endpoint.

The Agency recommended that two adequate and well-controlled trials be conducted to support the NCFB indication because (1) this was a new treatment indication and route of administration for ciprofloxacin; (2) there were too many uncertainties with regard to duration of treatment, frequency of administration and endpoints to allow for reliance on a single Phase 3 trial; (3) there were no relevant animal models; (4) given the proposed

chronicity of administration, there was a need for adequate assessment of safety in a reasonably large number of patients; and (5) the conduct of two independent studies would be important in providing strong replicative evidence supporting an overall demonstration of efficacy and safety.

Ciprofloxacin DPI has been granted orphan drug, qualified infectious disease product, fast track, and breakthrough therapy designations for the treatment of NCFB.

5 Clinical Pharmacology

Following oral inhalation of dry powder containing 32.5 mg ciprofloxacin, the mean peak concentration of ciprofloxacin in plasma (Cmax) in healthy subjects, COPD, and bronchiectasis patients ranged from 0.10 to 0.13 mg/L, which is at least 10-fold lower than the Cmax following oral and intravenous administration of ciprofloxacin at approved clinical doses. Forty-five minutes after oral inhalation of dry powder containing 32.5 mg ciprofloxacin, sputum concentrations were high (up to approximately 1000 mg/L) and beyond the solubility limit of ciprofloxacin in sputum, suggesting that ciprofloxacin concentrations in the lung have reached saturation. High inter-subject variability of sputum concentrations was observed. Higher dose (i.e., 48.75 mg q12h) did not result in higher ciprofloxacin exposure in sputum. Due to the low systemic exposure of ciprofloxacin following oral inhalation of ciprofloxacin dry powder, no dose adjustment is warranted for patients with hepatic or renal impairment and patients taking concomitant medications.

6 Microbiology

Ciprofloxacin, a fluoroquinolone, targets bacterial DNA gyrase and topoisomerase IV and stops DNA replication. Resistance occurs primarily as a result of alterations in the target enzymes; changes leading to reduced drug uptake or efflux; or plasmid mediated protection of the quinolone targets. Resistance generally occurs at a frequency of $<10^{-9}$ to $1x10^{-6}$. Ciprofloxacin is active against gram-negative and gram-positive bacteria including *Haemophilus influenzae, Moraxella catarrhalis*, methicillin sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*. Hollow fiber models showed a reduction in bacterial counts after exposure to simulated sputum lung concentrations (120 mg/L); however, regrowth was observed after 1 to 2 days post-exposure. In acute rat lung infection models, the reduction in lung *P. aeruginosa* burden with ciprofloxacin was similar or better than tobramycin. In the chronic rat lung infection model, ciprofloxacin reduced lung burden of susceptible *P. aeruginosa* in one cycle; however, 2 cycles of ciprofloxacin treatment reduced the lung burden of resistant *P. aeruginosa* by only 1 $\log_{10}$.

7 Sources of Clinical Data

7.1 Overview of Ciprofloxacin DPI Clinical Program

A total of 195 subjects (18 healthy subjects and 177 patients) participated in Phase 1 studies and were included in the Applicant's Summary of Clinical Safety. Patients included those with cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and NCFB. 111 participants received a single dose of Cipro DPI or placebo powder and 84 received multiple dose treatments of Cipro DPI or placebo. In total, approximately 164 healthy subjects and patients received at least one dose of Cipro DPI in Phase 1 studies with treatment ranging from 1 to 13 days.

Phase 2 study 12429 was a randomized, double-blind, placebo-controlled, multicenter study in patients with CF. Cipro DPI 32.5 mg or 48.75 mg or matching placebos were administered BID for 28 days followed by 28 days off-treatment. FEV_1 and bacteriological loads were assessed at baseline, during treatment (Day 7 to 9 and Day 14 to 16), at the EOT Day 28 to 30), and at 2 and 4 weeks post EOT. In this study, 93 patients with CF were exposed to 32.5 mg twice daily Cipro DPI for 28 days, 93 patients were exposed to 48.75 mg Cipro DPI twice daily for 28 days, and 100 patients received matching placebo. Neither Cipro DPI group was superior to placebo for the primary endpoint of change in FEV_1 from baseline to EOT. The Cipro DPI arms had a reduction in bacterial loads compared with the placebo arms while on therapy which was not sustained post EOT. Based on the higher incidence of adverse events, serious adverse events and adverse events leading to withdrawal in the 48.75 mg Cipro DPI dosing regimen and comparable bacterial load reductions in sputum, Bayer chose to continue development with Cipro 32.5 mg DPI instead of Cipro 48.75 mg DPI.

Phase 2 study 12965 was a randomized, double-blind, placebo-controlled, multicenter study in patients with NCFB. The primary efficacy variable was microbiological: total bacterial load expressed as $\log_{10}$ CFU per gram of sputum considering the following bacterial species: *P. aeruginosa, S. aureus, S. pneumoniae, H. influenzae, M. catarrhalis, Enterobacteriaceae* [*K. pneumoniae* or *K. oxytoca, S. marcescens, E. coli and P. mirabilis], S. maltophilia,* and *Achromobacter*. Changes in bacterial load were assessed during treatment (Day 8), at end of therapy (EOT) (Day 28), and at 3 follow-up visits (Days 42, 56, and 84). Cipro DPI 32.5 mg or placebo were administered BID for 28 days. In this study, 60 patients with NCFB received 32.5 mg Cipro DPI twice daily for 28 days and 64 patients received matching placebo powder. For the primary endpoint, the total bacterial load in sputum at EOT was reduced by 3.62 $\log_{10}$ CFU/g sputum for Cipro DPI vs. 0.27 $\log_{10}$ CFU/g sputum for placebo. By 8 weeks post EOT, the mean $\log_{10}$ CFU/g sputum counts in the two treatment groups were similar at approximately 6 $\log_{10}$ CFU/g sputum.

Cipro DPI was evaluated in two Phase 3 randomized, double-blind, placebo-controlled trials of 933 subjects with non-cystic fibrosis bronchiectasis (NCFB). Of these, 622 subjects received at least one dose of Cipro DPI (310 subjects received Cipro DPI 14 days on/off, and 312 subjects received Cipro DPI 28 days on/off). Additionally, 311

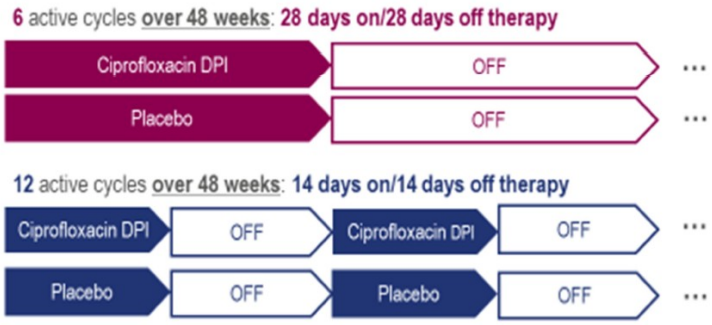
subjects received at least one dose of placebo powder (156 received the placebo 14 day on/off regimen and 155 received the placebo 28-day on/off regimen). It should also be noted that both trials did not include a comparator arm that did not receive any dry powder for inhalation. Without such a comparator, it is difficult to ascertain the incidence of adverse reactions due solely to inhaling a dry powder.

7.2 Phase 3 Trials

7.2.1 Study Design

Bayer conducted two Phase 3 trials (entitled, RESPIRE 1 and RESPIRE 2) with nearly identical study designs. They were randomized, double-blind, comparative trials that used placebo powder as the comparator. In both trials, patients received ciprofloxacin DPI 32.5 mg or placebo twice daily in 6 cycles of 28 days on/28 days off therapy or 12 cycles of 14 days on/14 days off therapy over a period of 48 weeks. Patients were randomized 2:1:2:1 to one of these four study arms: Cipro 14 days on/off, Placebo 14 days on/off, Cipro 28 days on/off and Placebo 28 days on/off.

Figure 1: Treatment Cycles in RESPIRE 1 & 2



Source: Applicant Figure

Table 1 shows the visit schedule in the RESPIRE trials which varies depending on the cycle number and the duration of treatment received (14 days or 28 days). Patients in the 28 day arms had fewer visits but more phone calls than patients in the 14 day arms. Patients in the 28 day arms had earlier EOT and EOS visits (Weeks 44 and 52) compared to patients in the 14 day arms (Weeks 46 and 54). All post-baseline visits shown below occurred within a 2 day window of the scheduled day (e.g. Day 28 visit occurred on Day 28 ± 2 days).

Table 1: Visit Schedule in RESPIRE 1 and RESPIRE 2

Week :	-4-0	BL	2	4	6	8	10	12	14	16	18	20	22	24
14 day Cycle:	Screening/ Baseline		1		2		3		4		5		6	
28 day Cycle:			1				2				3			
14 day arms	V1	V2	V3	V4	V5	V6	-	C	V7	C	-	V8	V9	V10
28 day arms	V1	V2	C	V3	C	V4	-	V5	C	C	-	V6	C	V7
Week:	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**52**	**54**
14 day Cycle:	7		8		9		10		11		12		Follow-up	
28 day Cycle:	4				5				6					
14 day arms	-	C	-	C	-	C	V11	V12	-	C	V13, EOT	V14	-	V15, EOS
28 day arms	-	C	-	C	-	V8	C	C	-	V9, EOT	-	V10	V11, EOS	

Source: Reviewer Table
C-Call, V-Visit, On/off therapy periods shaded/unshaded in grey, V1- Screening Visit within 28 days of Baseline, V2- Baseline Visit on Day 1, EOT- EOT Visit, EOS- End of Study Visit

The main inclusion criteria were: NCFB documented by CT scan; positive sputum culture for *P. aeruginosa, H. influenzae, M. catarrhalis, S. aureus, S. pneumoniae, S. maltophilia* or *B. cepacia* obtained at screening and with a history of ≥2 exacerbations in the past 12 months; FEV_1 ≥30% and <90% (post-bronchodilator); on a stable standard treatment regimen for bronchiectasis; and sputum production on the majority of days. The main exclusion criteria were: FEV_1 <30% and ≥90% (post-bronchodilator); active allergic bronchopulmonary aspergillosis; active and actively-treated non-tuberculous mycobacterial infection or tuberculosis; diagnosis of common variable immunodeficiency; recent significant hemoptysis (≥300 mL or requiring blood transfusion) in the 4 weeks before screening; primary diagnosis of COPD; and known CF or documented chronic bronchial asthma.

The primary efficacy endpoint was time to first pulmonary exacerbation. An important secondary endpoint was the frequency of exacerbations over the course of the study period. Additional evaluations included, but were not limited to determinations of the effect of therapy on bacterial eradication, health-related quality of life, occurrence of new pathogens not present at baseline, and FEV_1. Efficacy analyses were performed in a hierarchical manner evaluating the superiority of each of the active treatment regimens (separately) versus pooled placebo until the first endpoint for which the null hypothesis could not be rejected.

Primary endpoint:

In the RESPIRE studies, an exacerbation qualifying for the primary endpoint required that: ≥3 of the following signs or symptoms had worsened (beyond normal day-to-day variations) for at least 2 consecutive days after the start of worsening:

- Dyspnea
- Wheezing
- Cough
- 24 hour sputum volume
- Sputum purulence (color)

AND

- The presence of
  - Fever (body temperature >38˚C)

  OR
  - Malaise/fatigue

AND

- Systemic antibacterial treatment

A minimum of 4 weeks between one exacerbation onset and the beginning of the next exacerbation was required for the diagnosis of a new event.

Secondary Endpoints (to be tested in the following order):

- Frequency of exacerbation events (defined as exacerbations with systemic antibacterial use and presence of fever or malaise/fatigue, and worsening of at least 3 signs/symptoms over 48 weeks)
- Frequency of exacerbation events (defined as exacerbations with systemic antibacterial use and worsening of at least 1 sign/symptom over 48 weeks)
- Eradication of baseline pathogens
- Changes from baseline in patient-reported outcome Saint George's Respiratory Questionnaire (SGRQ) symptoms component score
- Occurrence of new pathogens not present at baseline
- Changes from baseline in patient-reported outcome Quality of Life Questionnaire-Bronchiectasis (QOL-B) respiratory symptoms domain score
- Improved lung function measured by FEV_1

Differences between the two studies included:

- RESPIRE 2 included additional investigation of ciprofloxacin concentration in fecal samples of subjects.
- RESPIRE 1 randomized 416 subjects and RESPIRE 2 randomized 521 subjects. The sample size in RESPIRE 2 was increased to 521 subjects due to a higher than expected dropout rate observed in RESPIRE 1.
- RESPIRE 1 was conducted in Europe, US, Latin America, Japan, and Australia/New Zealand, while RESPIRE 2 was conducted in Europe, US, Latin America/South Africa/Australia, and Asia.
- The allocation of the available study alpha of 0.05 was split differently for testing each of the Cipro arms. In order to control for multiplicity, Cipro 28 and Cipro 14

were each tested at α=0.025 in RESPIRE 1 versus α=0.001 and α=0.049 in RESPIRE 2.

- The primary approach for testing frequency of exacerbation differed between the trials. RESPIRE 1 used Poisson regression with an extrapolation approach to impute missing data from subjects with premature study termination. RESPIRE 2 used Poisson regression which included "log (time in study)" as an offset variable.

7.2.2 Demographics and Baseline Characteristics

In RESPIRE 1, 902 subjects were enrolled (486 screen failures) with 416 subjects randomized and included in the full analysis set (FAS). Countries that contributed at least 10% of overall patients in the FAS were Israel (12.7%), Australia (12.5%), New Zealand (12.3%), Spain (11.8%), Germany (11.3%) and the United States (10.6%). In RESPIRE 2, 1123 subjects were enrolled (602 screen failures) with 521 subjects randomized. Countries that contributed at least 10% of overall patients in the FAS were the Russian Federation (11.5%) and Bulgaria (10.4%).

In RESPIRE 1, in the FAS, the mean age of subjects was 64.7 years (range 22-89 years), 68.5% were women and 31.5% were men, and 87.3% were White. In the majority of subjects bronchiectasis was of either post-infective or idiopathic etiology (44.2% and 54.3%, respectively), and the majority of subjects (54.6%) had experienced two exacerbation episodes 12 months prior to screening. The three most frequent pathogens identified in sputum at screening were *P. aeruginosa* (59.6%), followed by *H. influenzae* (23.1%) and *S. aureus* (18%). Among baseline pathogens, ciprofloxacin resistance rates were *P. aeruginosa* 22.1%, *S. aureus* 22.4%, *S. maltophilia* 58.8% and *S. pneumoniae* 31.9%.

In RESPIRE 2, in the FAS, the mean age of subjects was 60.1 years (range: 18 to 91 years), 58% were female and 42% were male, and 77.4% were White. In the majority of subjects, bronchiectasis was of either post-infective or idiopathic etiology (66.2% and 33.2%, respectively), and the majority (77.9%) had experienced two exacerbation episodes 12 months prior to enrollment. The three most common baseline pathogens in sputum were *P. aeruginosa* (60.7%), *S. aureus* (25.4%), and *H. influenzae* (17.3%). Among baseline pathogens, ciprofloxacin resistance rates were *P. aeruginosa* 21%, *S. maltophilia* 43.4% and *B. cepacia* 100% (1 isolate).

The following **Tables 2-5** provide the demographic characteristics, subjects' NCFB history, baseline NCFB standard medication, and baseline pathogens of the study population from RESPIRE 1 and 2. These items were generally balanced across the treatment arms; however, there are differences seen between the two studies.

