FDA Opening Remarks

Thomas Smith, MD
Division of Anti-Infective Products

Antimicrobial Drugs Advisory Committee Meeting
November 16, 2017

Introduction

- NDA 209367: Ciprofloxacin dry powder for inhalation (DPI)
- Applicant: Bayer HealthCare Pharmaceuticals, Inc.
- Proposed indication: Reduction of exacerbations in non-cystic fibrosis bronchiectasis (NCFB) adult patients with respiratory bacterial pathogens
- Dosage form and strength: Capsule with inhalation powder; 32.5 mg ciprofloxacin
- Proposed dosing regimen: 32.5 mg twice daily in 14 day on/off cycles

Development Program

- One phase 2 trial and two phase 3 trials in patients with NCFB
- Reasons for conducting two phase 3 trials to support NCFB indication
  - There are no approved therapies for prevention or management of NCFB exacerbations
  - Studies of other inhaled antibacterial drugs (tobramycin, gentamicin, aztreonam, and colistin) for the prevention of NCFB exacerbations have yielded mixed results*
  - Uncertainties regarding duration of treatment, frequency of administration, and appropriate endpoints for this use with no prior successful trials
  - No relevant animal models of NCFB to explore dosing regimen, duration of therapy, and to provide supportive information
  - New indication and route of administration for ciprofloxacin
  - Two independent trials would provide replicative evidence of efficacy
  - Need for adequate safety assessment

*Publications referenced in FDA briefing document

Phase 2 Trial

- Randomized, double-blind, placebo-controlled trial comparing treatment with Cipro DPI 32.5 mg BID vs. placebo for 28 days in 124 patients with NCFB
- Primary efficacy variable: “total bacteriological load,” which included several potential pathogens and was measured as $\log_{10}$ cfu/g of sputum during treatment (day 8), at the end of treatment (day 29), and at follow-up visits
- At day 29, total bacterial load in sputum was reduced by 3.62 $\log_{10}$ cfu/g of sputum in the ciprofloxacin DPI group compared with 0.27 $\log_{10}$ cfu/g of sputum in the placebo group

Phase 3 Trials: RESPIRE 1 and 2

- Randomized, double-blind, placebo-controlled trials enrolling patients with NCFB and 2 or more exacerbations in previous 12 months
- Four arms; randomization 2:1 (cipro:placebo)
  - Cipro 28 (32.5 mg BID, 28 days on/off)
  - Placebo 28 (matching placebo powder)
  - Cipro 14 (32.5 mg BID, 14 days on/off)
  - Placebo 14 (matching placebo powder)
- 48 week treatment period

Phase 3 Trials: RESPIRE 1 and 2

- Primary endpoint: time to first exacerbation (TFE)
  - Exacerbation: fever, malaise or fatigue, worsening of 3 or more signs and symptoms, systemic antibacterial treatment
- Key secondary endpoint: frequency of exacerbations
- Additional secondary endpoints: pathogen eradication, St. George's Respiratory Questionnaire (change from baseline), occurrence of new pathogens, Quality of Life Questionnaire for Bronchiectasis (change from baseline), FEV_1

Phase 3 Trials: Statistical Considerations

- Cipro 28 and Cipro 14 each statistically tested against pooled placebo powder under separate hierarchies in each trial
- Primary endpoint tested first, followed by secondary endpoints in prespecified order
- Statistical testing stops after the first non-significant finding; **all other testing is exploratory**
- Statistical testing at α=0.025 for each Cipro arm in RESPIRE 1 and α=0.001 for Cipro 28 and α=0.049 for Cipro 14 in RESPIRE 2

Efficacy Results: Time to First Exacerbation

RESPIRE 1 (N=416)

	Cipro 28	Cipro 14
Days Prolonged	150 (336 vs. 186)	>150 (>336 vs. 186)
Hazard Ratio	0.73 (0.47, 1.15) p=0.065	0.53 (0.36, 0.80) p=0.0005
Event Rate	47.5% vs. 57.2% Δ = -9.7%	38.7% vs. 57.2% Δ = -18.6%

α=0.025 for each arm

Efficacy Results: Time to First Exacerbation

RESPIRE 2 (N=521)

	Cipro 28	Cipro 14
Days Prolonged	NE (>336 vs. >336)	NE (>336 vs. >336)
Hazard Ratio	0.71 (0.39, 1.27) p=0.051	0.87 (0.62, 1.21) p=0.397
Event Rate	32.7% vs. 42.0% Δ = -9.2%	38.6% vs. 42.0% Δ = -3.3%

NE=not estimable; α=0.001 for Cipro 28, α=0.049 for Cipro 14

Efficacy Results: Frequency of Exacerbations

RESPIRE 1

	Cipro 28	Cipro 14
Mean PEs (per subject)	0.82 vs. 0.91	0.63 vs. 0.91
Incidence Rate Ratio	0.86 (0.63, 1.18) p=0.294	0.73 (0.52, 1.08) p=0.038

Valid statistical comparison only for Cipro 14; α=0.025 for Cipro 14

Efficacy Results: Frequency of Exacerbations

RESPIRE 2

	Cipro 28	Cipro 14
Mean PEs (per subject)	0.40 vs. 0.70	0.58 vs. 0.70
Incidence Rate Ratio	0.56 (0.33, 0.95) p=0.0003	0.81 (0.61, 1.08) p=0.147

Not a valid statistical comparison since the primary endpoint was not met

Summary of Efficacy Results

- In RESPIRE 1, only the ciprofloxacin 14-day regimen had a statistically significant finding for the primary endpoint of time to first exacerbation; this treatment effect was not replicated in RESPIRE 2
- The ciprofloxacin 28-day regimen did not meet the pre-specified primary endpoint in either trial
- As the primary endpoint was not met for 3 of the 4 test arms, most secondary endpoint analyses are considered exploratory
- Lack of consistency of findings across endpoints
- No information about durability of efficacy findings over time

Safety Assessment

- 933 patients in pooled phase 3 safety population: 622 patients received at least one dose of Cipro DPI, 311 patients received at least one dose of placebo powder
- Similar rates of common treatment-emergent adverse events (AEs), AEs leading to withdrawal, serious AEs, and AEs leading to death in all groups
- Most treatment-emergent AEs appeared to be related to local effects of Cipro DPI: taste disorders, dyspnea, bronchospasm, hemoptysis, cough
- Without a comparator arm that did not receive any dry powder, it is difficult to evaluate adverse reactions due solely to inhaling the dry powder
- Patients treated with Cipro DPI more likely to have treatment-emergent ciprofloxacin-resistant *P. aeruginosa* cultured at any point post-baseline
- Unknown whether exposure beyond one year may lead to additional safety concerns, further increase in resistance to fluoroquinolones, or reduced treatment effect

Outline for the Day

- Presentations by the Applicant
- Presentations by the FDA
  - Christopher Kadoorie, PhD: Efficacy
  - Peter Kim, MD, MS: Safety
  - Thomas Smith, MD: Summary
- Lunch
- Open public hearing
- Questions for the committee

Question 1

- Has the applicant provided substantial evidence of the safety and effectiveness for the ciprofloxacin dry powder inhaler (DPI) 14-day regimen in delaying the time to first exacerbation after starting treatment?

a. If yes, please provide any recommendations concerning labeling.

b. If no, what additional studies/analyses are needed? Please discuss appropriate endpoints, drug regimens and trial duration.

Question 2

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

a. If yes, please provide any recommendations concerning labeling.

b. If no, what additional studies/analyses are needed? Please discuss endpoints, drug regimens and trial duration.