Table 2: Subject Demographics and Baseline Characteristics (FAS)

	RESPIRE 1			RESPIRE 2		
Category, n (%)	**Cipro 28 (N=141)**	**Cipro 14 (N=137)**	**Pooled Placebo (N=138)**	**Cipro 28 (N=171)**	**Cipro 14 (N=176)**	**Pooled Placebo (N=174)**
Age:						
Mean (median)	64.2 (66.0)	65.2 (67.0)	64.8 (67.0)	59.3 (61.0)	60.4 (62.0)	60.5 (62.0)
Gender:						
Male	40 (28.4)	49 (35.8)	42 (30.4)	79 (46.2)	80 (45.5)	60 (34.5)
Female	101 (71.6)	88 (64.2)	96 (69.6)	92 (53.8)	96 (54.5)	114 (65.5)
Race:						
White	124 (87.9)	115 (83.9)	124 (89.9)	135 (78.9)	133 (75.6)	135 (77.6)
Black/African	1 (0.7)	2 (1.5)	1 (0.7)	2 (1.2)	2 (1.1)	1 (0.6)
Asian	12 (8.5)	12 (8.8)	10 (7.2)	33 (19.3)	41 (23.3)	37 (21.3)
Other/Multiple/NR	4 (2.8)	8 (5.8)	3 (2.2)	1 (0.6)	0	1 (0.6)
Region:						
Europe	77 (54.6)	77 (56.2)	76 (55.1)	119 (69.6)	118 (67.0)	119 (68.4)
US/Canada	14 (9.9)	14 (10.2)	16 (11.6)	5 (2.9)	5 (2.8)	6 (3.4)
Asia	12 (8.5)	11 (8.0)	10 (7.2)	33 (19.3)	39 (22.2)	36 (20.7)
LA/Aus/NZ*	38 (27.0)	35 (25.5)	36 (26.1)	14 (8.2)	14 (8.0)	13 (7.5)
Chronic Macrolide Use						
Yes	22 (15.6)	25 (18.2)	21 (15.2)	14 (8.2)	13 (7.4)	15 (8.6)
No	119 (84.4)	112 (81.8)	117 (84.8)	157 (9.8)	163 (92.6)	159 (91.4)
P. aeruginosa at baseline						
Positive	83 (58.9)	83 (60.6)	86 (62.3)	99 (57.9)	107(60.8)	109 (62.6)
Negative	58 (41.1)	54 (39.4)	52 (37.7)	72 (42.1)	69 (39.2)	65 (37.4)
FEV1 % predicted at baseline						
< 50%	44 (31.2)	41 (29.9)	40 (29.0)	65 (38.0)	78 (44.3)	75 (43.1)
≥ 50%	97 (68.8)	96 (70.1)	98 (71.0)	106 (62.0)	98 (55.7)	99 (56.9)

*LA: Latin America, Aus: Australia, NZ: New Zealand

Table 3: NCFB history for subjects in RESPIRE 1 and 2– integrated analysis (FAS)

	RESPIRE 1			RESPIRE 2		
NCFB, n (%)	**Cipro 28 (N=141)**	**Cipro 14 (N=137)**	**Pooled Placebo (N=138)**	**Cipro 28 (N=171)**	**Cipro 14 (N=176)**	**Pooled Placebo (N=174)**
Etiology						
Idiopathic	70 (49.6)	81 (59.1)	75 (54.3)	43 (25.1)	62 (35.2)	68 (39.1)
Post-Infective	68 (48.2)	59 (39.4)	62 (44.9)	126 (73.7)	113 (64.2)	106 (60.9)
Other	3 (2.1)	2 (1.5)	1 (0.7)	2 (1.2)	1 (0.6)	0
Number of acute exacerbations in the previous 12 months						
1	0	1 (0.7)	0	0	0	0
2	79 (56.0)	72 (52.6)	76 (55.1)	136 (79.5)	134 (76.1)	136 (78.2)
3	34 (24.1)	36 (26.3)	29 (21.0)	22 (12.9)	26 (14.8)	25 (14.4)
4	10 (7.1)	8 (5.8)	21 (15.2)	9 (5.3)	10 (5.7)	7 (4.0)
> 4	18 (12.8)	19 (13.9)	12 (8.6)	4 (2.3)	6 (3.4)	6 (3.4)
Number of exacerbation episodes with sputum culture performed						
0	60 (42.6)	65 (47.4)	60 (43.5)	83 (48.5)	83 (47.2)	71 (40.8)
1	52 (36.9)	43 (31.4)	47 (34.1)	52 (30.4)	60 (34.1)	63 (36.2)
2	18 (12.8)	18 (13.1)	24 (17.4)	32 (18.7)	25 (14.2)	35 (20.1)
3	7 (5.0)	5 (3.6)	5 (3.6)	3 (1.8)	6 (3.4)	4 (2.3)
> 3	4 (2.8)	5 (3.6)	2 (1.4)	4 (2.3)	8 (4.5)	5 (2.9)
Number of exacerbation episodes with systemic antibiotic treatment						
0	9 (6.4)	7 (5.1)	7 (5.1)	3 (1.8)	6 (3.4)	4 (2.3)
1	11 (7.8)	9 (6.6)	10 (7.2)	14 (8.2)	9 (5.1)	12 (6.9)
2	64 (45.4)	62 (45.3)	63 (45.7)	121 (70.8)	131 (74.4)	123 (70.7)
3	30 (21.3)	32 (23.4)	25 (18.1)	20 (11.7)	17 (9.7)	22 (12.6)
> 3	27 (9.2)	24 (17.5)	33 (23.8)	13 (7.6)	13 (7.4)	13 (7.5)
Number of exacerbation episodes with hospitalization						
0	113 (80.1)	106 (77.4)	105 (76.1)	106 (62.0)	96 (54.5)	100 (57.5)
1	20 (14.2)	23 (16.8)	24 (17.4)	38 (22.0)	36 (21.0)	40 (23.0)
2	7 (5.0)	4 (2.9)	5 (3.6)	24 (14.0)	35 (19.9)	29 (16.7)
3	1 (0.7)	0	3 (2.2)	3 (1.8)	7 (4.0)	4 (2.3)
> 3	0	3 (2.2)	1 (0.7)	0	1 (0.6)	1 (0.6)
Scan compatible with BE						
No	4 (2.8)	3 (2.2)	0	0	0	0
Yes	137 (97.2)	134 (97.8)	138 (100)	171 (100)	176 (100)	174 (100)
Type of CT scan						
CT Scan	30 (21.3)	26 (19.0)	27 (19.6)	93 (54.4)	84 (47.7)	85 (48.9)
HRCT	111 (78.7)	111 (81.0)	111 (80.4)	78 (45.6)	92 (52.3)	89 (51.1)

Source: Partially adapted from CSR Table 8-5 (RESPIRE 1) and Table 8-6 (RESPIRE 2)

Table 4: Medications for NCFB reported at screening and/or baseline (FAS)

	RESPIRE 1			RESPIRE 2		
Concomitant medication, n (%)	**Cipro 28 (N=141)**	**Cipro 14 (N=137)**	**Pooled Placebo (N=138)**	**Cipro 28 (N=171)**	**Cipro 14 (N=176)**	**Pooled Placebo (N=174)**
Number of subjects with specification	**114 (100)**	**113 (100)**	**108 (100)**	**129 (100)**	**113 (100)**	**112 (100)**
Mucolytics	26 (22.8)	27 (23.9)	23 (21.3)	48 (37.2)	47 (41.6)	38 (33.9)
Long acting β -agonist bronchodilators	40 (35.1)	34 (30.1)	37 (34.3)	25 (19.4)	16 (14.2)	20 (17.9)
Short acting β -agonist bronchodilators	57 (50.0)	56 (49.6)	56 (51.9)	46 (35.7)	37 (32.7)	35 (31.3)
Long-acting anticholinergic bronchodilators	24 (21.1)	31 (27.4)	23 (21.3)	30 (23.3)	28 (24.8)	24 (21.4)
Short-acting anticholinergic bronchodilators	8 (7.0)	5 (4.4)	10 (9.3)	10 (7.8)	9 (8.0)	10 (8.9)
Low-dose systemic corticosteroids	6 (5.3))	4 (3.5)	1 (0.9)	2 (1.6)	0	3 (2.7)
Inhaled corticosteroids	54 (47.4)	53 (46.9)	46 (42.6)	26 (20.2)	17 (15.0)	15 (13.4)
Long-term oral macrolides	22 (19.3)	24 (21.2)	20 (18.5)	14 (10.9)	11 (9.7)	15 (13.4)
Theophylline	3 (2.6)	5 (4.4)	1 (0.9)	17 (13.2)	14 (12.4)	11 (9.8)
Other long term antibiotics than macrolides	2 (1.8)	0	2 (1.9)	2 (1.6)	1 (0.9)	1 (0.9)

Source: Partially adapted from CSR Table 8-6 (RESPIRE 1) and Table 8-9 (RESPIRE 2)
Note: Subjects could be treated with more than one therapy at screening/baseline

Table 5: Number of subjects with baseline pathogens in sputum culture – (FAS)

	RESPIRE 1			RESPIRE 2		
Organisms Identified, n (%)	**Cipro 28 (N=141)**	**Cipro 14 (N=137)**	**Pooled Placebo (N=138)**	**Cipro 28 (N=171)**	**Cipro 14 (N=176)**	**Pooled Placebo (N=174)**
Number of subjects (denominator)	**141 (100)**	**137 (100)**	**138 (100)**	**129 (100)**	**113 (100)**	**112 (100)**
H. influenzae	34 (24.1)	34 (24.8)	42 (30.4)	38 (22.4)	25 (14.2)	27 (15.6)
M. catarrhalis	9 (6.4)	7 (5.1)	9 (6.5)	8 (4.7)	11 (6.3)	11 (6.4)
P. aeruginosa	83 (58.9)	83 (60.6)	86 (62.3)	99 (58.2)	107 (60.8)	109 (63.0)
S. maltophilia	2 (1.4)	9 (6.6)	0	7 (4.1)	8 (4.5)	5 (2.9)
B. cepacia	0	0	0	1 (0.6)	0	3 (1.7)
S. aureus	34 (24.1)	26 (19.0)	29 (21.0)	42 (24.7)	43 (24.4)	47 (27.2)
S. pneumoniae	11 (7.8)	11 (8.0)	12 (8.7)	14 (8.2)	11 (6.3)	10 (5.8)
Other	3 (2.1)	1 (0.7)	5 (3.6)	0	0	0

Source: Partially adapted from CSR Table 8-9 (RESPIRE 1) and Table 8-8 (RESPIRE 2)
Note: Subjects could have more than one pathogen

8 Evaluation of Efficacy

8.1 Subject Disposition

The overall study completion rate in RESPIRE 1 and RESPIRE 2 was 80.3% and 84.8% respectively. In both trials, completion rates for Cipro 28 and Cipro 14 were slightly higher than in the Pooled Placebo arm at 83.7% and 81.0% vs. 76.1% in RESPIRE 1 and 86.5% and 85.8% vs. 82.2% in RESPIRE 2. The most common primary reason for discontinuing the trial was 'Withdrawal by Subject' which was observed in 66/82 (80%) of discontinuations in RESPIRE 1 and 50/79 (63%) of discontinuations in RESPIRE 2. Since patients could miss the last off-cycle of therapy and still be assessed as a study completer according to CRF completion guideline, completion rates of the treatment period (including the late follow-up) rates are also shown. These rates were also slightly higher in the Cipro arms at 78.2% and 70.8% vs. 65.2% in RESPIRE 1 and 80.1% and 80.7% vs. 77.6% in RESPIRE 2 (see **Table 6**).

Table 6: Subject Disposition in RESPIRE 1 and 2

Category, n (%)	Cipro 28	Cipro 14	Pooled Placebo	Overall
RESPIRE 1				
Randomized (FAS)	141 (100)	137 (100)	138 (100)	416 (100)
Treated (Safety)	141 (100)	136 (99.3)	137 (99.3)	414 (99.5)
Per-protocol	124 (87.9)	117 (85.4)	116 (84.1)	357 (85.8)
Completing treatment period	110 (78.2)	97 (70.8)	90 (65.2)	297 (71.4)
Completing trial	118 (83.7)	111 (81.0)	105 (76.1)	334 (80.3)
Not completing trial	23 (16.3)	26 (19.0)	33 (23.9)	82 (19.7)
Withdrawal by Subject	16	24	26	66
Lost to follow-up	3	0	1	5
Death	2	0	5	7
Other	1	2	1	3
Not reported	1	0	0	1
RESPIRE 2				
Randomized (FAS)	171 (100)	176 (100)	176 (100)	521 (100)
Treated (Safety)	171 (100)	174 (98.9)	176 (100)	519 (99.6)
Per-protocol	146 (85.4)	162 (92.0)	156 (88.6)	464 (89.1)
Completing treatment period	137 (80.1)	142 (80.7)	135 (77.6)	414 (79.5)
Completing trial	148 (86.5)	151 (85.8)	143 (82.2)	442 (84.8)
Not completing trial	23 (13.5)	25 (14.2)	31 (17.8)	79 (15.2)
Withdrawal by Subject	17	17	16	50
Lost to follow-up	0	1	4	5
Death	1	2	3	6
Adverse Event	1	2	3	6
Other	1	1	2	4
Not Reported	3	2	3	8

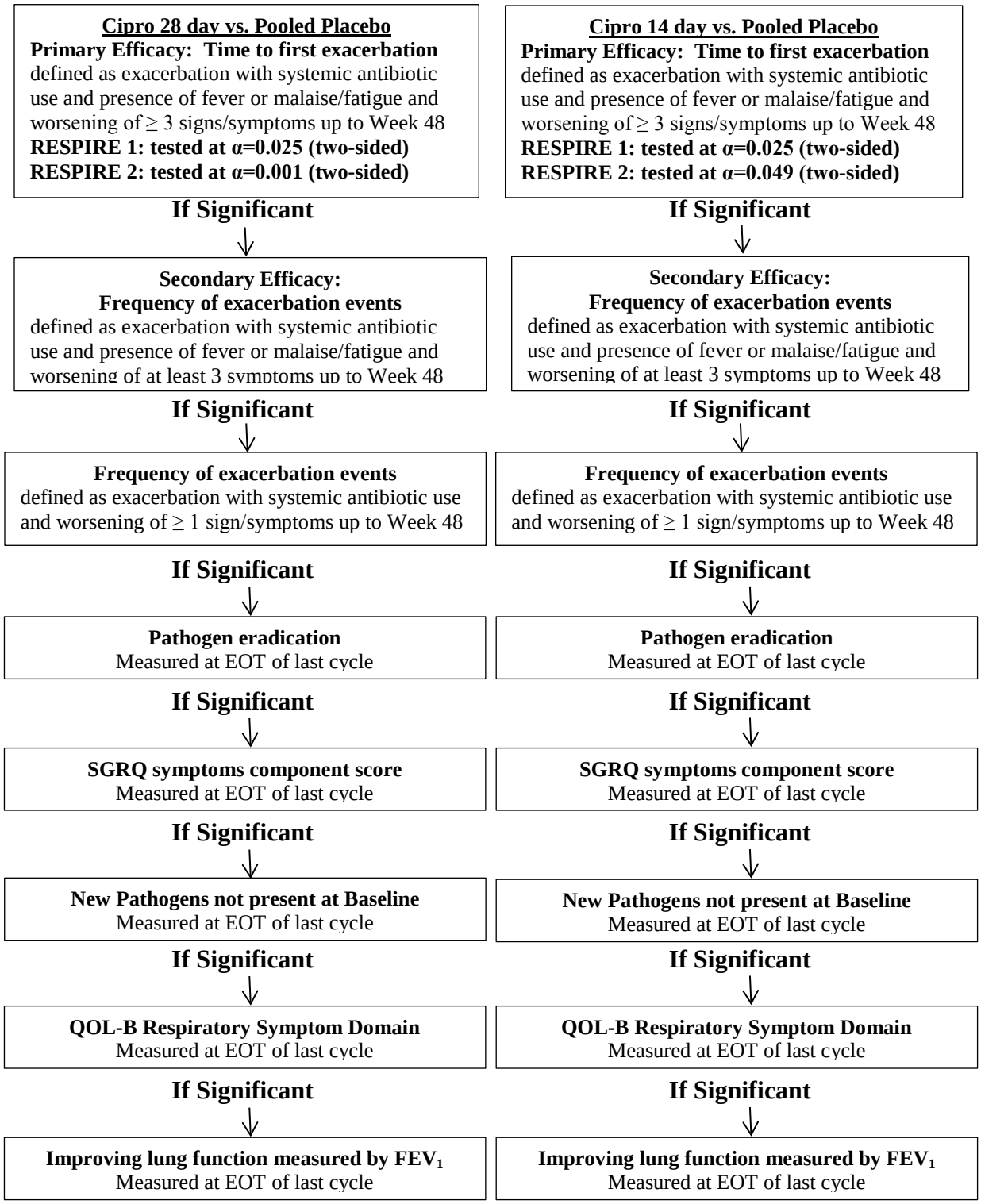
Source: Partially Adapted from Tables 14.1 / 7 - 14.1 / 9 in CSRs
Notes: Treatment period includes last off-cycle. If treatment was completed, and only the last off-cycle was missing, the patient could be assessed as completer according to CRF completion guidelines. Patients with deaths can discontinue for reasons other than 'death.'