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ADMINISTRATION

Presentation of Clinical Efficacy

Christopher Kadoorie, PhD
Statistical Reviewer
Division of Biometrics IV

Antimicrobial Drugs Advisory Committee Meeting
November 16, 2017

Outline

- Overview
- Study Design
- Demographics
- Findings
- Additional Analyses
- Points to Consider
- Summary

Overview: Applicant's Development Plan

- Study 12429 (Phase 2, CF)
  - ➢8 week study (4 weeks on/ 4 weeks off treatment)
  - ➢Cipro DPI 32.5mg (N=93) or 48.75mg (N=93) BID vs. Matching Placebo (N=100)
  - ➢Neither Cipro arm showed FEV1 improvement at 4 weeks (primary endpoint)

- Study 12965 (Phase 2, NCFB)
  - ➢4 week study with 8 week follow-up
  - ➢Cipro 32.5 mg DPI, BID (N=60) vs. Matching Placebo (N=64)
  - ➢Cipro showed reduction in total bacterial load at 4 weeks (EOT) , $p < 0.001$

- Study 15625, RESPIRE 1 (Phase 3, NCFB) (N=416)
  - ➢May 2013 to March 2016

- Study 15626, RESPIRE 2 (Phase 3, NCFB) (N=521)
  - ➢April 2014 to October 2016

Study Design- RESPIRE 1 & 2

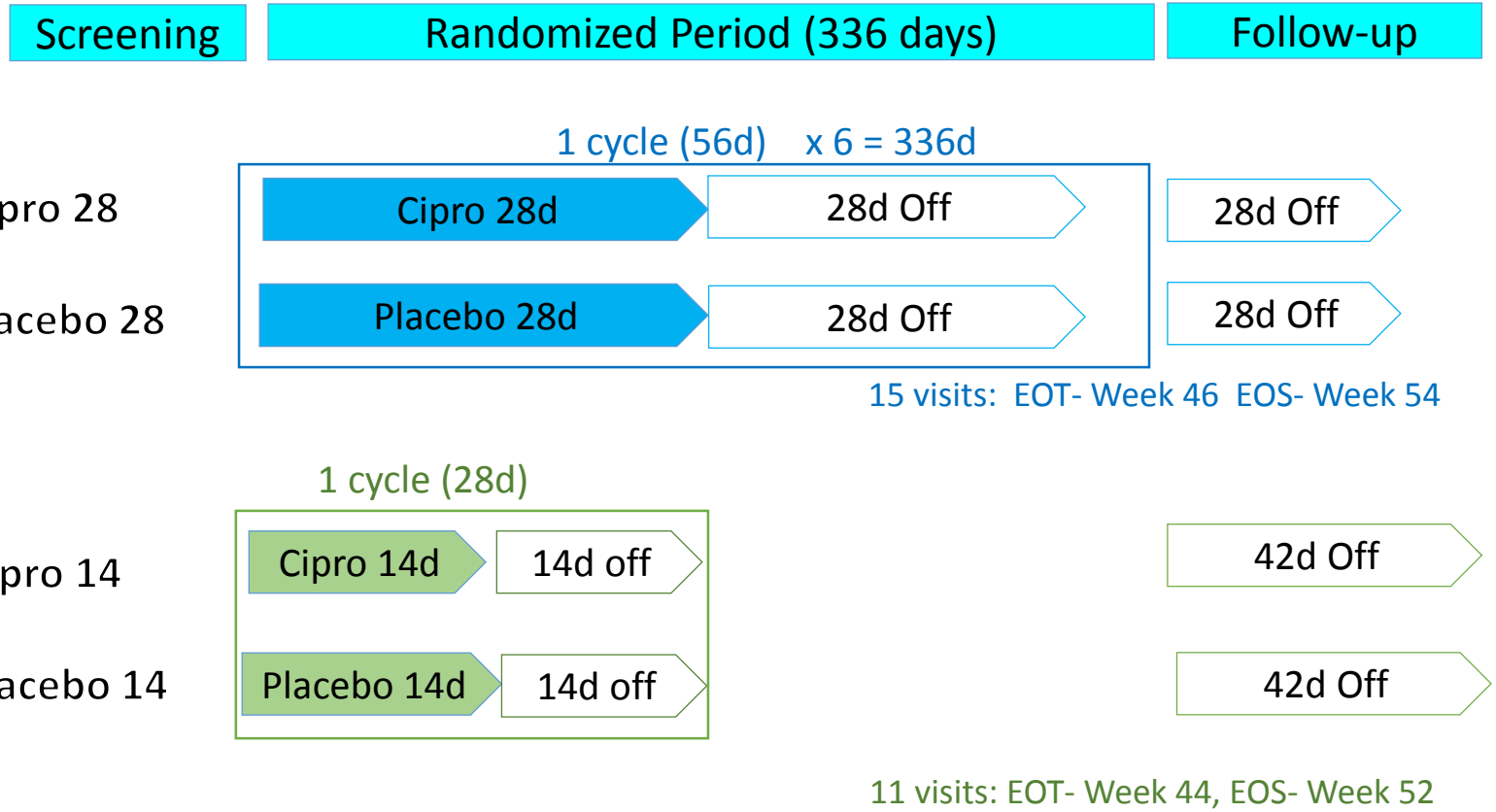
- Phase 3, randomized, double-blind, placebo-controlled, multi-center trials with nearly identical designs

- Key inclusion criteria:
  - Age ≥ 18 years
  - Diagnosis of NCFB (non-CF idiopathic or post-infectious bronchiectasis by CT scan including 2 or more lobes and dilated airways)
  - Positive sputum culture for pre-defined pathogen
  - FEV1 % predicted ≥ 30% and < 90%
  - 2 or more exacerbations in previous 12 months
  - Stable regimen of standard treatment (bronchodilators, anticholinergics, inhaled corticosteroids, mucolytics) or macrolides

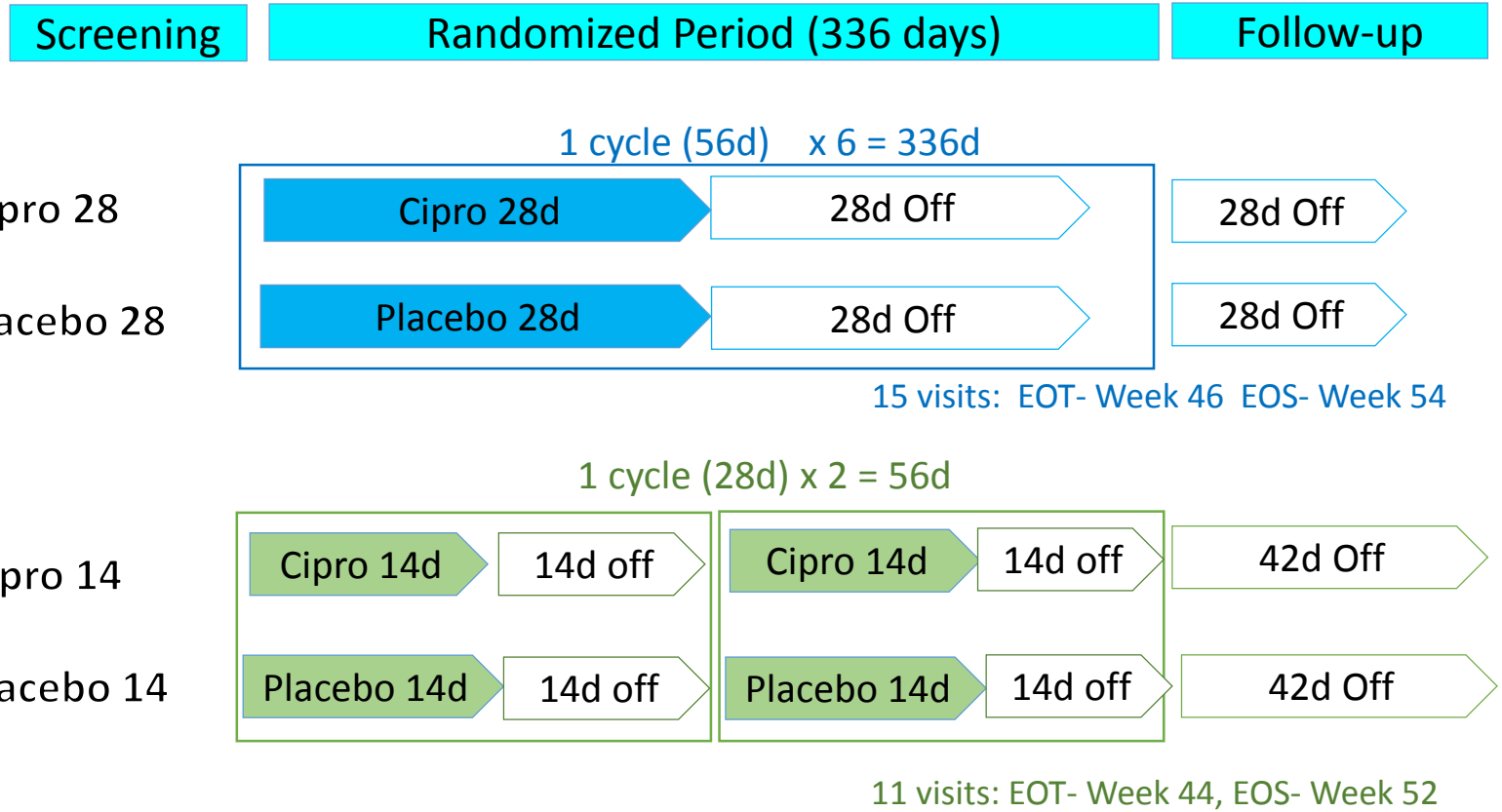
Study Design- RESPIRE 1 & 2 (Cont.)