8.2 Statistical Methodologies

The analysis population used in the primary and secondary analyses was the FAS. For the primary analysis, a Cox Proportional Hazards model was used to test for differences in time to first exacerbation (TFE) between the Cipro groups and Pooled Placebo controlling for the macrolide status, presence of *P. aeruginosa* and geographical region. For the key secondary analysis of frequency of exacerbations (FOE), a Poisson model (including the same covariates) with adjustment for overdispersion was used. In RESPIRE 1, a pre-specified extrapolation was used to estimate the number of exacerbations in patients not completing the study. In RESPIRE 2, a different approach was pre-specified to account for patients not completing the study. This approach used log (time in study) as an offset variable in the Poisson regression.

To control the overall type I error rate associated with testing primary and secondary endpoints in two treatment regimens (Cipro 14 and Cipro 28) against placebo, separate hierarchical testing sequences of primary, key secondary and other secondary endpoints were pre-specified for each regimen with statistical testing at $\alpha=0.025$ for each Cipro arm in RESPIRE 1 and $\alpha=0.001$ for Cipro 28 and $\alpha=0.049$ for Cipro 14 in RESPIRE 2. If the primary endpoint was significant for a Cipro regimen then the next endpoint in the sequence (i.e., key secondary endpoint) was tested within that Cipro regimen. Statistical testing would only continue to the next endpoint in the hierarchy if the preceding endpoint in the hierarchy showed significance. Endpoints which could not be statistically tested were considered to be exploratory. The hierarchical testing strategy is shown in **Figure 2**.

Figure 2: Statistical Testing in the RESPIRE 1 and RESPIRE 2 Trial



Source: Reviewer Figure

8.3 Efficacy Findings

8.3.1 Pre-test for Pooling Placebo Arms

Prior to conducting the primary analyses of RESPIRE 1 and RESPIRE 2, a pre-test (as pre-specified in the study protocols) was performed to determine whether the pooling of placebo arms is justified (i.e., Placebo 28 vs. Placebo 14 for each trial). If the placebo arms were not significantly different at α=0.05 (two-sided), comparisons for each Cipro arm would be against Pooled Placebo in primary and secondary analyses. Otherwise comparisons would be against matched placebo (i.e., Cipro 14 vs. Placebo 14 and Cipro 28 vs. Placebo 28).

In **Table 7** & **Figure 3**, differences in the placebo arms for individual (and combined) trials favored Placebo 28 over Placebo 14 and were more pronounced in RESPIRE 1. Since these differences were not statistically significantly different in either trial, comparisons of each Cipro therapy in primary and secondary analyses were against Pooled Placebo.

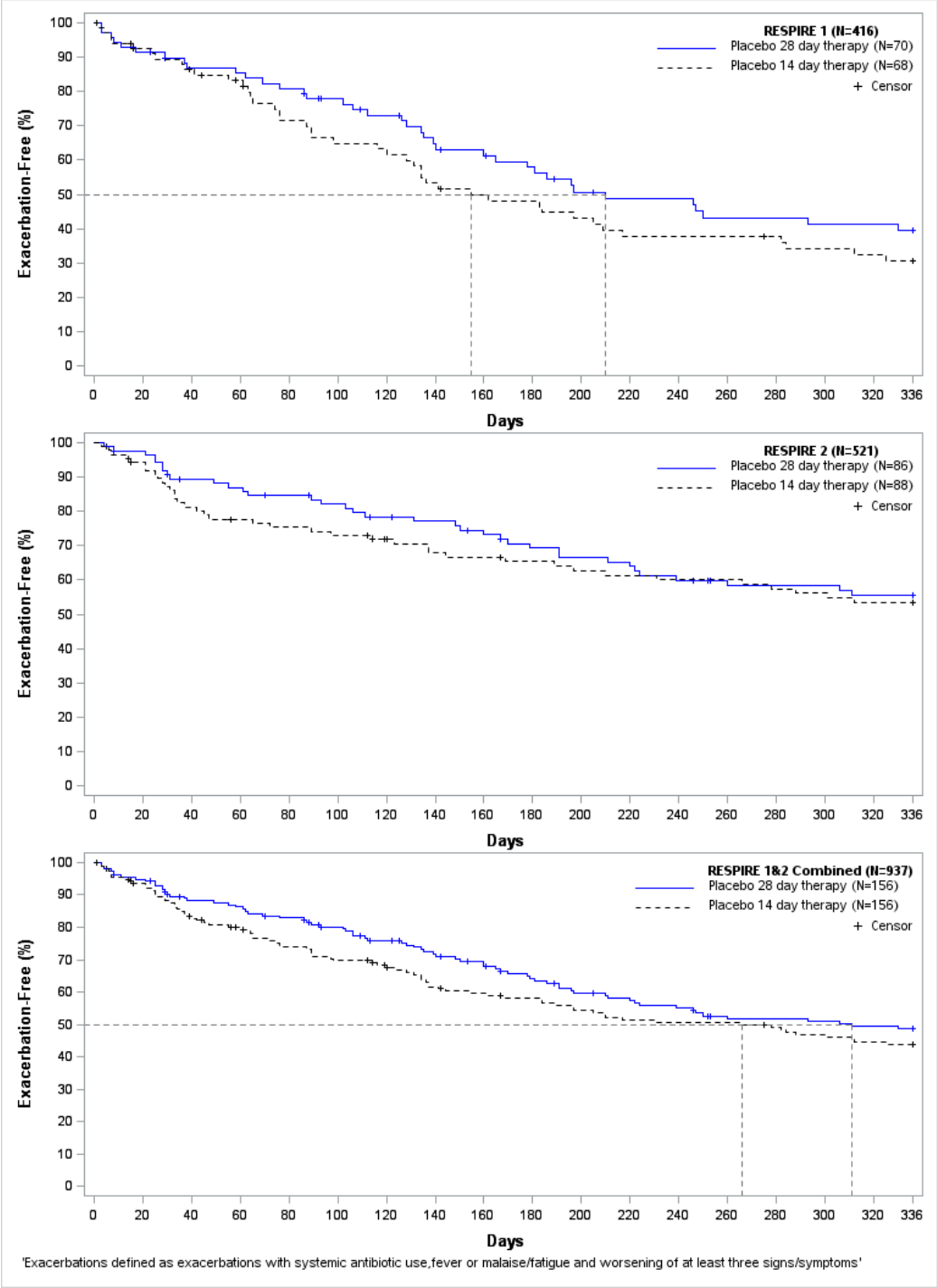
Table 7: Pre-Test – Time to First Exacerbation, Placebo 28 vs. Placebo 14 (FAS)

Trial	Percent with PE	Difference in PE Rate	Median Time to PE (days)	Days Prolonged	Hazard Ratio (95% CI)	p-value
RESPIRE-1	37/70 (52.9%) vs. 42/68 (61.8%)	-8.9 %	210 vs. 155 days	55 days	HR=0.74 (0.47,1.15)	p=0.183
RESPIRE-2	35/86 (40.7%) vs. 38/88 (43.2%)	-2.5 %	> 336 vs. > 336 days	NE	HR=0.87 (0.55, 1.38)	p=0.557
Combined Trials	72/156 (46.2 %) vs. 80/156 (51.3%)	-5.1 %	311 vs. 266 days	45 days	HR=0.81 (0.59, 1.11)	p=0.187

Source: Reviewer Table

Notes: Comparisons: Placebo 28 vs. Placebo 14, Differences: Placebo 28 – Placebo 14, Hazard ratios < 1 favor Placebo 28, NE: Not Estimable

Figure 3: Pre-Test –Time to First Exacerbation, Placebo 28 vs. Placebo 14 (FAS)



8.3.2 Primary Analysis of Time to First Exacerbation

Cipro 14

In RESPIRE 1, Cipro 14 showed a prolonged median TFE of more than 150 days vs. Pooled Placebo **(Table 8** and **Figure 4)**. The hazard ratio was highly significant at 0.53 (97.5% CI: 0.36, 0.80), p=0.0005. The percentage of patients with a PE (pulmonary exacerbation) during the trial was lower for Cipro 14 at 38.7% vs. 57.2%, a difference of -18.6%.

In RESPIRE 2, a similar finding was not observed with Cipro 14 for TFE; HR=0.87 (97.5% CI: 0.39, 1.27), p=0.397. The median TFE could not be compared since more than 50% of patients in both arms did not experience an exacerbation during the trial. The percentage of patients with a PE during the study was also slightly lower for Cipro 14 vs. Pooled Placebo at 38.6% vs. 42.0%, a difference of -3.3%.

In the combined trials, exploratory findings showed a prolonged median TFE against Pooled Placebo of >336 days vs. 284 days, a difference of >52 days. The exact difference could not be estimated due to censoring. The hazard ratio was 0.69 (97.5% CI: 0.52, 0.90), p=0.002. The percentage of patients experiencing a PE during the trial was also lower for Cipro 14 vs. Pooled Placebo at 38.7% vs. 48.7%, a difference of -9.9%.

Cipro 28

In RESPIRE 1, Cipro 28 showed a prolonged TFE of 150 days vs. Pooled Placebo; however, this finding was not significant, HR= 0.73 (97.5% CI: 0.50, 1.07), p=0.065 (α=0.025 (two-sided)) **(Table 8** and **Figure 4)**. The percentage of patients experiencing a PE during the trial was lower in Cipro 28 vs. Pooled Placebo at 47.5% vs. 57.2%, a difference of -9.7%.

In RESPIRE 2, similar estimates were observed, however, Cipro 28 was tested against Pooled Placebo at a stricter significance level of α=0.001(two-sided). Findings were not significant, HR=0.71 (99.9% CI: 0.39, 1.27), p=0.051. The median TFE was not estimable in either of the study arms due to censoring. The percentage of patients experiencing a PE during the trial was lower in Cipro 28 than in Pooled Placebo at 32.7% vs. 42.0%, a difference of -9.2%.

In the combined trials, exploratory analyses comparing Cipro 28 vs. Pooled Placebo showed a prolonged median TFE of > 336 days vs. 284 days, a difference of >52 days. The exact difference could not be estimated due to censoring. The hazard ratio was 0.72 (97.5% CI: 0.55, 0.95), p=0.008. The percentage of patients experiencing a PE during the trial was lower for Cipro 28 vs. Pooled Placebo at 39.4% vs. 48.7%, a difference of -9.3%.

Table 8: Primary Endpoint-Time to First Exacerbation (FAS)

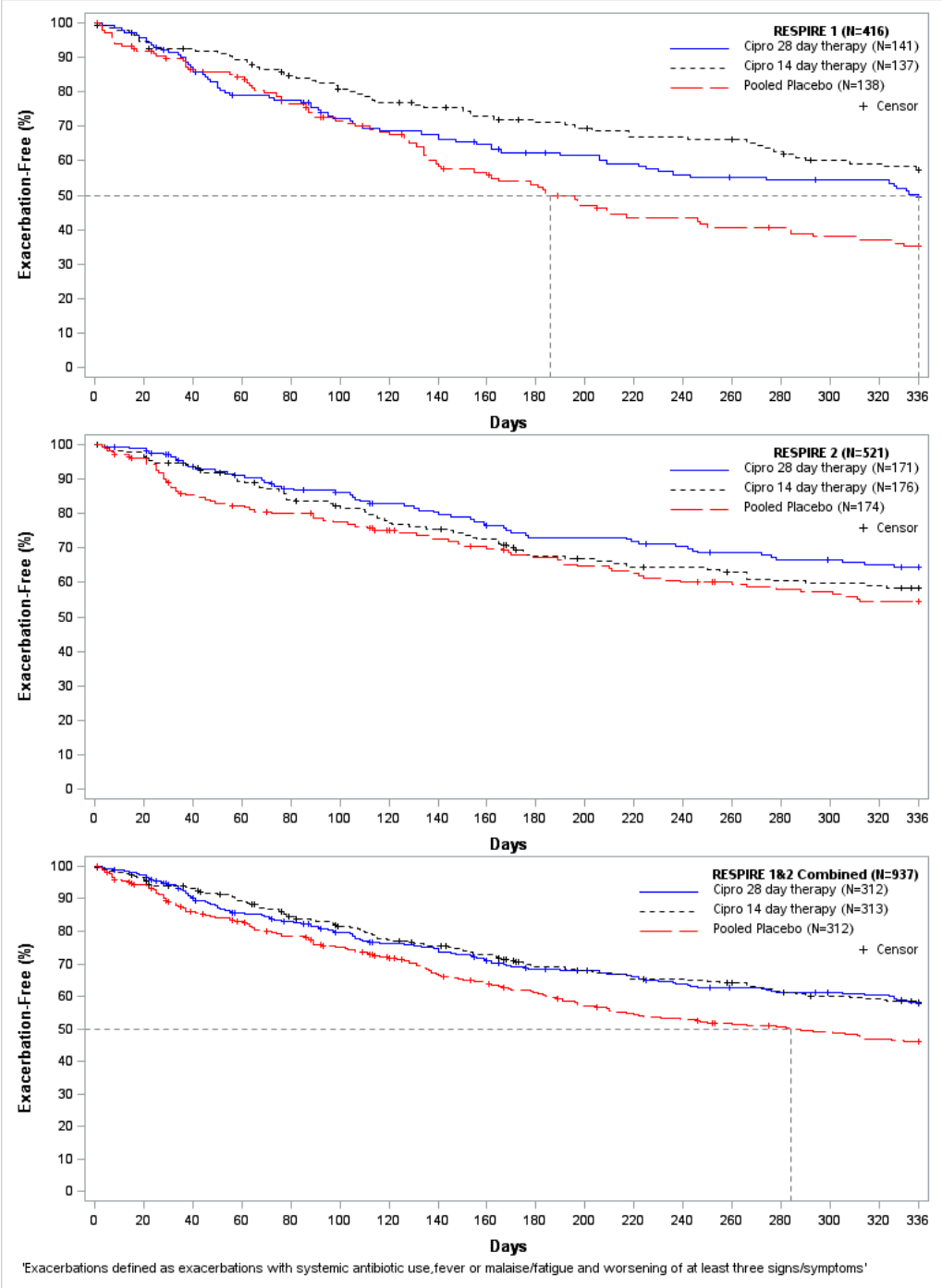
	Percent with PE Cipro vs. Pooled Placebo	**Difference in PE Rate (**Cipro – Placebo)	**Median Time to First PE** Cipro vs. Pooled Placebo	**Days Prolonged with Treatment**	**Hazard Ratio (CI)[2]** (Cipro / Placebo)	**p-value [1]**
CIPRO 28						
RESPIRE 1	67/141 (47.5%) vs. 79/138 (57.2%)	-9.7%	336 vs. 186 days	150 days	0.73 (0.50, 1.07)	p=0.065
RESPIRE 2	56/171 (32.7%) vs. 73/174 (42.0%,	-9.2%	> 336 vs. > 336 days	NE	0.71 (0.39, 1.27)	p=0.051
Combined trials	123/312 (39.4%) vs. 152/312 (48.7%)	-9.3%	> 336 vs. 284 days	> 52 days	0.72 (0.55,0.95)	p=0.008
CIPRO 14						
RESPIRE 1	53/137 (38.7%) vs. 79/138 (57.2%)	-18.6%	> 336 days vs. 186 days	> 150 days	0.53 (0.36, 0.80)	p=0.0005
RESPIRE 2	68/176 (38.6%) vs. 73/174 (42.0%)	-3.3%	> 336 vs. > 336 days	NE	0.87 (0.62, 1.21)	p=0.397
Combined trials	121/313 (38.7%) vs. 152/312 (48.7%)	-9.9%	> 336 vs. 284 days	> 52 days	0.69 (0.52, 0.90)	p=0.002

Source: Reviewer Table

1 P-values are for primary analyses in RESPIRE 1 and RESPIRE 2 and an exploratory analysis in RESPIRE 1&2 Combined.

2 Significance levels used in confidence intervals (CIs) vary according to the significance levels used for statistical testing. For RESPIRE 1, 97.5% CIs are used, for RESPIRE 2, a 99.9% CI (Cipro 28 day) or a 95.1% CI (Cipro 14 day) is used and for RESPIRE 1&2 Combined, 95% CIs are used.

Figure 4: Kaplan-Meier Plot: Primary Endpoint- Time to First Exacerbation (FAS)



Source: Reviewer Figure

8.3.3 Secondary Analysis of Frequency of Exacerbations

Under the pre-specified hierarchical strategy, confirmatory testing of the first secondary endpoint (frequency of exacerbations) against Pooled Placebo, and all subsequent endpoints, could not be performed for Cipro 28 (both trials) and for Cipro 14 (RESPIRE 2) because the respective findings for the primary endpoint of TFE were not significant. In RESPIRE 1, confirmatory testing of Cipro 14 could only be performed up to the first secondary endpoint (FOE) which failed to show significance. With the exception of a statistically significant finding observed for one comparison (i.e., Cipro 14 day vs. Pooled Placebo for the primary endpoint in RESPIRE 1), all other comparisons were considered to be exploratory or not statistically significant. As indicated in **Figure 2** there was the potential for up to 32 comparisons to show statistical significance (8 endpoints in each of two Cipro arms across two trials).

Table 9 and **Figure 5** show a descriptive comparison of the number and percent of patients in the Cipro and pooled placebo arms by number of exacerbations experienced.

Table 10 shows findings from the pre-specified hierarchical testing of frequency of exacerbation endpoints (second and third endpoints tested in the hierarchy).

Table 11 shows findings for frequency of exacerbation events where the number of events a patient can have is truncated to 2, 3 or 4 to limit the influence of patients with larger numbers of exacerbations. In these analyses, Cipro 28 tended to fare better than Cipro 14 with differences most pronounced for truncation at 2 events (i.e., categories of '0', '1' '≥2'). FOE with truncation at two events is more sensitive to changes from '≥2' to '1' or from '1' to '0' which may be more clinically meaningful than other possible changes for FOE without truncation (e.g. '5' to '4').

Cipro 28

In RESPIRE 1, comparisons for frequency of exacerbations (Cipro 28 vs. Pooled Placebo) favored Cipro 28 but were not significant: mean of 0.82 vs. 0.91 exacerbations, IRR = 0.86 (97.5% CI: 0.63, 1.18), p=0.294. In RESPIRE 2, these comparisons favored Cipro 28 over Pooled Placebo and were nominally significant: mean of 0.40 vs. 0.70, IRR=0.56 (99.9% CI: 0.33, 0.95), p=0.0003. In the combined trials, comparisons favored Cipro 28: mean of 0.59 vs. 0.79, IRR=0.72 (97.5% CI: 0.56, 0.91), p=0.002.

In RESPIRE 1, comparisons for frequency of exacerbations using an alternative definition for exacerbation showed similar results.

Cipro 14

In RESPIRE 1, comparisons of frequency of exacerbations for Cipro 14 vs. Pooled Placebo showed Cipro 14 as having fewer exacerbations but did not reach significance: mean of 0.63 vs. 0.91 exacerbations, IRR=0.73 (97.5% CI: 0.52, 1.03), p=0.038 > α=0.025. In RESPIRE 2, comparisons also favored Cipro 14 but did not reach significance: mean of 0.58 vs. 0.70, IRR=0.81 (95.1% CI: 0.61, 1.08), p=0.147. In the

combined trials, findings favored Cipro 14: mean of 0.59 vs. 0.79, IRR=0.75 (97.5% CI: 0.59, 0.95), p=0.007.

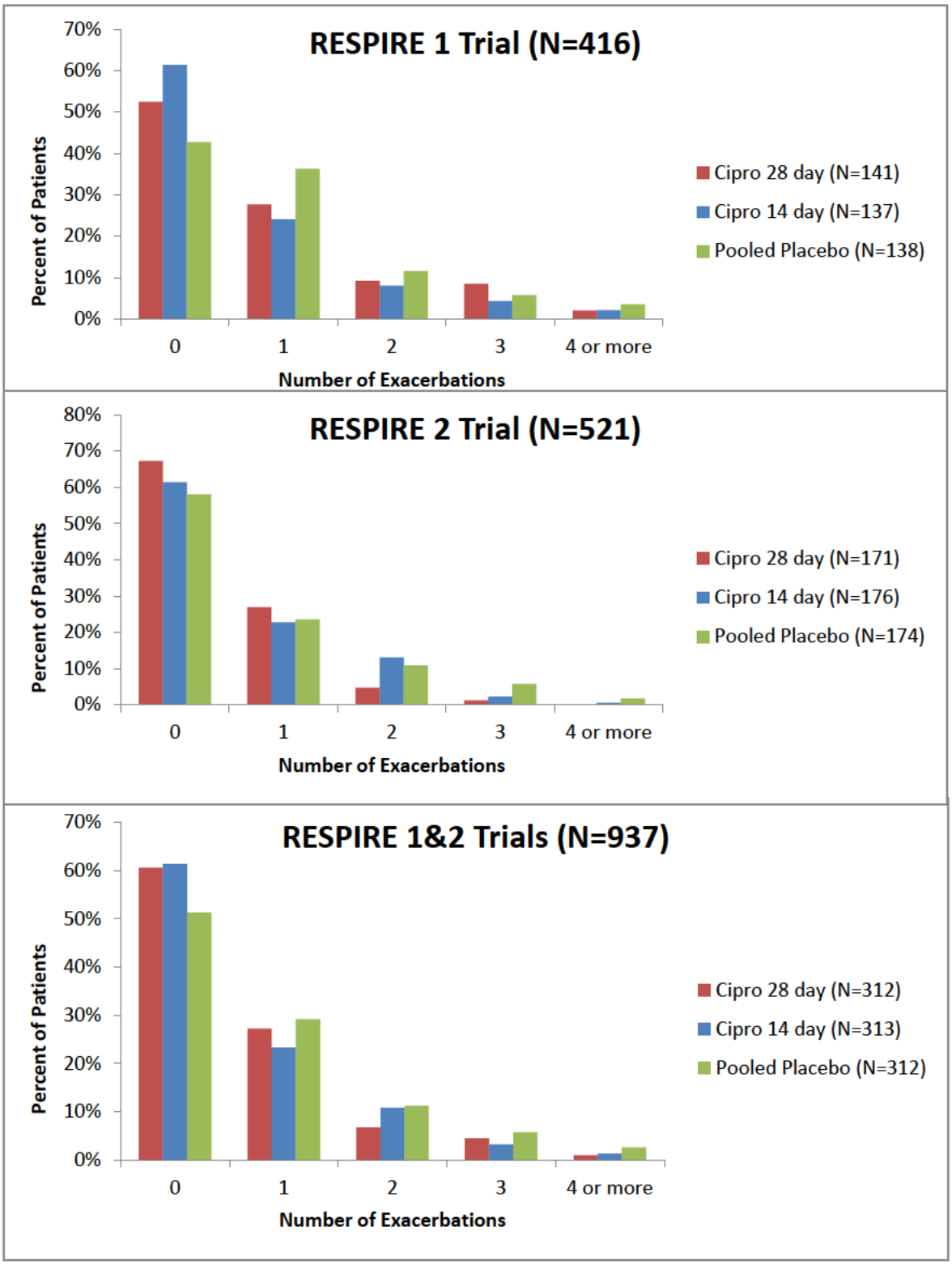
In RESPIRE 1, comparisons for frequency of exacerbations using an alternative definition for exacerbation showed similar results.

Table 9: Number (%) of Patients by Frequency of Exacerbations

Frequency of Exacerbations	CIPRO 28 (n, %)	CIPRO 14 (n, %)	Pooled Placebo (n, %)
RESPIRE 1	**N=141**	**N=137**	**N=138**
0	74 (52.5%)	84 (61.3)	59 (42.8)
1	39 (27.7)	33 (21.4)	50 (36.2)
2	13 (9.2)	11 (8.0)	16 (11.6)
3	12 (8.5)	6 (4.4)	8 (5.8)
4	1 (0.7)	2 (1.5)	5 (3.6)
5	1 (0.7)	1 (0.7)	0
6	1 (0.7)	0	0
RESPIRE 2	**N=171**	**N=176**	**N=174**
0	115 (67.3%)	108 (61.4)	101 (58.0)
1	46 (26.9)	40 (22.7)	41 (23.6)
2	8 (4.7)	23 (13.1)	19 (10.9)
3	2 (1.2)	4 (2.3)	10 (5.7)
4	0	1 (0.6)	2 (1.1)
5	0	0	1 (0.6)
6	0	0	0
Combined Studies	**N=312**	**N=313**	**N=312**
0	189 (60.6%)	192 (61.3)	160 (51.3)
1	85 (27.2)	73 (23.3)	91 (29.2)
2	21 (6.7)	34 (10.9)	35 (11.2)
3	14 (4.5)	10 (3.2)	18 (5.8)
4	1 (0.3)	3 (1.0)	7 (2.2)
5	1 (0.3)	1 (0.3)	1 (0.3)
6	1 (0.3)	0	0

Source: Reviewer Table

Figure 5: Patients (%) by Frequency of Exacerbations



Source: Reviewer Figure

Table 10: Analysis of Frequency of Exacerbations

Regimen by Trial	**Mean PEs per subject (unadjusted)** Cipro vs. Placebo	**Incidence Rate Ratio (CI)**[1,2,3] Cipro/Placebo	**p-value**
CIPRO 28			
FOE			
RESPIRE 1	0.82 vs. 0.91	0.86 (0.63, 1.18)	p=0.294
RESPIRE 2	0.40 vs. 0.70	0.56 (0.33, 0.95)	p=0.0003
Combined trials	0.60 vs. 0.79	0.72 (0.56, 0.91)	p=0.002
FOE (with alternative definition)[4]			
RESPIRE 1	1.14 vs. 1.22	0.87 (0.66, 1.16)	p=0.276
RESPIRE 2	0.54 vs. 0.85	0.63 (0.39, 1.01)	p=0.001
Combined trials	0.81 vs. 1.02	0.77 (0.62, 0.96)	p=0.006
CIPRO 14			
FOE			
RESPIRE 1	0.63 vs. 0.91	0.73 (0.52, 1.03)	p=0.038
RESPIRE 2	0.58 vs. 0.70	0.81 (0.61, 1.08)	p=0.147
Combined trials	0.59 vs. 0.79	0.75 (0.59, 0.95)	p=0.007
FOE (with alternative definition)[4]			
RESPIRE 1	0.89 vs. 1.22	0.74 (0.55, 1.00)	p=0.023
RESPIRE 2	0.72 vs. 0.85	0.84 (0.64, 1.09)	p=0.181
Combined trials	0.81 vs. 1.02	0.77 (0.62,0.96)	p=0.008

Source: Reviewer Table

[1] 99.9% CIs (Cipro 28) and 95.1% CIs (Cipro 14) used in RESPIRE 2, otherwise 97.5% CIs used

[2] Poisson regression uses extrapolation of the number of events for subjects observed for less than 48 weeks in RESPIRE 1, otherwise it uses time in study as an offset.

[3]Adjustment is made for over-/underdispersion, geographic region, pre-therapy positive culture for *P. aeruginosa*, chronic macrolide use and study (for Combined trials).

[4] Exacerbation defined as exacerbation with systemic antibiotic use and worsening of ≥ 1 signs/symptoms up to Week 48

Table 11: Frequency of Exacerbation with Truncation at 2, 3 and 4 Events

Incidence Rate Ratio (CI) P-value	CIPRO 28 vs. Pooled Placebo			CIPRO 14 vs. Pooled Placebo		
	RESPIRE 1	RESPIRE 2	Combined Trials	RESPIRE 1	RESPIRE 2	Combined Trials
2 events	0.82 (0.60, 1.12) p=0.158	0.63 (0.38, 1.07) p=0.004	0.73 (0.58, 0.92) p=0.003	0.68 (0.48, 0.95) p=0.010	0.89 (0.67, 1.18) p=0.424	0.79 (0.62, 0.99) p=0.019
3 events	0.85 (0.62, 1.17) p=0.256	0.58 (0.34, 0.99) p=0.0007	0.72 (0.57, 0.91) p=0.002	0.68 (0.48, 0.97) p=0.014	0.83 (0.63, 1.11) p=0.205	0.76 (0.60, 0.96), p=0.008
4 events	0.84 (0.60, 1.16) p=0.220	0.57 (0.33, 0.96), p=0.0004	0.71 (0.56, 0.90) p=0.001	0.68 (0.48, 0.97) p=0.015	0.82 (0.62, 1.09) p=0.165	0.75 (0.59, 0.95) p=0.006

Source: Partially Adapted from Sponsor Tables 1.2 / 1 – 1.2/ 18 (Response to Information Request of 8/23/2017)
[1] 99.9% CIs (Cipro 28) and 95.1% CIs (Cipro 14) used in RESPIRE 2, otherwise 97.5% CIs used

8.3.4 Other Secondary Analyses

Other secondary analyses considered changes from baseline to EOT of the last cycle for other secondary endpoints (fourth to eighth endpoints hierarchically tested): #4: 'pathogen eradication', #5 'Quality of Life- SGRQ symptoms component', #6 'occurrence of new pathogens not present at baseline,' #7 'Quality of Life- QOL-B Respiratory symptom domain' and #8 'Changes in FEV_1'. However, primary consideration was given to clinical endpoints that reflect a direct patient benefit. Analyses of endpoints related to quality of life and FEV_1 did not show a consistent treatment benefit across trials.