- Randomization 2:1 (Cipro vs. Placebo) to one of four arms:
  - Cipro 28 (28 days on/28 days off Cipro therapy, 32.5mg BID)
  - Placebo 28 (matching placebo)
  - Cipro 14 (14 days on/14 days off Cipro therapy, 32.5mg BID)
  - Placebo 14 (matching placebo)
- Study period of 336 days (48 weeks) plus follow-up
- Stratification by: presence of *P.aeruginosa*, geographical region and macrolide use at baseline
- Placebo 28 and Placebo 14 pooled in analyses based on a pre-test

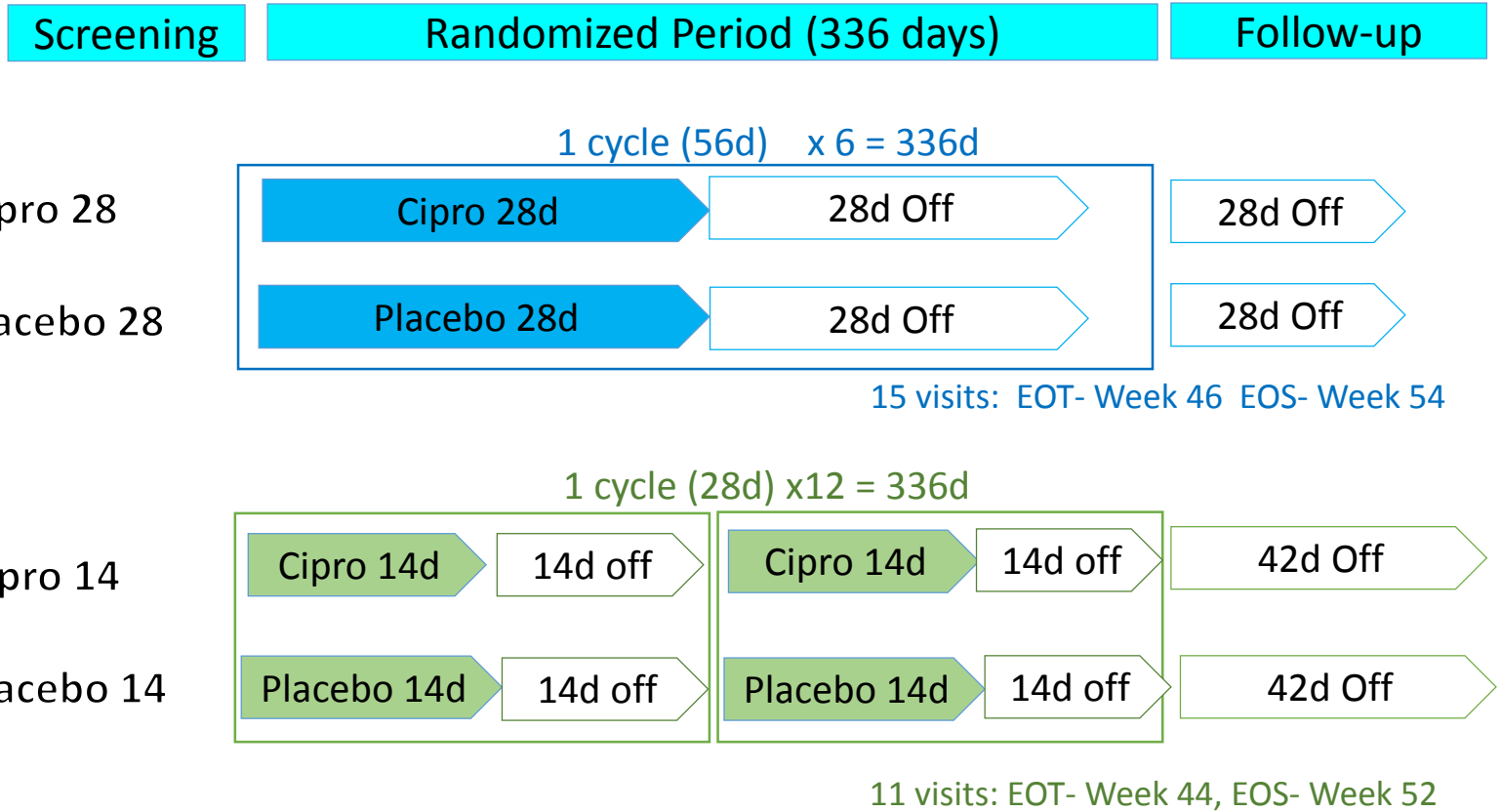
Study Design- RESPIRE 1 & 2



Study Design- RESPIRE 1 & 2



Study Design- RESPIRE 1 & 2



Study Design- Endpoints

- Primary- Time to first exacerbation, TFE

Exacerbation: systemic antibiotic use, fever or malaise/fatigue, worsening of ≥ 3 signs/symptoms

- Key Secondary- Frequency of exacerbations, FOE

Exacerbation: same as above

- FOE (≥ 1 sign/symptom)

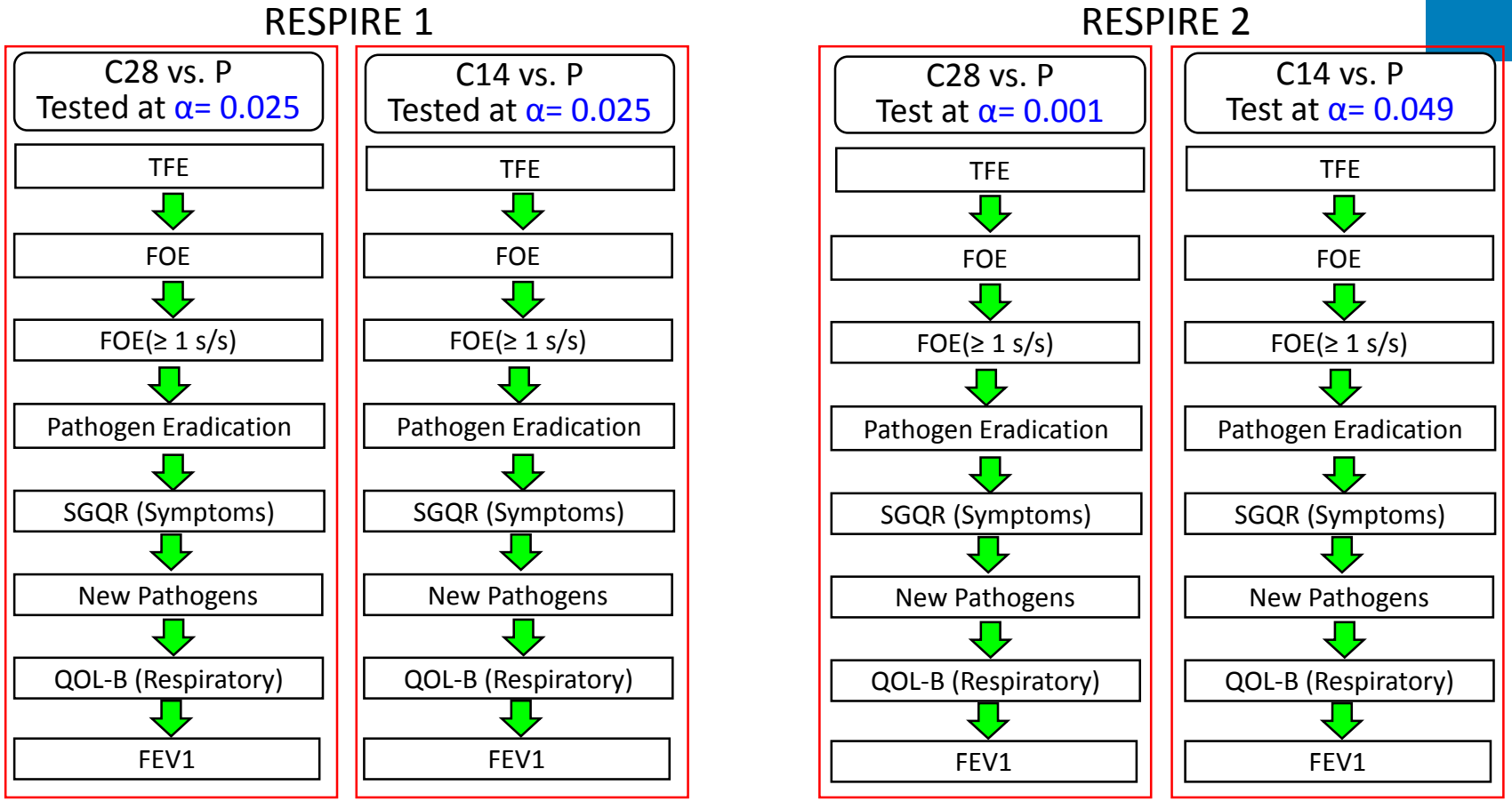
Exacerbation: systemic antibiotic use and worsening of ≥ 1 sign/symptom

- Other Secondary Endpoints (changes from baseline to EOT)
  - Pathogen eradication
  - St. George's Questionnaire-Respiratory, SGQR (Symptoms Component)
  - Occurrence of new pathogens not present at baseline
  - Quality of Life-bronchiectasis, QOL-B (Symptoms Domain Score)
  - FEV1

Hierarchical Statistical Testing- RESPIRE 1 & 2

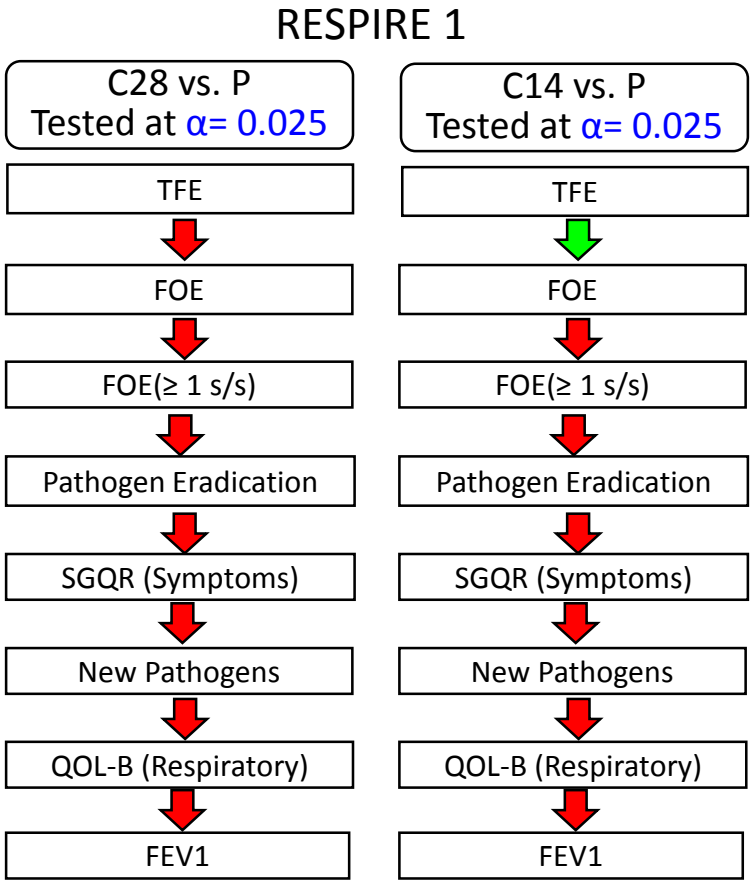
- Cipro 28 and Cipro 14 were each **statistically** tested against Pooled Placebo under separate hierarchies in each trial
- Hierarchies were identical except for the α-levels used for testing
- Under each hierarchy, the primary endpoint (TFE) is first tested followed by the secondary endpoints (as ordered in previous slide)
- Statistical testing stops after the first non-significant finding, **all other testing is exploratory**

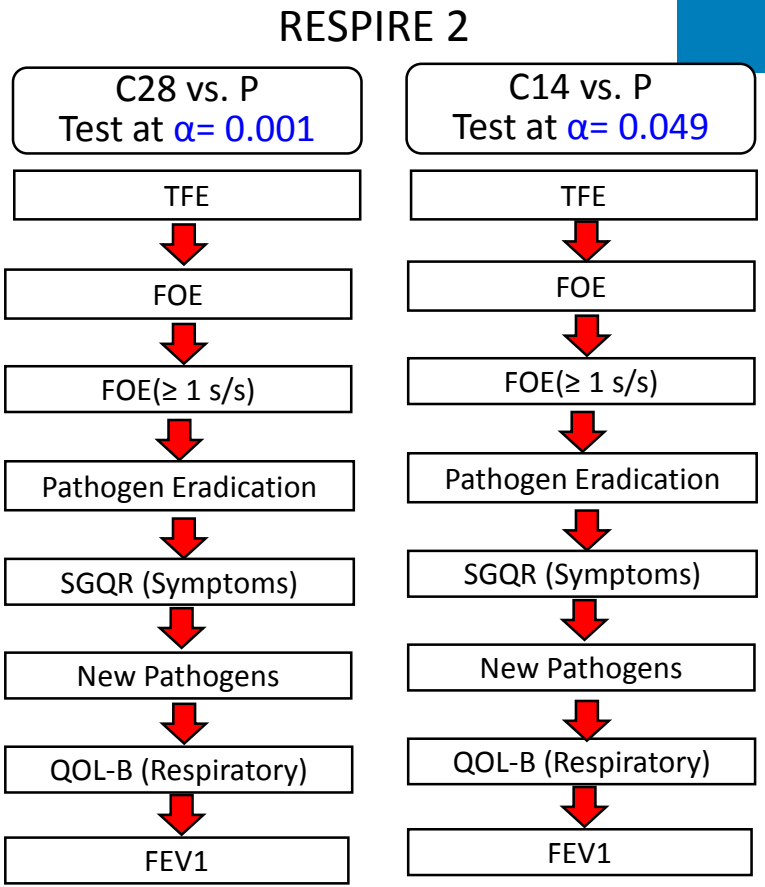
Hierarchical Statistical Testing



C28- Cipro 28, C14- Cipro 14, P-Pooled Placebo

Hierarchical Statistical Testing: Findings





C28- Cipro 28, C14- Cipro 14, P-Pooled Placebo

Statistical Methods

- Primary and secondary analyses used all randomized subjects adjusting for presence of PA, geographical region, macrolide use at baseline