Table 12: Other Secondary Endpoints Hierarchically Tested by the Applicant (FAS)

Changes from Baseline to EOT vs. Pooled Placebo	RESPIRE 1			RESPIRE 2		
	CIPRO 28	CIPRO 14	Pooled Placebo	CIPRO 28	CIPRO 14	Pooled Placebo
Pathogen eradication						
Yes, n (%)	34 (24.1)	39 (28.5)	23 (16.7)	54 (31.6)	63 (35.8)	55 (31.6)
Odds ratio:	1.16 p=0.672	2.35 p=0.018	- -	1.16 p=0.602	1.34 p=0.316	- -
SGRQ Symptoms Component Score						
Change from BL:	-8.2	-7.2	-0.8	-8.9	-9.0	-7.3
LS Mean Difference:	-5.21 p=0.064	-7.59 p=0.009	- -	-1.44 p=0.530	-1.40 p=0.545	- -
Occurrence of New Pathogens not present at Baseline						
Yes, n (%)	5 (3.5)	7 (5.1)	11 (8.0)	7 (4.1)	7 (4.0)	18 (10.3)
Odds ratio:	0.36 p=0.058	0.56 p=0.257	- -	0.41 p=0.053	0.29 p=0.007	- -
QOL-B Respiratory Symptom Domain Score						
Change from BL:	7.7	6.7	6.4	11.6	10.9	9.0
LS Mean Difference:	1.18 p=0.619	2.47 p=0.322	- -	2.75 p=0.234	2.22 p=0.325	- -
FEV_1 (L)						
Change from BL:	-0.01	-0.03	0.02	0.04	-0.04	0.00
LS Mean Difference:	-0.03 p=0.370[1]	-0.05 p=0.194[1]		0.04 p=0.310	-0.04 p=0.266[1]	- -

Source: Reviewer Table

[1] p-value for testing the superiority of Placebo over Cipro

Notes: Odds Ratio: Cipro/Placebo, Differences: Cipro – Placebo, Odds ratios < 1 favor Cipro, positive differences (> 0) in QOL-B and FEV1 favor Cipro. Negative differences (< 0) in SGRQ favor Cipro

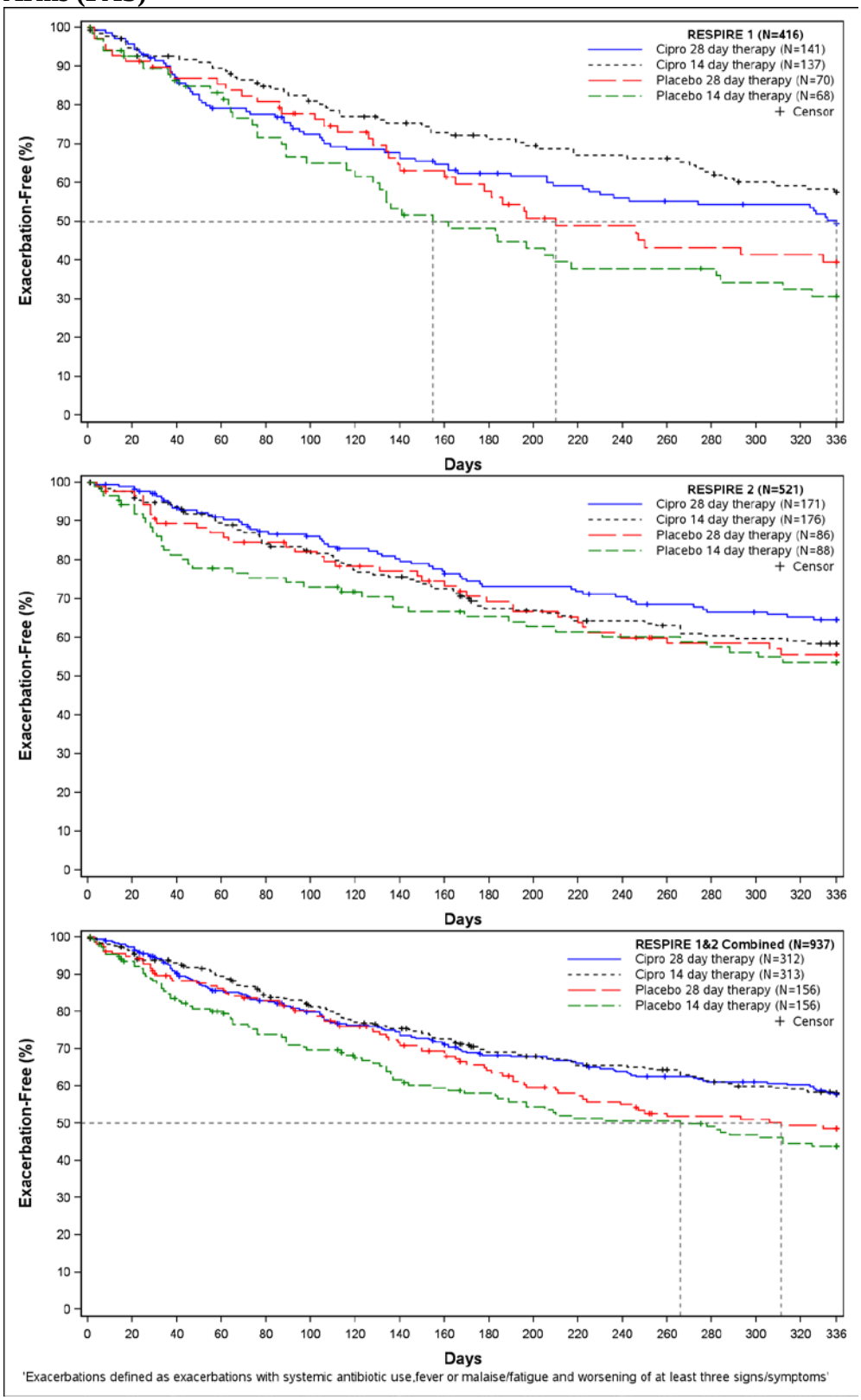
In RESPIRE 1, higher eradication rates were observed for *H. influenzae* and *P. aeruginosa*, but not *S. aureus* compared to placebo, whereas in RESPIRE 2, higher eradication rates were observed for *H. influenzae* and *S. aureus* but not *P. aeruginosa.*

8.3.5 Additional Sensitivity Analyses

Time to First Exacerbation without Pooling Placebo Arms

Figure 6 presents a Kaplan-Meier plot of time to first exacerbation without the pooling of Placebo 14 and Placebo 28 arms. This plot better shows the relative size of effects due to the drug (Cipro 28 vs. Placebo 28, Cipro 14 vs. Placebo 14) and regimen (Placebo 28 vs. 14). At the end of the study (Day 336) in the combined trials, the drug effect from Cipro 14 vs. Placebo 14 is slightly larger than the drug effect of Cipro 28 vs. Placebo 28. Both of these drug effects appear to be at least twice as large as the effect of the placebo regimen (Placebo 28 – Placebo 14). As noted earlier, since this regimen effect did not reach significance at the α=0.05 (two-sided) level for TFE, primary and secondary analyses compared Cipro 14 and Cipro 28 to pooled placebo rather than the matched placebo arms. Note that due to the inherent differences between the 14 day and 28 day regimens which are not blinded (Table 1), differential sets of biases and effects are expected from each regimen. It is preferable to consider the combined effect from both the drug and regimen which can be accomplished by comparing each Cipro therapy to a common standard independent of the regimen used (i.e. Pooled Placebo). In contrast, comparing each Cipro therapy against its matched placebo adjusts for the regimen used and evaluates the effect of only the drug.

Figure 6: Kaplan-Meier Plot: Time to First Exacerbation without Pooling Placebo Arms (FAS)



Time to Premature Discontinuation

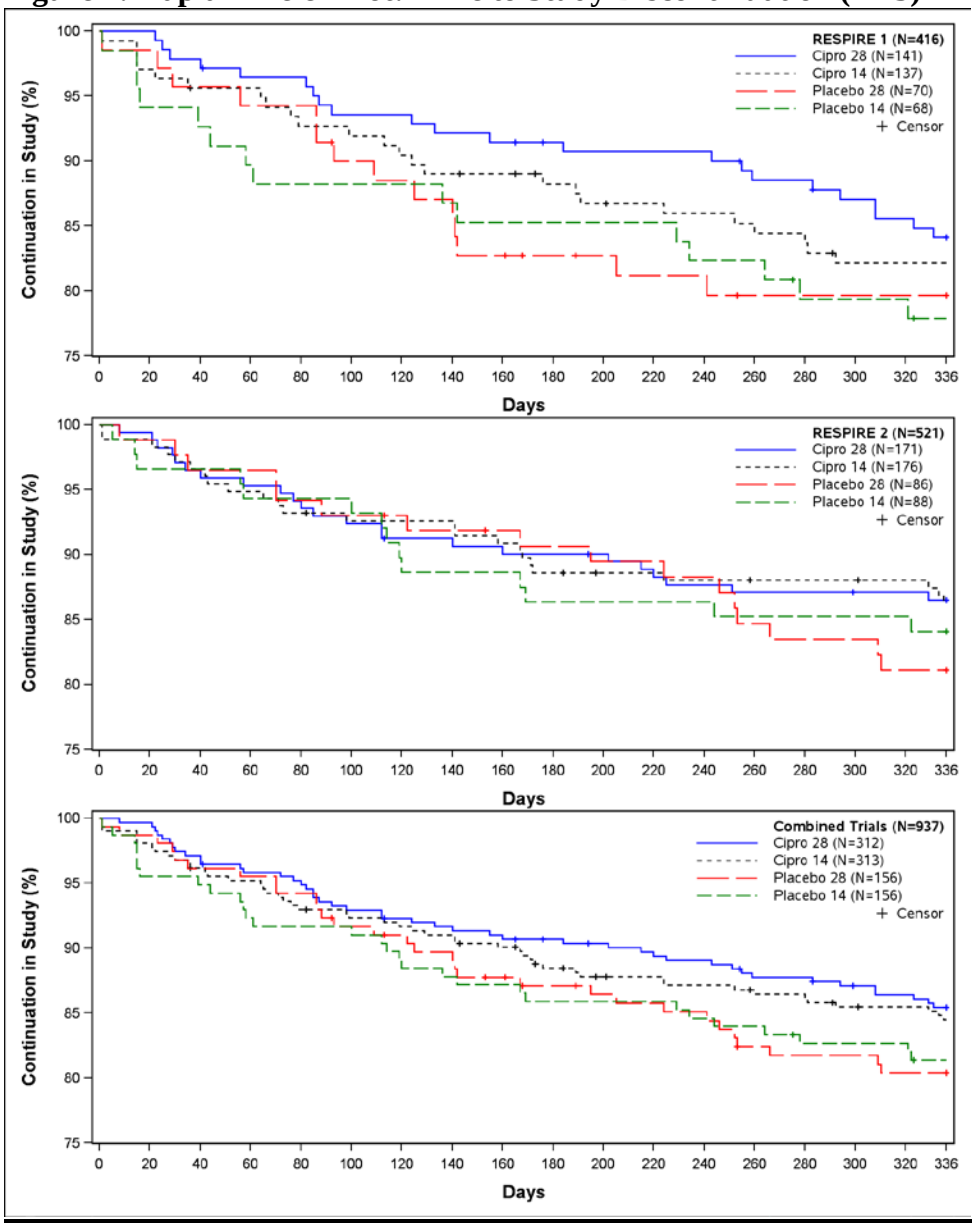
Treatment differences in patient discontinuations from the study can potentially impact TFE and FOE analysis findings since the risk of an exacerbation in such dropouts may be different (higher) than the risk of patients continuing in the trial. In FOE analyses, this can also affect the average follow-up time between treatments and make a direct comparison based on the observed frequency of exacerbations unclear. **Table 13** shows a treatment comparison for time to discontinuation in the trials. In the combined trials, Pooled Placebo showed a consistently shorter time to discontinuation compared with either Cipro arm though not statistically significant. In **Figure 7**, a Kaplan-Meier plot for the combined trials shows a clear separation among the Cipro 28 and Cipro 14 vs. the Placebo 28 and Placebo 14 arms in time to discontinuation.

Table 13: Number (%) of Patients Remaining in Study (FAS)

Cipro vs. Pooled Placebo	**Percent Prematurely Discontinuing Study**	**Difference in discontinuation rate** (Cipro – Placebo)	**Hazard Ratio (CI)[1]** (Cipro / Placebo)	**p-value [1]**
CIPRO 28				
RESPIRE 1	23/141 (16.3%) vs. 33/138 (23.9%)	-7.6%	0.69 (0.41, 1.19)	p=0.184
RESPIRE 2	23/171 (13.5%) vs. 31/174 (17.8%)	-4.4%	0.77 (0.45, 1.33)	p=0.348
Combined trials	46/312 (14.7%) vs. 64/312 (20.5%)	-5.8%	0.73 (0.50, 1.06)	p=0.100
CIPRO 14				
RESPIRE 1	26/137 (19.0%) vs. 33/138 (23.9%)	-4.9%	0.58 (0.45, 1.26)	p=0.278
RESPIRE 2	25/176 (14.2%) vs. 31/174 (17.8%)	-3.6%	0.81 (0.48, 1.37)	p=0.423
Combined trials	51/313 (16.3%) vs. 64/312 (20.5%)	-4.2%	0.78 (0.54, 1.14)	p=0.198

Source: Reviewer Table
95% Significance levels used in confidence intervals (CIs).

Figure 7: Kaplan-Meier Plot: Time to Study Discontinuation (FAS)



Note: Y-axis is truncated.

Time to First Exacerbation with Alternative Approaches for Censoring

In the primary analysis, patients discontinuing from the trial (dropouts) were censored at the time of discontinuation and counted as not having an event (non-informative censoring). **Table 14** shows findings using an alternative assumption where patients discontinuing from the trial are counted as having an event at the time of discontinuation. While such an assumption may over-estimate the true event rate, comparisons using both assumptions can show the potential effect that treatment differences in dropout rates can have on primary analysis findings.

Table 14: Sensitivity Analysis of Time to First Exacerbation- Patients Censored before Study Completion Counted as Having an Event at Time of Censoring (FAS)

Cipro vs. Pooled Placebo	**Percent with PE[2]**	**Difference in PE Rate (**Cipro – Placebo)	**Median Time to First PE**	**Days Prolonged with Treatment**	**Hazard Ratio (CI)[1]** (Cipro / Placebo)	**p-value [1]**
CIPRO 28						
RESPIRE 1	81/141 (57.5%) vs. 100/138 (72.5%)	-15.0%	236 days vs. 141.5 days	94.5 days	0.70 (0.50, 0.98)	p=0.017
RESPIRE 2	76/171 (44.4%) vs. 94/174 (54.0%)	-9.6%	> 336 vs. 263 days	> 73 days	0.75 (0.45, 1.25)	p=0.063
Combined trials	157/312 (50.3%) vs. 194/312 (48.7%)	-11.9%	334 vs. 191 days	143 days	0.72 (0.57, 0.92)	p=0.003
CIPRO 14						
RESPIRE 1	72/137 (52.6%) vs. 100/138 (72.5%)	-19.9%	292 days vs. 141.5 days	150.5 days	0.58 (0.41, 0.82)	p=0.0004
RESPIRE 2	89/176 (50.6%) vs. 94/174 (54.0%)	-3.5%	331 vs. 263 days	68 days	0.89 (0.66, 1.19)	p=0.421
Combined trials	161/313 (51.4%) vs. 194/312 (48.7%)	-10.7%	322 vs. 191 days	131 days	0.72 (0.57, 0.92)	p=0.002

Source: Reviewer Table

3 P-values are for primary analyses in RESPIRE 1 and RESPIRE 2 and an exploratory analysis in RESPIRE 1&2 Combined.

4 Significance levels used in confidence intervals (CIs) vary according to the significance levels used for statistical testing. For RESPIRE 1, 97.5% CIs are used, for RESPIRE 2, a 95.1% CI (Cipro 14 day) or a 99.9% CI (Cipro 28 day) is used and for RESPIRE 1&2 Combined, 95% CIs are used.

8.3.6 Efficacy Findings by Gender, Race, Age and Geographic Region

Cipro 14

Subgroup analyses of time to first exacerbation by baseline characteristics of age, sex, race and geographic region for Cipro 14 vs. Pooled Placebo are shown for RESPIRE 1 and for RESPIRE 2 in **Figure 9**. In RESPIRE 1, hazard ratios (Cipro 14/Pooled Placebo) and the associated upper confidence limits tended to be smaller (more favorable) in females and patients ≥65 years and less favorable among patients in Northern Europe. In RESPIRE 2, estimates strongly favored females vs. males, HR=0.64 (95.1% CI: 0.38, 1.07) vs. HR=1.49 (95.1% CI: 0.78, 2.84) and were also less favorable in patients ≥65 years and patients who were non-white where estimates exceeded 1. Estimates also tended to be slightly more favorable in Northern Europe. Overall, there were no clear trends among subgroups across both trials with the possible exception being females who fared better than males in both trials, especially RESPIRE 2.

Cipro 28

The corresponding subgroup analyses for Cipro 28 vs. Pooled Placebo are shown in **Figure 8**. In RESPIRE 1, the hazard ratios (Cipro 28/Pooled Placebo) and associated upper confidence limits were more favorable in patients from Southern Europe and US/Japan/Latin America. Point estimates were also lower, though more variable, among male vs. female and non-white vs. white patients. In RESPIRE 2, hazard ratios and confidence limits were more favorable in patients < 65 years, females, non-whites and less favorable among patients from 'Other' geographic regions (i.e., US, Canada, Latin America, South Africa and Australia). Overall, there were no clear trends across both trials in any specific subgroup.

Figure 8: Subgroup Analyses: Time to First Exacerbation by Age, Sex, Race, Geographic Region, Cipro 28 Day vs. Pooled Placebo, RESPIRE 1, 2

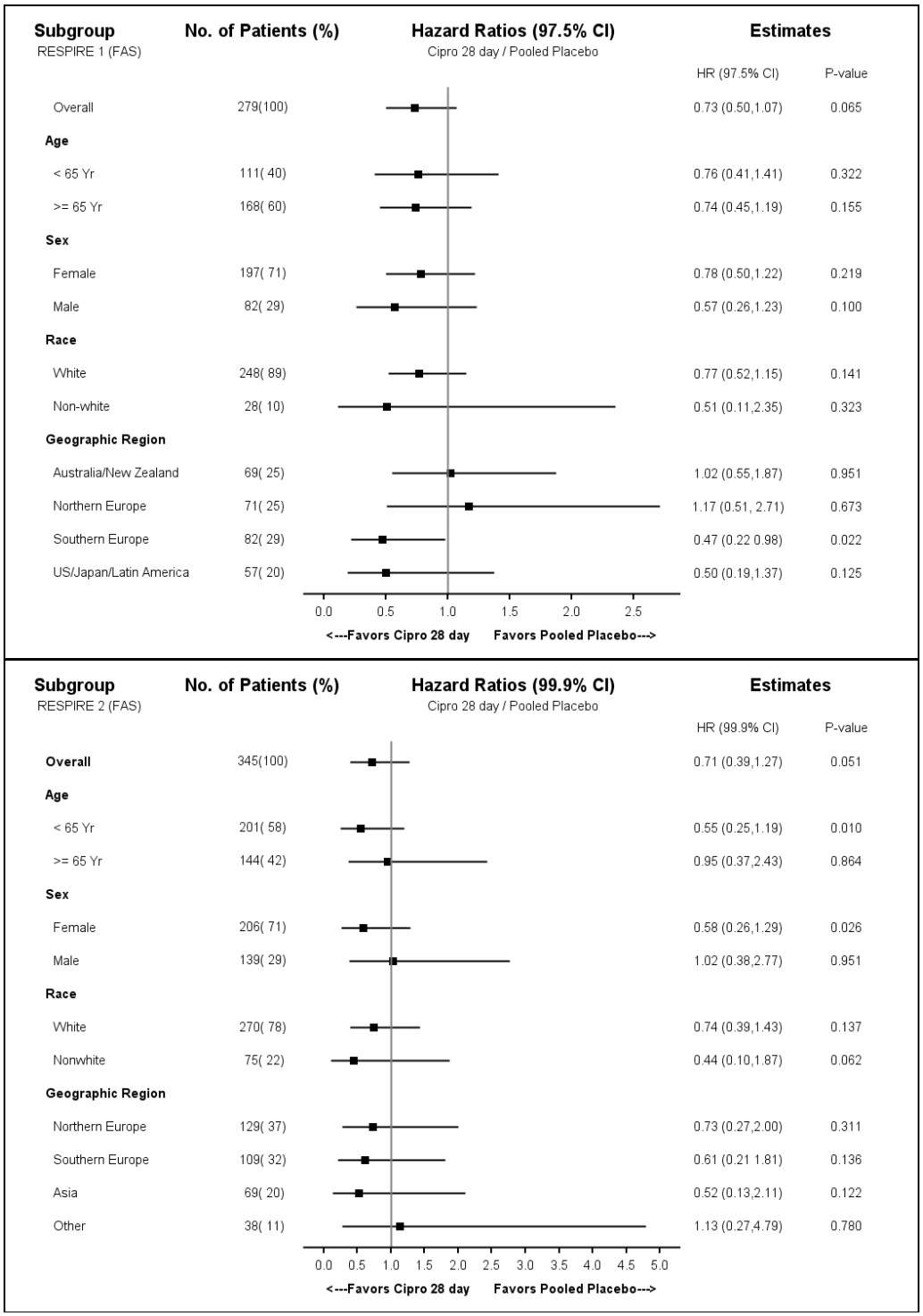
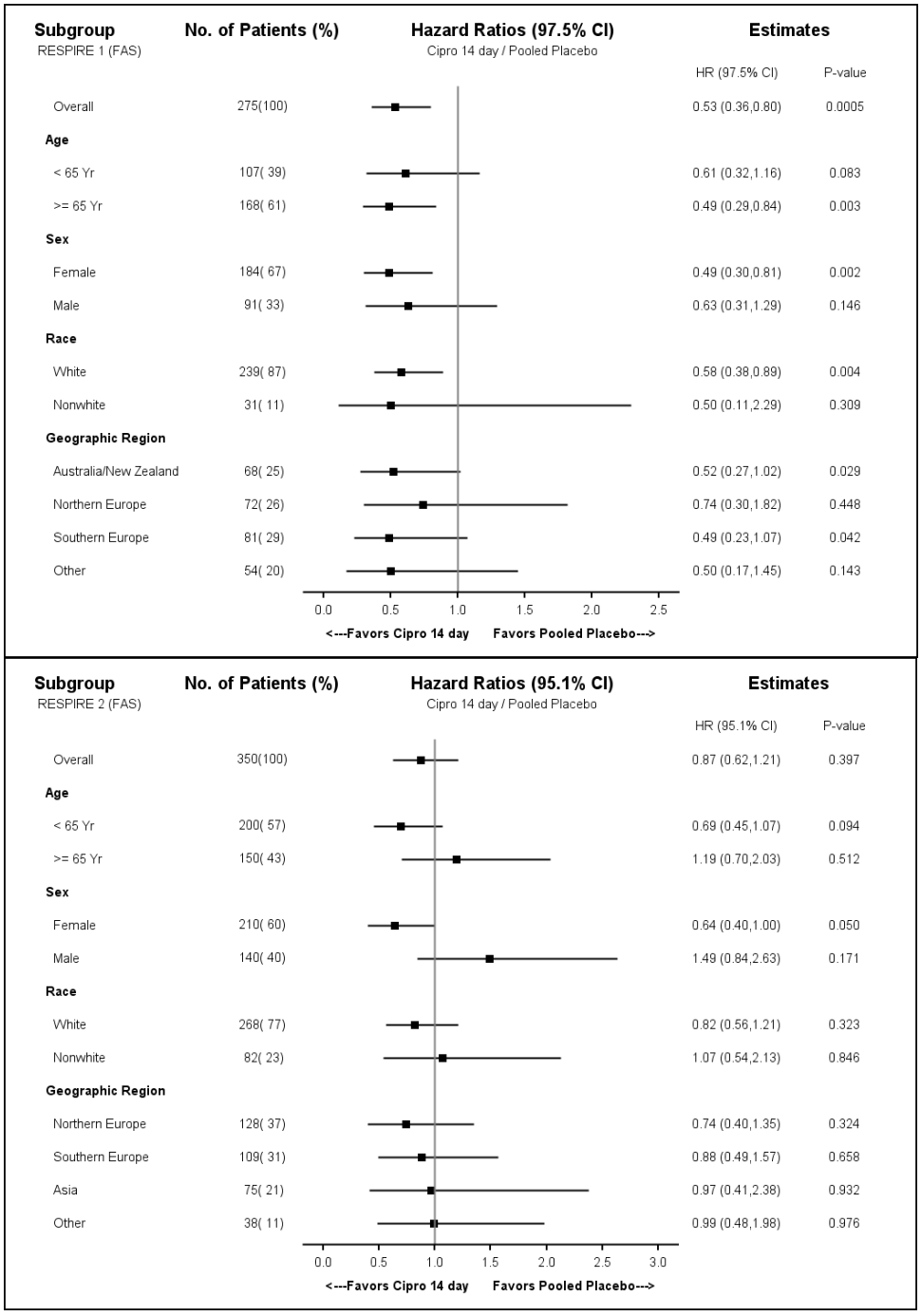


Figure 9: Subgroup Analyses, Time to First Exacerbation by Age, Sex, Race, Geographic Region, Cipro 14 Day vs. Pooled Placebo, RESPIRE 1, 2



8.4 Efficacy Summary

For Cipro 14, RESPIRE 1 showed a prolonged time to first exacerbation versus Pooled Placebo (median TFE: > 336 days vs. 186 days, p-value = 0.0005 < α = 0.025). Cipro 14 also showed a reduction in frequency of exacerbations which approached significance, (mean: 0.63 vs. 0.91 exacerbations, p-value = 0.038 > α=0.025). In RESPIRE 2, the median TFE was > 336 for both arms, p=0.397 > α=0.049. Due to the lack of significance, the key secondary endpoint of frequency of exacerbations could not be statistically tested. Exploratory testing of Cipro 14 vs. Pooled Placebo in frequency of exacerbations showed a mean frequency of 0.58 vs. 0.70 exacerbations, p-value =0.147.

For Cipro 28, in RESPIRE 1, the median TFE was 336 days vs. 186 days. This difference did not reach statistical significance, p-value = 0.065 > α = 0.025, and the mean frequency of exacerbations was 1.14 vs. 1.22, p-value = 0.276. In RESPIRE 2, Cipro 28 had a median time to first exacerbation that was > 336 days, p-value = 0.051 > α = 0.001. Exploratory testing of Cipro 28 vs. Pooled Placebo for frequency of exacerbations showed a mean of 0.54 vs. 0.85 exacerbations, p-value = 0.0003.

Uncertainties related to the Efficacy Results:

The reasons for requiring two trials in this indication for replicative evidence of efficacy and safety were based on the following considerations:

(1) This is a new treatment indication and route of administration for ciprofloxacin
(2) There were uncertainties with regard to duration of treatment, frequency of administration and endpoints
(3) Previous trials of inhaled antibacterial drugs in NCFB patients have failed to demonstrate efficacy
(4) There are no relevant animal models
(5) An adequate safety database is needed.

While the results for the Cipro 14-day regimen in RESPIRE 1 demonstrate an effect on prolongation of time to first exacerbation, we have reservations about the overall treatment benefit with inhaled Cipro DPI in NCFB patients based on the results of the various endpoints measured. The results for the 14-day regimen were not consistent between the two trials, with a large treatment effect on time to first exacerbation in RESPIRE 1 which was not replicated in RESPIRE 2. The 28-day regimen did not meet the pre-specified primary endpoint in either trial.

Cipro 14-day Regimen:
Primary Endpoint: In RESPIRE 1, the Cipro 14-day regimen, in addition to standard of care therapies, increased the time to the first pulmonary exacerbation (TFE); however, in RESPIRE 2, the Cipro 14-day regimen did not achieve a statistically significant improvement in TFE.

Secondary Endpoints: In RESPIRE 1, the Cipro 14-day regimen failed to demonstrate a statistically significant improvement in the first secondary endpoint of reduction in the

frequency of exacerbation events after demonstrating a statistically significant improvement in TFE. In RESPIRE 2, the Cipro 14-day regimen did not demonstrate a statistically significant improvement in TFE so formal testing of secondary endpoints could not be performed.

Cipro 28-day Regimen:
Primary Endpoint: The Cipro 28-day regimen did not achieve statistically significant superiority for the primary endpoint versus pooled placebo in either Phase 3 trial based on the pre-specified analysis plan.

Secondary Endpoints: Since the Cipro 28-day regimen did not achieve a statistically significant result for TFE in either Phase 3 trial, formal testing of secondary endpoints could not be performed. It should be noted that in RESPIRE 1 none of the secondary endpoints for the Cipro 28-day regimen achieved nominal statistical significance. In RESPIRE 2, only the first secondary endpoint of reduction in frequency of exacerbations achieved nominal statistical significance.

Additionally, pulmonary function, as measured objectively by FEV_1, did not improve in either trial for either the Cipro 14- or 28-day regimens. Results for the two patient-reported outcomes assessments, QOL-B and SGRQ symptom component score, were not consistent between studies or Cipro regimens. Microbiologic secondary endpoints related to eradication of baseline pathogens and the occurrence of new pathogens versus placebo were not consistent between the two trials.

With regard to the design of the Phase 3 trials, and based on our current understanding of the disease under study, we note that time to first exacerbation (TFE) has limitations since it is unclear that delaying the time to first exacerbation on study therapy compared to placebo over approximately one year of observation, translates into a clinically meaningful benefit for a patient population that would most likely be on this therapy for long durations. Additionally, we note the trial to trial heterogeneity which cannot be explained, and the magnitude of the treatment effect, which even if statistically significant, may not be clinically meaningful.

Finally, the duration of the Phase 3 trials may not have been long enough to adequately assess whether Cipro DPI reduces the frequency of exacerbations to a clinically meaningful extent and whether such an effect would be durable beyond approximately one year. Tied to the question of whether the trials were of adequate duration to assess efficacy, there is also uncertainty as to whether a longer duration of exposure to Cipro DPI, as would be expected in clinical practice (likely lifelong after starting therapy), would result in additional safety issues and bacterial resistance leading to erosion of efficacy over time.