- TFE tested using a Cox Proportional Hazards Model

- FOE tested using:
  - Poisson regression: Pre-specified extrapolation to estimate number of exacerbations among dropouts (RESPIRE 1)
  - Poisson regression: log (time in study) as an offset variable (RESPIRE 2)

- Other secondary analyses used CMH (Cochran-Mantel-Haenszel) (CMH) or ANCOVA (Analysis of covariance) testing without imputation for missing data

Demographics

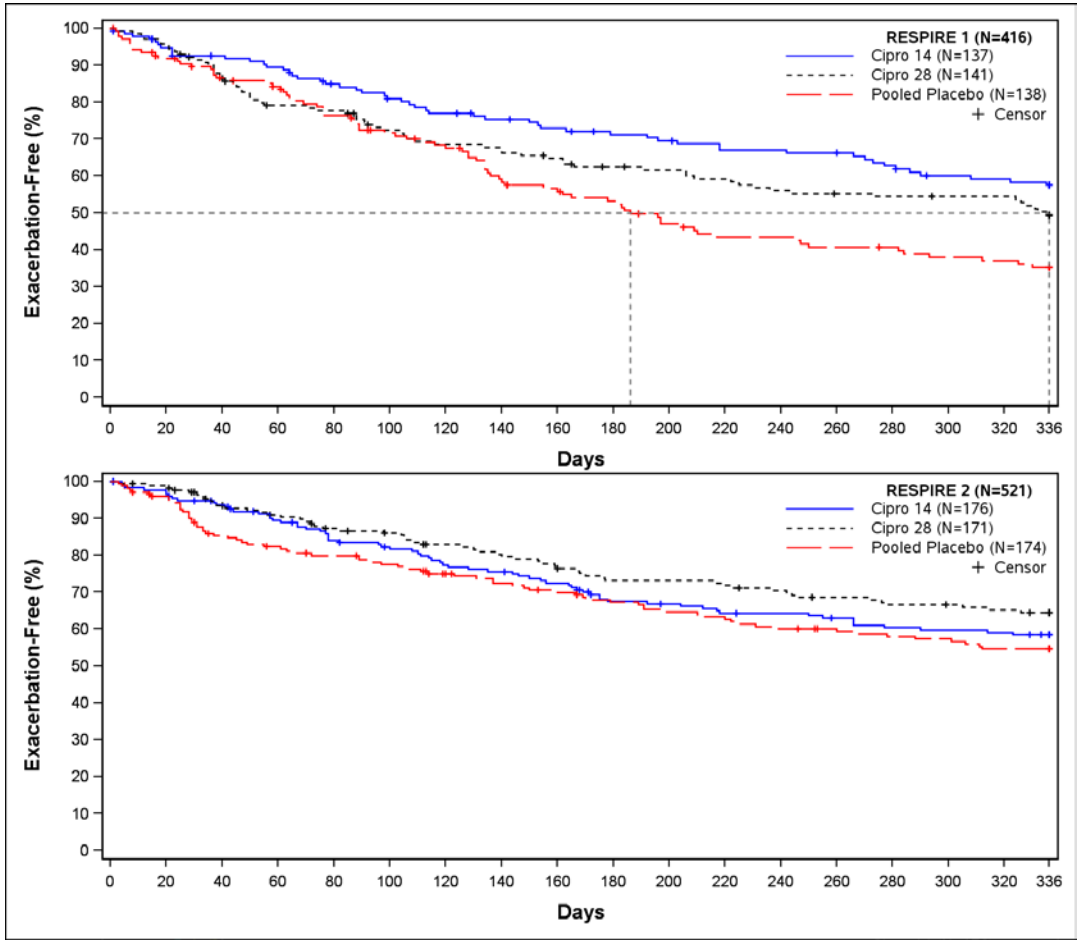
	RESPIRE 1 (N=416)			RESPIRE 2 (N=521)		
	C28	**C14**	**P**	**C28**	**C14**	**P**
N	141	137	138	171	176	174
Age (yrs), mean (median)	64 (66)	65 (67)	65 (67)	59 (61)	60 (62)	61 (62)
Gender, n (%)						
Male	40 (28)	49 (36)	42 (30)	79 (46)	80 (46)	60 (35)
Female	101 (72)	88 (64)	96 (70)	92 (54)	96 (55)	114 (66)
Race, n (%)						
White	124 (88)	115 (84)	124 (90)	135 (79)	133 (76)	135 (78)
Black	1 (1)	2 (2)	1 (1)	2 (1)	2 (1)	1 (1)
Asian	12 (9)	12 (9)	10 (7)	33 (19)	41 (23)	37 (21)
Other/Not reported	4 (3)	8 (6)	3 (2)	1 (1)	0	1 (1)
Region, n (%)						
Europe	77 (55)	77 (56)	76 (55)	119 (70)	118 (70)	119 (68)
US/Canada	14 (10)	14 (10)	16 (12)	5 (3)	5 (3)	6 (3)
Asia	12 (9)	11 (8)	10 (7)	33 (19)	39 (22)	36 (21)
L.America/Aus/NZ	38 (27)	35 (26)	36 (26)	14 (8)	14 (8)	13 (8)
Chronic Macrolide Use, n (%)						
Yes	22 (16)	25 (18)	21 (15)	14 (8)	13 (7)	5 (9)
No	119 (84)	112 (82)	117 (85)	157 (92)	163 (93)	159 (91)
P.aeruginosa, n (%)						
Positive	83 (59)	83 (61)	86 (62)	99 (58)	107 (61)	109 (63)
Negative	58 (41)	54 (39)	52 (38)	72 (41)	69 (39)	65 (37)
FEV1 % Predicted, n (%)						
< 50%	44 (31)	41 (30)	40 (29)	65 (38)	78 (44)	75 (43)
≥ 50%	97 (69)	96 (70)	98 (71)	106 (62)	98 (56)	99 (57)

Time to First Exacerbation (Primary Endpoint)

	C28 vs. P	C14 vs. P
RESPIRE 1		
Hazard Ratio (HR):	0.73 (97.5% CI: 0.50, 1.07)	0.53 (97.5% CI: 0.36, 0.80)
P-value	p=0.065 > 0.025 **(NS)**	p=0.0005 < 0.025 **(S)**
Percent with PE, Δ:	47.5% vs. 57.2% , -9.7%	38.7% vs. 57.2%, -18.6%
RESPIRE 2		
HR:	0.71 (99.9% CI: 0.39, 1.27)	0.87 (95.1% CI: 0.62, 1.21)
P-value	p=0.051 > 0.001 **(NS)**	p=0.397 > 0.049 **(NS)**
Percent with PE, Δ:	32.7% vs. 42.0%, -9.2%	38.6% vs. 42.0%, -3.3%

C28- Cipro 28, C14- Cipro 14, P- Pooled Placebo, NS- Not statistically significant, S- Statistically Significant, PE- Pulmonary Exacerbation, Δ - treatment difference (Cipro – Pooled Placebo),

Time to First Exacerbation (Primary Endpoint)