9 Evaluation of Safety

9.1 Safety Summary

A total of 195 subjects (18 healthy subjects and 177 patients) who participated in Phase 1 studies were included in the Applicant's Summary of Clinical Safety. Patients included those with cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and NCFB. 111 participants received a single dose of Cipro DPI (dry powder for inhalation) or placebo powder and 84 received multiple dose treatments of Cipro DPI or placebo. In total, approximately 164 healthy subjects and patients received at least one dose of Cipro DPI in Phase 1 studies with treatment ranging from 1 to 13 days. Common treatment-emergent adverse events (TEAEs) included: abnormal product taste/dysgeusia, headache, bronchospasm, dyspnea, cough, and nasopharyngitis.

In the Phase 2 study 12429, 93 patients with CF were exposed to 32.5 mg twice daily Cipro DPI for 28 days, 93 patients were exposed to 48.75 mg Cipro DPI twice daily for 28 days, and 100 patients received matching placebo (65 to match the 32.5 mg dosing regimen and 35 to match the 48.75 mg dosing regimen). Based on the higher incidence of adverse events, serious adverse events and adverse events leading to withdrawal in the 48.75 mg Cipro DPI dosing regimen and comparable bacterial load reductions in sputum, Bayer chose to continue development with Cipro 32.5 mg DPI instead of Cipro 48.75 mg DPI. In the Phase 2 study 12965, 60 patients with NCFB received 32.5 mg Cipro DPI twice daily for 28 days and 64 patients received matching placebo powder; 68.3% of Cipro 32.5 mg DPI subjects and 65.6% of placebo subjects experienced TEAEs. Similar numbers of subjects in each group experienced Serious Adverse Events (SAEs) and Adverse Events (AEs) that led to withdrawal. The most common TEAEs in the Cipro DPI group were: product taste abnormal /dysgeusia (20%), bronchiectasis (11.7%), headache (6.7%), nausea (5%), and bronchospasm (5%).

The safety of Cipro DPI was evaluated in two Phase 3 randomized, double-blind, placebo-controlled trials of 933 subjects with NCFB. Of these, 622 subjects received at least one dose of Cipro DPI (310 subjects received Cipro DPI 14 days on/off, and 312 subjects received Cipro DPI 28 days on/off). Additionally, 311 subjects received at least one dose of placebo powder (156 received the placebo 14 day on/off regimen and 155 received the placebo 28-day on/off regimen). There were 375 females and 247 males who received Cipro DPI.

In the Phase 3 trials, the safety profile of Cipro DPI was similar to placebo powder with regard to the rates of common TEAEs, AEs leading to premature study drug termination, SAEs, and AEs leading to death. However, it should also be noted that the Phase 3 trials did not include a comparator arm that did not receive any dry powder for inhalation. Without such a comparator, we were unable to ascertain the incidence of adverse reactions due solely to inhaling a dry powder (placebo or otherwise).

Table 15 provides an overview of the TEAEs in the safety analysis population (SAF) derived from the two Phase 3 trials, RESPIRE 1 and RESPIRE 2.

Table 15: Overview of the TEAEs – integrated analysis [safety analysis population (SAF)]

Type of Treatment-Emergent AE (TEAE)	Ciprofloxacin DPI 14 days on/off N=310 n (%)	Ciprofloxacin DPI 28 days on/off N=312 n (%)	Placebo 14 days on/off N=156 n (%)	Placebo 28 days on/off N=155 n (%)	Pooled Placebo N=311 n (%)	Total N=933 n (%)
AEs	239 (77.1)	204 (65.4)	113 (72.4)	117 (75.5)	230 (74)	673 (72.1)
Severe AEs	48 (15.5)	38 (12.2)	32 (20.5)	19 (12.3)	51 (16.4)	137 (14.7)
Serious AEs	68 (21.9)	56 (18)	45 (28.9)	28 (18.1)	73 (23.5)	197 (21.1)
Serious non-fatal AEs	65 (21)	55 (17.6)	42 (26.9)	28 (18.1)	70 (22.5)	190 (20.4)
AEs resulting in death	4 (1.3)	6 (1.9)	4 (2.6)	1 (0.6)	5 (1.6)	15 (1.6)
AEs resulting in withdrawal	27 (8.7)	20 (6.4)	17 (10.9)	12 (7.74)	29 (9.3)	76 (8.1)
SAEs resulting in withdrawal	5 (1.6)	6 (1.9)	6 (3.9)	2 (1.3)	8 (2.6)	19 (2)

Note: Frequency data are based on the number of subjects with the event.
Modified from Applicant's Table 2-2, page 20 of the Summary of Clinical Safety (SCS), submitted 6/30/17.

The low incidence of systemic effects is likely due to the localized deposition of the drug product in the lungs.

The following list includes AEs that were likely due to Cipro DPI.

Hemoptysis: Hemoptysis was an event of special interest. Though the incidence between Cipro DPI and placebo groups was similar [Cipro 14-day group: 33 (10.7%), Placebo 14-day group: 17 (10.9%); Cipro 28-day group: 27 (8.7%), Placebo 28-day group: 15 (9.7%)], it is difficult to definitively rule out that the events were not related to study therapy. It is plausible that any powder inhaled by this patient population could cause bronchial irritation, coughing episodes, and resultant hemoptysis.

Dyspnea: The incidence of dyspnea was higher in the Cipro DPI groups as compared to the placebo groups. The number of subjects who experienced this event by treatment group follows: Cipro 14-day group: 26 (8.4%), Placebo 14-day group: 6 (3.9%), Cipro 28-day group: 20 (6.4%), Placebo 28-day group: 6 (3.9%). Placebo 28-day group: 8 (5.2%). It is plausible that any powder inhaled by this patient population could cause bronchial irritation and resultant dyspnea.

Headache: The incidence of headache was higher in the Cipro DPI groups as compared to the placebo groups. The number of subjects who experienced this event by treatment

group follows: Cipro 14-day group: 24 (7.7%), Placebo 14-day group: 2 (1.3%), Cipro 28-day group: 21 (6.7%), Placebo 28-day group: 7 (4.5%).

Cough: The incidence of cough was higher in the Cipro 14-day group [20 (6.5%)] as compared to the Placebo 14-day group [6 (3.9%)]. The Cipro 28-day group [20 (6.4%)] had a lower incidence of cough compared to the Placebo 28-day group [14 (9.0%)]. It is plausible that any powder inhaled by this patient population could cause bronchial irritation and resultant cough.

Bronchospasm: Bronchospasm was an event of special interest. Though the incidence of bronchospasm was similar or slightly lower in the Cipro DPI groups as compared to the Placebo groups, it is difficult to definitively rule out that the events were not related to study therapy [Cipro 14-day group: 14 (4.5%), Placebo 14-day group: 9 (5.8%), Cipro 28-day group: 10 (3.2%), Placebo 28-day group: 10 (6.5%)]. It is plausible that any powder inhaled by this patient population could cause bronchial irritation and resultant bronchospasm.

Fatigue: The incidence of fatigue was higher in the Cipro 14-day group [14 (4.5%)] as compared to the Placebo 14-day group [1 (0.6%)]. The Cipro 28-day group [8 (2.6%)] had a similar incidence of fatigue compared to the Placebo 28-day group [4 (2.7%)]. It is difficult to rule out the possibility that the events were not due to study therapy.

Taste disorder: Taste disorders were noted in all phases of clinical development of Cipro DPI. In Phase 3 trials, the incidence of taste disorders (dysgeusia, product taste abnormal, ageusia) was higher in the Cipro DPI groups as compared to the placebo groups, excluding duplication of subjects who were reported as having more than one of these events: Cipro 14-day group: 14 (4.5%), Placebo 14-day group: 1 (0.6%), Cipro 28-day group: 18 (5.8%), Placebo 28-day group: 3 (1.9%).

Dizziness: The incidence of dizziness was higher in the Cipro 14-day group [11 (3.6%)] as compared to the Placebo 14-day group [0]. The Cipro 28-day group [3 (1%)] had a similar incidence of dizziness compared to the Placebo 28-day group [3 (1.9%)]. Dizziness is listed as an adverse reaction in the CIPRO IV and oral labels.

Malaise: The incidence of malaise was higher in the Cipro DPI groups as compared to the placebo groups: Cipro 14-day group: 7 (2.3%), Placebo 14-day group: 1 (0.6%), Cipro 28-day group: 7 (2.2%), Placebo 28-day group: 0.

Oral candidiasis: The incidence of oral candidiasis was higher in the Cipro DPI groups as compared to the placebo groups: Cipro 14-day group: 5 (1.6%), Placebo 14-day group: 1 (0.6%), Cipro 28-day group: 5 (1.6%), Placebo 28-day group: 1 (0.7%).
It is plausible that oral candidiasis may be related to Cipro DPI given that inhalation of a broad spectrum antibacterial drug through the mouth could eliminate normal bacterial flora resulting in oral candidiasis.

Arthralgia: The incidence of arthralgia was higher in the Cipro DPI groups as compared to the placebo groups: Cipro 14-day group: 6 (1.9%), Placebo 14-day group: 0, Cipro 28-day group: 7 (2.2%), Placebo 28-day group: 3 (1.9%). Arthralgia is listed as an adverse reaction in the CIPRO IV and oral labels.

Paresthesias: The incidence of paresthesias was slightly higher in the Cipro 28-day group [4 (1.28%)] as compared to the Placebo 28-day group [0]. The Cipro 14-day group [2 (0.65%)] had a similar incidence of paresthesia compared to the Placebo 14-day group [1 (0.64%)]. Paresthesia is listed as an adverse reaction in the CIPRO IV and oral labels.

Mouth ulceration: The incidence of mouth ulceration was slightly higher in the Cipro DPI groups as compared to the placebo groups [Cipro 14-day group: 2 (0.7%), Placebo 14-day group: 0, Cipro 28-day group: 5 (1.6%), Placebo 28-day group: [0]. It is possible that long term inhalation of ciprofloxacin powder by mouth may cause oral mucosal irritation and resultant ulceration. The longer exposure per cycle in the Cipro 28-day regimen may be the reason for the higher incidence in this group.

Aspergillus test positive: The incidence of having a positive test for Aspergillus was higher in the Cipro DPI groups as compared to the placebo groups: Cipro 14-day group: 8 (2.6%), Placebo 14-day group: 1 (0.6%), Cipro 28-day group: 6 (1.9%), Placebo 28-day group: 0. It is possible that long term inhalation of ciprofloxacin DPI by mouth may reduce or eliminate normal flora in the oral cavity and bronchial tree predisposing subjects to increased colonization with *Aspergillus* species. Of note, regular testing for Aspergillus was not performed in all subjects. This event would be clinically important if colonization resulted in infection due to *Aspergillus* species. Of note, one subject in the Cipro 14-day group experienced bronchopulmonary aspergillosis allergic, one subject in the Cipro 14-day group experienced bronchopulmonary aspergillosis, and one subject in Placebo 14-day group experienced aspergilloma.

Hypersensitivity type reactions were noted in subjects on Cipro DPI, though not at a higher incidence than pooled placebo in the Phase 3 trials. Hypersensitivity [by standardized MedDRA query (SMQ) narrow search] occurred in 93 (10%) of subjects in the combined safety database for RESPIRE 1 and 2. Preferred terms identified in the search included: “bronchospasm”, “allergic sinusitis”, “rhinitis allergic”, “rash”, “periorbital edema” (1 subject in Cipro 28 group), “mouth swelling” (1 subject in placebo 28 group), “swollen tongue” (1 subject in Cipro 28), and “swollen face” (1 subject in Cipro 28). Additionally, one subject from the Cipro 28 group experienced bronchospasm which was considered a serious adverse event.

Given that study therapy was limited to slightly less than one year in the Phase 3 trials it is unknown whether exposure at the proposed dose of 32.5 mg BID beyond a year may lead to additional concerns, such as, additional safety signals or increased resistance to fluoroquinolones given that patients will likely remain on this drug product for long durations and potentially for the remainder of their lives. Evidence for the development bacterial resistance to ciprofloxacin was noted over the course of the Phase 3 trials. Subjects with ciprofloxacin susceptible baseline isolates who later had an isolate that

yielded a MIC value classified as ciprofloxacin resistant were defined as having developed resistance. The proportion of subjects with treatment-emergent resistance (i.e., subjects with the same species susceptible before start of treatment and resistant at any time point post-baseline) were higher in the active treatment groups compared to placebo (**Table 16**). Most of the resistance development was observed in *P. aeruginosa* (**Table 17**).

Table 16: Number of subjects with any ciprofloxacin-resistant pathogens in sputum samples from RESPIRE 1 and 2 studies (Full analysis set).

RESPIRE 1						
Resistance		CIPRO DPI 28 N = 141 n (%)	CIPRO DPI 14 N = 137 n (%)	Placebo 28 N = 70 n (%)	Placebo 14 N = 68 n (%)	Pooled placebo N = 138 n (%)
Resistance at baseline	Yes	39 (27.7%)	34 (24.8%)	16 (22.9%)	13 (19.1%)	29 (21.0%)
	No	102 (72.3%)	103 (75.2%)	54 (77.1%)	55 (80.9%)	109 (79.0%)
Development of resistance (baseline to end of study)	Yes	13 (9.2%)	10 (7.3%)	3 (4.3%)	0	3 (2.2%)
	No	76 (53.9%)	79 (57.7%)	38 (54.3%)	36 (52.9%)	74 (53.6%)
Development of resistance (baseline to any time during study)	Yes	**37 (26.2%)**	**28 (20.4%)**	**10 (14.3%)**	**7 (10.3%)**	**17 (12.3%)**
	No	104 (73.8%)	109 (79.6%)	60 (85.7%)	61 (89.7%)	121 (87.7%)
RESPIRE 2						
Resistance		CIPRO DPI 28 N = 171 n (%)	CIPRO DPI 14 N = 176 n (%)	Placebo 28 N = 86 n (%)	Placebo 14 N = 88 n (%)	Pooled placebo N = 174 n (%)
Resistance at baseline	Yes	28 (16.4%)	37 (21.0%)	10 (11.6%)	23 (26.1%)	33 (19.0%)
	No	143 (83.6%)	139 (79.0%)	76 (88.4%)	65 (73.9%)	141 (81.0%)
Development of resistance (baseline to end of study)	Yes	10 (5.8%)	12 (6.8%)	3 (3.5%)	1 (1.1%)	4 (2.3%)
	No	104 (60.8%)	120 (68.2%)	58 (67.4%)	64 (72.7%)	122 (70.1%)
Development of resistance (baseline to any time during study)	Yes	**28 (16.4%)**	**37 (21.0%)**	**4 (4.7%)**	**6 (6.8%)**	**10 (5.7%)**
	No	143 (83.6%)	139 (79.0%)	82 (95.3%)	82 (93.2%)	164 (94.3%)

Baseline resistance: Number of subjects with at least one resistant isolate at baseline
Development of resistance (pre-treatment - end of study): Number of subjects with same species susceptible before start of treatment and resistant at end of study
Development of resistance (pre-treatment - any point during study): Number of subjects with same species susceptible before start of treatment and resistant at any other time point

Table 17: Number of subjects with treatment-emergent development of ciprofloxacin-resistant pathogens in sputum sample by pre-specified pathogen in RESPIRE 1 and 2

Organisms	RESPIRE 1			RESPIRE 2		
	Cipro DPI 28 on/off N = 141 N (%)	Cipro DPI 14 on/off N = 137 N (%)	Pooled Placebo N = 138 N (%)	Cipro DPI 28 on/off N = 171 N (%)	Cipro DPI 14 on/off N = 176 N (%)	Pooled Placebo N = 174 N (%)
H. influenzae	4 (2.8)	2 (1.5%)	0	3 (1.8%)	3 (1.7%)	0
M. catarrhalis	0	0	0	0	0	0
P. aeruginosa	30 (21.3)	23 (16.8)	15 (10.9)	53 (30.9)	76 (43.2)	38 (21.8)
S. maltophilia	0	1 (0.7)	0	9 (5.2)	11 (62.5)	5 (2.9)
B. cepacia	0	0	0	1 (0.6)	1 (0.6)	3 (1.7)
S. aureus	3 (2.1)	1 (0.7)	2 (1.4)	5 (2.9)	6 (3.4)	7 (4.0)
S. pneumoniae	1 (0.7)	1 (0.7)	0	1 (0.6)	5 (2.8)	1 (0.6)

Given that NCFB patients enrolled in the Phase 3 trials were in their mid-sixties, patients may conceivably be on Cipro DPI for 10 or more years. The Applicant did attempt to evaluate for class effects. Given the much lower systemic exposure associated with Cipro DPI as compared to orally or parenterally administered ciprofloxacin, AEs associated with quinolone class effects were not observed to a significant extent in the 48-week Phase 3 trials. The systemic exposure of 32.5 mg inhaled ciprofloxacin is over ten times lower than that observed with 250 mg oral ciprofloxacin. However, it is possible that poor inhalation technique could result in increased deposition of ciprofloxacin in the oral cavity, which could result in oral ingestion and potentially higher levels of systemic exposure. It should be noted that one subject in RESPIRE 1 who received the Cipro 14-day regimen and had no prior history of tendon disorder experienced left Achilles heel tendinopathy of moderate intensity which the study investigator deemed related to study therapy. Overall, incidence of tendon disorders was similar between the treatment groups and ranged between 1.0% and 1.6% among the Cipro DPI groups and pooled placebo.