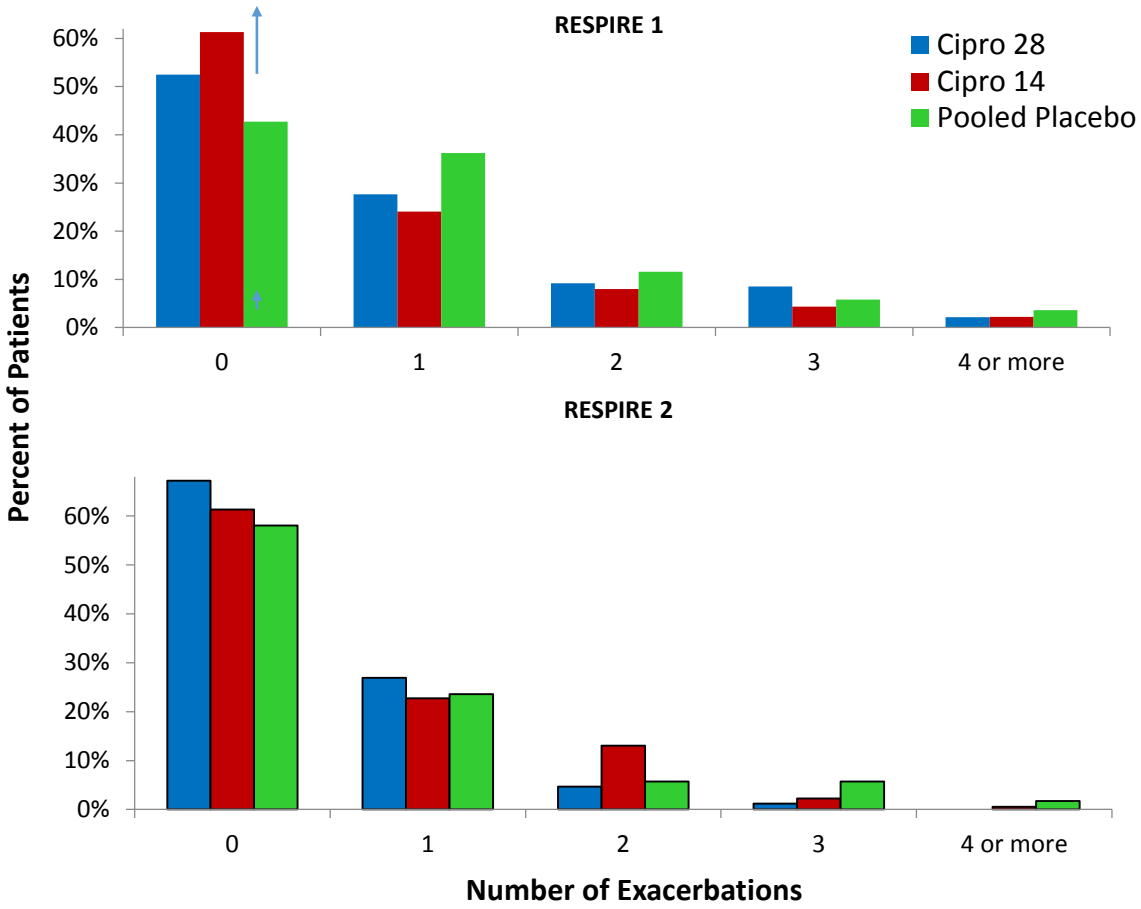


Frequency of Exacerbations

	FOE (key secondary endpoint)		FOE (≥ 1 s/s) (third endpoint tested)	
	C28 vs. P	**C14 vs. P**	**C28 vs. P**	**C14 vs. P**
RESPIRE 1				
IRR (97.5% CI)	0.86 (0.63, 1.18)	0.73 (0.52, 1.03)	0.87 (0.66, 1.16)	0.74 (0.55, 1.00)
P-value	p=0.294	p=0.038 > 0.025 **(NS)**	p= 0.276	p=0.023
Mean PEs:	0.82 vs. 0.91	0.63 vs. 0.91	1.14 vs. 1.22	0.89 vs. 1.22
RESPIRE 2				
IRR (99.9%/95.1%)	0.56 (0.33, 0.95)	0.81 (0.61, 1.08)	0.63 (0.39, 1.01)	0.84 (0.64, 1.09)
P-value	p=0.0003	p=0.147	p=0.001	p=0.181
Mean PEs:	0.40 vs. 0.70	0.58 vs. 0.70	0.54 vs. 0.85	0.72 vs. 0.85

IRR- Incidence Rate Ratio, PE- Pulmonary Exacerbation, s/s- sign/symptom, IRRs < 1 favor Cipro

Distribution of Patients by FOE



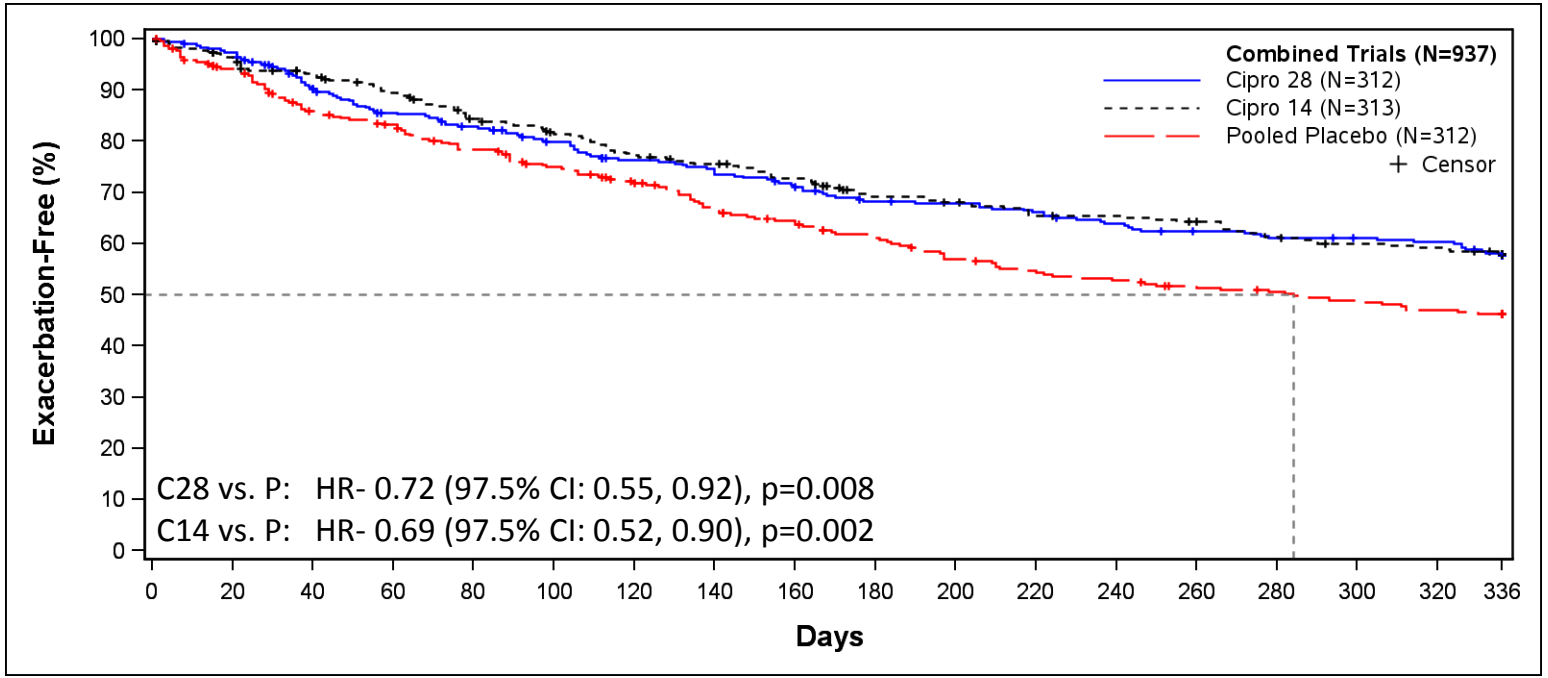
Other Secondary Endpoints

	RESPIRE 1		RESPIRE 2	
	C28 vs. P	**C14 vs. P**	**C28 vs. P**	**C14 vs. P**
Pathogen Eradication				
Yes, %	24.1 vs. 16.7	28.5 vs. 16.7	31.6 vs. 31.6	35.8 vs. 31.6
Odds ratio *(>1 better)*	1.16	2.35	1.16	1.34
P-value	p=0.294	p=0.018	p=0.602	p=0.316
SGRQ Symptoms Domain				
Change from BL:	-8.2 vs. -0.8	-7.2 vs. -0.8	-8.9 vs. -7.3	-9.0 vs. -7.3
LS Mean difference: *(<0 better)*	-5.21	-7.59	-1.44	-1.40
P-value	p=0.064	p=0.009	p=0.530	p=0.545
Occurrence of New Pathogens				
Yes, %:	3.5 vs. 8.0	5.1 vs. 8.0	4.1 vs. 10.3	4.0 vs. 10.3
Odds Ratio: (*<1 better*)	0.36	0.56	0.41	0.29
P-value	p=0.058	p=0.257	p=0.053	p=0.007
QOL-B Respiratory Symptoms				
Change from BL:	7.7 vs. 6.4	6.7 vs. 6.4	11.6 vs. 9.0	10.9 vs. 9.0
LS Mean Difference: *(>0 better)*	1.18	2.47	2.75	2.22
P-value	p=0.619	p=0.322	p=0.234	p=0.325
FEV1 (L)				
Change from BL:	-0.01 vs. 0.02	-0.03 vs. 0.02	0.04 vs. 0.0	-0.04 vs. 0.0
LS Mean Difference: *(>0 better)*	-0.03	-0.05	0.04	-0.04
P-value	p=0.370	p=0.194	p=0.310	p=0.266

Additional Analyses

- Combined Trials (RESPIRE 1 and RESPIRE 2)
  - Time to First Exacerbation
  - Frequency of Exacerbations
- Matched Comparisons Not Pooling Placebo Arms
  - C28 vs. P28
  - C14 vs. P14
- Durations of Exacerbations (SAEs)

Combined Trials: Time to First Exacerbation

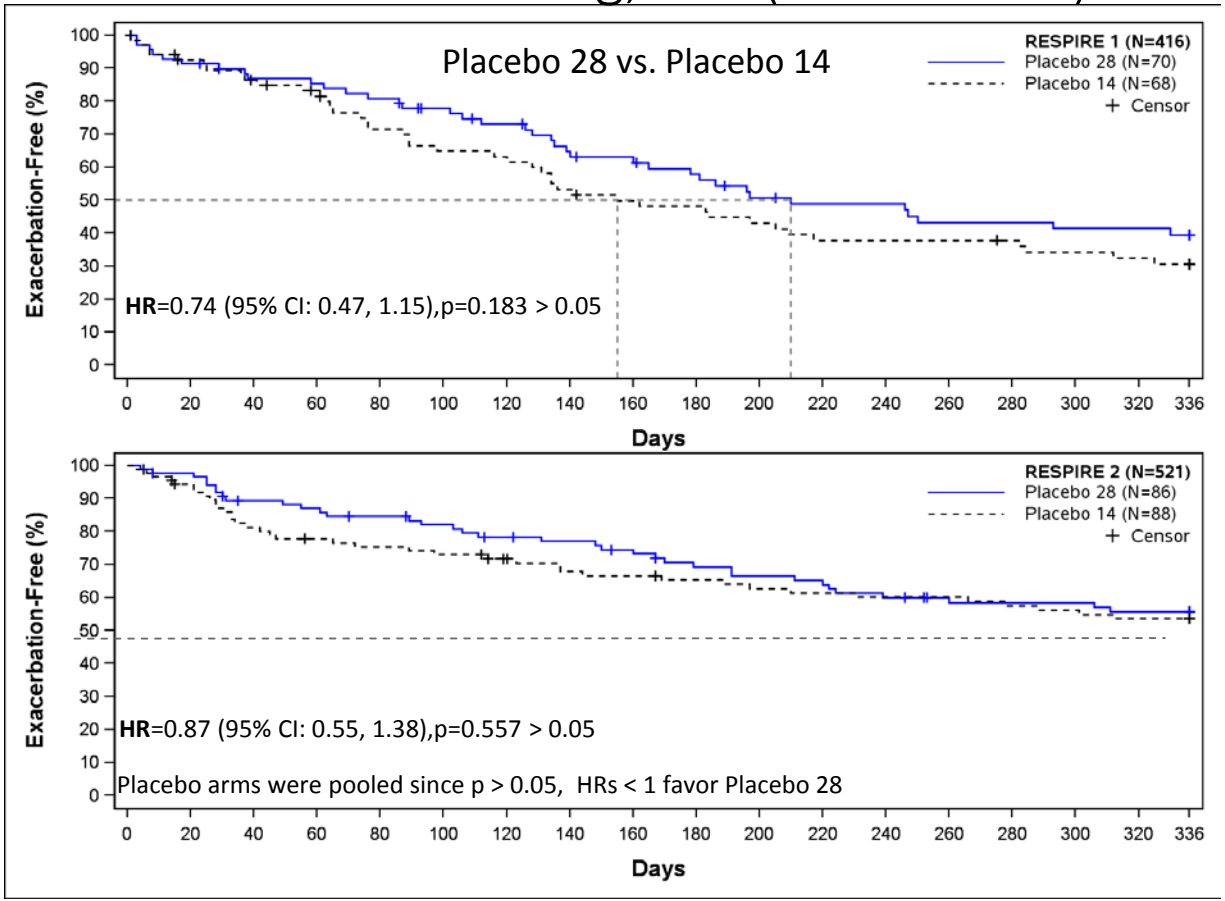


Combined Trials: Frequency of Exacerbations

	FOE	
	C28 vs. P	**C14 vs. P**
IRR (97.5% CI)	0.72 (0.56, 0.91)	0.75 (0.59, 0.95)
P-value	p=0.002	p=0.007
Mean PEs :	0.60 vs. 0.79	0.59 vs. 0.79

	FOE (≥ 1 s/s)	
	C28 vs. P	**C14 vs. P**
IRR (97.5% CI)	0.77 (0.62, 0.96)	0.77 (0.62, 0.96)
P-value	p=0.006	p=0.008
Mean PEs :	0.81 vs. 1.02	0.81 vs. 1.02

Pre-test for Pooling, TFE (P28 vs. P14)



Matched Comparisons (Not Pooling Placebo Arms)

- Although the placebo arms were pooled in the analyses based on a non-significant pre-test, possible differences suggested further analyses
- Other factors also suggest further analyses
  - Differences in the number and timing of visits
  - Differences in the treatment schedule
  - Lack of blinding between the 28 and 14 day arms
- Methodologies followed those of the individual trials
- Overall conclusions based on these analyses were similar as analyses with pooling placebos:
  - TFE was significant only in RESPIRE 1 for the 14-day cycle
  - TFE was not significant for the 28-day cycle in either trial

Duration of Exacerbations (SAEs)

- Interpretation of TFE and FOE findings may be unclear if one treatment has exacerbations of longer duration.
  - May indicate more severe exacerbations
  - Can decrease a patient's risk interval for FOE

- The RESPIRE trials did not record the resolution date of exacerbations, therefore duration of exacerbations could not be estimated

- However, durations of exacerbation classified as serious adverse events (SAEs) were recorded (133 of 610 (21%) of exacerbations)

Duration of Exacerbations (SAEs)

	Cipro 28	Cipro 14	Pooled Placebo
RESPIRE 1	N=141	N=137	N=138
Exac. SAE (%)	21 (14.9)	9 (6.6)	18 (13.0)
Duration			
Mean± sd (days)	10.4 ± 8.1	7.7 ± 7.5	18.8 ± 21.8
Median (IQR)	8.0 (6.0-11.0)	5.0 (3.0-7.0)	10.5 (6.0-25.0)
RESPIRE 2	N=171	N=176	N=174
Exac. SAE (%)	20 (11.7)	30 (17.0)	35 (20.1)
Duration			
Mean± sd	14.4 ± 7.6	12.4 ± 7.7	14.7 ± 11.1
Median (IQR)	13.5 (8.5-19.5)	10.0 (8.0-15.0)	11.0 (9.0-18.0)

Source: Partially Adapted from Applicant Table, sd - standard deviation, IQR- Interquartile range