It is unlikely that dosage adjustment would be needed in patients with hepatic or renal impairment since the systemic exposure to ciprofloxacin in Cipro DPI is anticipated to be low.

9.2 Methods

Given that the two Phase 3 trials had nearly identical study designs, safety data from each treatment arm were pooled across the two trials. Additionally, safety data from all of the placebo arms were also pooled to form a “Pooled Placebo” arm to increase the sample size of the placebo group for comparison purposes.

9.3 Study Discontinuation

Table 18 provides the incidence of TEAEs leading to premature discontinuation/withdrawal.

Table 18: TEAEs leading to premature discontinuation – integrated analysis (Safety Population)

Type of TEAE leading to premature treatment discontinuation	Cipro 14 N=310 n (%)	Cipro 28 N=312 n (%)	Pooled Placebo N=311 n (%)	Total N=933 n (%)
Any TEAE	27 (8.7)	20 (6.4)	29 (9.3)	76 (8.1)
Any SAE	5 (1.6)	6 (1.9)	8 (2.6)	19 (2.0)

Cipro 14=Ciprofloxacin DPI 14 on/off, Cipro 28=Ciprofloxacin DPI 28 on/off
Modified from Applicant's Table 2-10, page 35 of the SCS, submitted 6/30/17.

The incidence of TEAEs and SAEs resulting in premature discontinuation was fairly balanced between the treatment groups. Of the TEAEs leading to premature discontinuation, the following may have been related to Cipro DPI: dyspnea, dysgeusia, ageusia, headache, bronchospasm, hemoptysis, cough, nasal dryness, oral pain, nausea, vomiting, abdominal discomfort/pain/fullness, fatigue, malaise/weakness, asthenia, insomnia/sleep disorder, neck stiffness, muscle twitching, tendon discomfort, chest tightness/discomfort, rash, and retinal vasculitis.

9.4 Deaths

There were 6 treatment-emergent deaths in RESPIRE 1 and 9 treatment-emergent deaths in RESPIRE 2. A treatment-emergent death was defined as any death that occurred during the period from the first administration of study medication through 30 days after administration on the last dose of study medication. In combining both trials, 4 subjects (1.3%) in the Cipro DPI 14-day group, 6 subjects (1.9%) in the Cipro DPI 28-day group, 1 subject (0.6%) in the placebo 28-day group, and 4 subjects (2.6%) in the placebo 14-day group [5 subjects (1.6%) in the pooled placebo group] experienced treatment-emergent deaths. The treatment-emergent deaths appeared to be related to underlying co-morbid conditions and unrelated to study therapy.

Table 19 includes the treatment-emergent deaths in RESPIRE 1 and 2.

Table 19: Treatment-emergent deaths in RESPIRE 1 and 2 – Safety Population

PID (age/sex)[a]	Trial	PT event[b]	Day of Death[c]
Cipro 14 group			
200100004 (76/M)	RESPIRE 1	Pneumonia, aspiration	256/18
420010006 (77/F)	RESPIRE 2	Gastrointestinal hemorrhage	226/15
510200008 (35/F)	RESPIRE 2	Bronchiectasis	199/1
760090010 (72/M)	RESPIRE 2	Esophageal carcinoma	147/1
Cipro 28 group			
200070004 (78/F)	RESPIRE 1	Cor pulmonale	124/7
700060024 (88/F)	RESPIRE 1	Pneumonia	44/32
180020001 (49/M)	RESPIRE 2	Congestive cardiomyopathy	36/10
430020006 (61/M)	RESPIRE 2	Bronchiectasis	221/26
470100007 (79/M)	RESPIRE 2	Bronchiectasis	216/20
670040008 (78/M)	RESPIRE 2	Cor pulmonale	36/8
Placebo 14 group			
700050016 (57/M)	RESPIRE 1	Complications of transplant surgery	351/29
700080014 (88/F)	RESPIRE 1	Pneumonia	238/5
400020013 (88/F)	RESPIRE 2	Bronchiectasis	70/2
890030001 (78/F)	RESPIRE 2	Bronchiectasis	100/2
Placebo 28 group			
700040008 (82/M)	RESPIRE 1	Pulmonary hemorrhage	143/10

PID: Patient identifier

a: age in years / M=male or F=female.

b: MedDRA preferred term.

c: Relative to start date / stop date of study drug.

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; Placebo 14=Placebo 14 on/off; Placebo 28=Placebo 28 on/off

RESPIRE 1 Source: Tables 14.3.2/1 and 14.3.2/8; RESPIRE 2 Source: Tables 14.3.2/1 and 14.3.2/9

9.5 Serious Adverse Events

Table 20 contains the nonfatal treatment-emergent SAEs occurring in at least 2 subjects in the Phase 3 trials (by incidence) using the safety analysis population.

Table 20: Nonfatal treatment-emergent SAEs occurring in at least 2 subjects in the Phase 3 trials (by incidence)

Dictionary Derived Term	Ciprofloxacin DPI, treatment regimen 14 days on/off	Ciprofloxacin DPI, treatment regimen 28 days on/off	Placebo, treatment regimen 14 days on/off	Placebo, treatment regimen 28 days on/off	Total Subjects
Total No. of Subjects per Treatment Group	310 (100.00%)	312 (100.00%)	156 (100.00%)	155 (100.00%)	933 (100.00%)
Subjects with TE nonfatal SAEs	65 (20.97%)	55 (17.63%)	42 (26.92%)	28 (18.06%)	190 (20.36%)
Bronchiectasis	31 (10.00%)	33 (10.58%)	20 (12.82%)	16 (10.32%)	100 (10.72%)
Pneumonia	6 (1.94%)	6 (1.92%)	4 (2.56%)	2 (1.29%)	18 (1.93%)
Hemoptysis	4 (1.29%)	4 (1.28%)	4 (2.56%)	2 (1.29%)	14 (1.50%)
Infective exacerbation of bronchiectasis	4 (1.29%)	2 (0.64%)	3 (1.92%)	0 (0.00%)	9 (0.96%)
Chronic obstructive pulmonary disease	3 (0.97%)	0 (0.00%)	0 (0.00%)	1 (0.65%)	4 (0.43%)
Respiratory failure	2 (0.65%)	0 (0.00%)	0 (0.00%)	1 (0.65%)	3 (0.32%)
Cardiac failure	1 (0.32%)	0 (0.00%)	0 (0.00%)	2 (1.29%)	3 (0.32%)
Cerebrovascular accident	1 (0.32%)	1 (0.32%)	0 (0.00%)	0 (0.00%)	2 (0.21%)
Osteoarthritis	1 (0.32%)	0 (0.00%)	0 (0.00%)	1 (0.65%)	2 (0.21%)
Pulmonary embolism	1 (0.32%)	1 (0.32%)	0 (0.00%)	0 (0.00%)	2 (0.21%)
Atrial flutter	0 (0.00%)	2 (0.64%)	0 (0.00%)	0 (0.00%)	2 (0.21%)
Cellulitis	0 (0.00%)	1 (0.32%)	1 (0.64%)	0 (0.00%)	2 (0.21%)

In general, the incidence of nonfatal SAEs was similar in all four treatment groups. The Placebo 14-day group had the highest rate of nonfatal SAEs with an incidence of 27%. The other three treatment groups had nonfatal SAE incidences ranging from 18-21%. Of note, the top six nonfatal SAEs were of respiratory origin. Of these, the proportions of subjects that experienced these SAEs were similar between the treatment groups. The majority of the SAEs appeared to be related to subjects' underlying co-morbid conditions and unrelated to study therapy.

9.6 Treatment-Emergent Adverse Events (TEAEs)

The following TEAEs with an incidence of approximately 1% or greater occurred more frequently (approximately 1% more frequently) in either Cipro DPI group compared with the respective placebo group: fatigue, malaise, headache, dizziness, paresthesia, anxiety, product taste abnormal, dysgeusia, decreased appetite, dyspnea, dyspnea exertional, cough, sputum increased, dysphonia, increased viscosity of bronchial secretion, sputum discolored, nasopharyngitis, pharyngitis, tonsillitis, mouth ulceration, oral candidiasis, tooth extraction, respiratory tract infection viral, influenza, bronchitis, lower respiratory tract infection, upper respiratory tract inflammation, rales, seasonal allergy, chronic obstructive pulmonary disease, Aspergillus test positive, dyspepsia, gastroesophageal reflux disease, diarrhea, hemorrhoids, weight decreased, hypercholesterolemia, arthralgia, neck pain, spinal osteoarthritis, back pain,

musculoskeletal chest pain, rheumatoid arthritis, sciatica, contusion, hematuria, erythema, eczema, peripheral swelling, and orthostatic hypotension.

The following TEAEs with an incidence of approximately 1% or greater occurred more frequently (approximately 1% more frequently) in both the Cipro 14-day on/off group and the Cipro 28-day on/off group as compared with their respective placebo groups: malaise, headache, dysgeusia, dyspnea, oral candidiasis, respiratory tract infection viral, and Aspergillus test positive.

No treatment-specific clinically meaningful changes from baseline were detected in chemistry, hematology, coagulation, or urinalysis parameters.

9.7 Adverse Reactions of Special Interest and Submission Specific Safety Issues

Adverse events of special interest (AESI) included: bronchospasm [by preferred term (PT)], hemoptysis (by PT), hypersensitivity [by standardized MedDRA query (SMQ) narrow search], tendinopathies and ligament disorders (by SMQ narrow search), and the occurrence of non-tuberculous mycobacteria and *Aspergillus spp.*

Please refer to the safety summary for additional details. Of note, no cases of non-tuberculosis mycobacteria infections were reported.

10 Points for Advisory Committee Discussion

1. Has the applicant provided substantial evidence of the safety and effectiveness of the 14-day regimen in delaying the time to first exacerbation after starting treatment?
   - If yes, please provide any recommendations concerning labeling.
   - If no, what additional studies/analyses are needed?

2. Has the applicant provided substantial evidence of the safety and effectiveness of the 28-day regimen in delaying the time to first exacerbation after starting treatment?

   - If yes, please provide any recommendations concerning labeling.
   - If no, what additional studies/analyses are needed?

3. In future trials for this patient population, what would be the most clinically meaningful primary endpoint? What is the appropriate trial duration?

11 References

1. Barker et al. Clinical manifestations and diagnosis of bronchiectasis in adults. From UpToDate.com. Topic last updated on 8/28/17. Last accessed on 10/10/17.
2. Barker AF. Bronchiectasis. N Engl J Med. 2002 May 2; 346(18):1383-93.
3. King PT, et al. Characterisation of the onset and presenting clinical features of adult bronchiectasis. Respir Med. 2006 Dec;100(12):2183-9.
4. Hester KL, et al. Fatigue in bronchiectasis. QJM. 2012 Mar;105(3):235-40.
5. Weycker D, et al. Prevalence and economic burden of bronchiectasis [obstructive airways disease]. Clin Pulm Med. 2005; 12:205.
6. Seitz AE, et al. Trends in bronchiectasis among medicare beneficiaries in the United States, 2000 to 2007. Chest. 2012 Aug;142(2):432-439.
7. Chan SC, et al. Shed syndecan-1 restricts neutrophil elastase from alpha1-antitrypsin in neutrophilic airway inflammation. Am J Respir Cell Mol Biol. 2009 Nov;41(5):620-8.
8. Chalmers JD, et al. Mechanisms of immune dysfunction and bacterial persistence in non-cystic fibrosis bronchiectasis. Mol Immunol. 2013 Aug;55(1):27-34.
9. Chalmers JD, et al. Management of bronchiectasis in adults. Eur Respir J. 2015 May;45(5):1446-62.
10. Hill AT, et al.; the EMBARC/BRR definitions working group. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. Eur Respir J. 2017 Jun 8;49(6).
11. Gao YH, et al. The role of viral infection in pulmonary exacerbations of bronchiectasis in adults: a prospective study. Chest. 2015 Jun;147(6):1635-1643.
12. Pasteur MC, et al. An investigation into causative factors in patients with bronchiectasis. Am J Respir Crit Care Med. 2000 Oct;162(4 Pt 1):1277-84.
13. Angrill J, et al. Bacterial colonisation in patients with bronchiectasis: microbiological pattern and risk factors. Thorax. 2002 Jan;57(1):15-9.
14. Finch S, et al. A Comprehensive Analysis of the Impact of Pseudomonas aeruginosa Colonization on Prognosis in Adult Bronchiectasis. Ann Am Thorac Soc. 2015 Nov;12(11):1602-11.
15. Aliberti S, et al. Clinical phenotypes in adult patients with bronchiectasis. Eur Respir J. 2016 Apr;47(4):1113-22.
16. Barker AF, et al. Tobramycin solution for inhalation reduces sputum Pseudomonas aeruginosa density in bronchiectasis. Am J Respir Crit Care Med. 2000 Aug;162(2 Pt 1):481-5.
17. Scheinberg P, et al. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. Chest. 2005 Apr;127(4):1420-6.

18. Murray MP, et al. A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2011 Feb 15;183(4):491-9.
19. Drobnic ME, et al. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with Pseudomonas aeruginosa. Ann Pharmacother. 2005 Jan;39(1):39-44.
20. Barker AF, et al. Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. Lancet Respir Med. 2014 Sep;2(9):738-49.
21. Haworth CS, et al. Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. Am J Respir Crit Care Med. 2014 Apr 15;189(8):975-82.
22. Barker et al. Treatment of bronchiectasis in adults. From UpToDate.com. Topic last updated on 8/3/17. Last accessed on 10/11/17.