Points to Consider

- Limitations in Endpoints Used
  - Time to first exacerbation may not be an appropriate measure of efficacy in a chronic setting
  - Frequency of exacerbations can be influenced by a small subset of patients. Risk intervals are unclear.
  - Clinical relevance of other secondary endpoints is not clear.
- Magnitude of the treatment effect (true placebo effect is unknown, unclear if inhaling vehicle has possible negative effect)
- Limited effects in non-exacerbation related endpoints (e.g. FEV1)
- Longer term efficacy unknown (e.g. resistance over time)

Summary

- Findings generally trended towards Cipro benefit, but lacked consistency:
  - Among common endpoints between trials
  - Among related endpoints within the same trial
  - Between Cipro 28 and Cipro 14 within the same trial

- Combined analyses, though exploratory, showed consistency in treatment effects for Cipro 28 and Cipro 14 for both TFE and FOE
  - Mutually supportive evidence
  - Type I error concerns with these findings were mitigated by the small observed p-values
  - However, size of treatment effect should be considered

Thank You

Presentation of Clinical Safety

Peter Kim, MD, MS
Medical Officer
Division of Anti-Infective Products

NDA 209367
Antimicrobial Drugs Advisory Committee Meeting
November 16, 2017

Outline

- Safety Assessments
  - Phase 1
  - Phase 2
  - Phase 3
- Conclusions

Phase 1 Safety

- Phase 1 studies
  - 195 participants [18 healthy subjects and 177 patients (CF, COPD, NCFB)]
    - 164 healthy subjects and patients received ≥1 dose of ciprofloxacin dry powder for inhalation (Cipro DPI) ranging from 1 to 13 days
      - » Common treatment-emergent adverse events (TEAEs) included: product taste abnormal, dysgeusia, headache, bronchospasm, dyspnea, cough, and nasopharyngitis

CF=cystic fibrosis, COPD=chronic obstructive pulmonary disease, NCFB=non-cystic fibrosis bronchiectasis

Phase 2 Safety (1)

- Study 12429 in CF patients
  - 93 exposed to Cipro DPI 32.5 mg BID for 28 days,
  - 93 exposed to Cipro DPI 48.75 mg BID for 28 days,
  - 100 received matching placebo powder
    - Based on the higher incidence of adverse events (AEs), serious adverse events (SAEs), and AEs leading to withdrawal in the 48.75 mg regimen and comparable bacterial load reductions in sputum, Bayer chose to continue development with 32.5 mg regimen

BID=twice a day, mg=milligrams

Phase 2 Safety (2)

- Study 12965 in NCFB patients
  - 60 received Cipro DPI 32.5 mg BID for 28 days
  - 64 received matching placebo powder
    - Similar numbers in each group experienced TEAEs, SAEs, and AEs leading to withdrawal
    - Common TEAEs in the Cipro DPI group: product taste abnormal (13.3%), bronchiectasis (11.7%), dysgeusia (6.7%), headache (6.7%), nausea (5%), and bronchospasm (5%)

Phase 3 Safety

- Two Phase 3 trials: RESPIRE 1 and 2
  - 933 subjects included in the pooled Phase 3 safety population
    - 622 subjects received at least one dose of Cipro DPI 32.5 mg
      - 310 subjects received 14-day Cipro DPI regimen
      - 312 subjects received 28-day Cipro DPI regimen
    - 311 subjects received at least one dose of placebo powder
      - 156 received the 14-day placebo regimen
      - 155 received the 28-day placebo regimen

Summary of Pooled Phase 3 Safety

Type of Treatment-Emergent AE (TEAE)	Cipro DPI 14 days on/off	Placebo 14 days on/off	Cipro DPI 28 days on/off	Placebo 28 days on/off
	N=310	**N=156**	**N=312**	**N=155**
	n (%)	n (%)	n (%)	n (%)
AEs	239 (77.1)	113 (72.4)	204 (65.4)	117 (75.5)
Serious AEs	68 (21.9)	45 (28.9)	56 (18)	28 (18.1)
Serious non-fatal AEs	65 (21)	42 (26.9)	55 (17.6)	28 (18.1)
Fatal AEs	4 (1.3)	4 (2.6)	6 (1.9)	1 (0.6)

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.

Phase 3 TEAEs Leading to Premature Treatment Discontinuation

Type of TEAE leading to premature treatment discontinuation	Cipro 14 days on/off	Placebo 14 days on/off	Cipro 28 days on/off	Placebo 28 days on/off
	N=310	N=156	N=312	N=155
	n (%)	n (%)	n (%)	n (%)
Any TEAE	27 (8.7)	17 (10.9)	20 (6.4)	12 (7.7)
Any SAE	5 (1.6)	6 (3.9)	6 (1.9)	2 (1.3)

Modified from Applicant's Table 2-2, page 35 of the SCS, submitted 6/30/17. Frequency data are based on the number of subjects with the event.

- Examples of TEAEs leading to treatment discontinuation possibly related to Cipro DPI based on review of case report forms and narratives included:
  - Dyspnea, dysgeusia, ageusia, headache, bronchospasm, hemoptysis, cough, fatigue, malaise/weakness, asthenia, insomnia/sleep disorder, neck stiffness, muscle twitching, tendon discomfort, chest tightness/discomfort, rash, and retinal vasculitis

Serious Non-fatal TEAEs in ≥3 Subjects in a Cipro DPI Group in Phase 3 Trials

Dictionary Derived Term	Cipro DPI 14 days on/off	Placebo 14 days on/off	Cipro DPI 28 days on/off	Placebo 28 days on/off
Total No. of Subjects per Treatment Group	310 (100.00%)	156 (100.00%)	312 (100.00%)	155 (100.00%)
Subjects with nonfatal SAEs	65 (20.97%)	42 (26.92%)	55 (17.63%)	28 (18.06%)
Bronchiectasis	31 (10.00%)	20 (12.82%)	33 (10.58%)	16 (10.32%)
Pneumonia	6 (1.94%)	4 (2.56%)	6 (1.92%)	2 (1.29%)
Hemoptysis	4 (1.29%)	4 (2.56%)	4 (1.28%)	2 (1.29%)
Infective exacerbation of bronchiectasis	4 (1.29%)	3 (1.92%)	2 (0.64%)	0 (0.00%)
Chronic obstructive pulmonary disease	3 (0.97%)	0 (0.00%)	0 (0.00%)	1 (0.65%)

Deaths in Phase 3 Trials

Trial	Cipro 14 days on/off	Cipro 28 days on/off	Pooled Placebo
	4/310 (1.3%)	**6/312 (1.9%)**	**5/311 (1.6%)**
RESPIRE 1 (6 deaths)	n=1	n=2	n=3
	Aspiration pneumonia	Pneumonia	Pneumonia
		Cor pulmonale	Pulmonary hemorrhage
			Complications of transplant surgery
RESPIRE 2 (9 deaths)	n=3	n=4	n=2
	Bronchiectasis	Bronchiectasis (n=2)	Bronchiectasis (n=2)
	Gastrointestinal hemorrhage	Cor pulmonale	
	Esophageal carcinoma	Congestive cardiomyopathy	

Phase 3 TEAEs with Higher Incidence in Pooled Cipro DPI group versus Pooled Placebo

- Taste Disorders
- Dyspnea
- Headache
- Fatigue
- Malaise
- Oral Candidiasis
- Dizziness
- Paresthesias
- Arthralgia
- Mouth ulceration
- Aspergillus Test Positive

Phase 3 TEAEs Most Likely Due to Inhaling a Dry Powder

- The following AEs occurred at similar rates in both Cipro DPI and placebo groups; however, it is plausible that inhaling the dry powder caused irritation of the respiratory tract resulting in these AEs:
  - Hemoptysis
  - Cough
  - Bronchospasm
- Without a comparator arm that did not receive any dry powder, it is difficult to ascertain the incidence of adverse reactions due solely to inhaling the dry powder

Evaluation for Fluoroquinolone Class Effects

- Systemic exposure to Cipro DPI is at least 10-fold lower than following orally or intravenously administered ciprofloxacin at approved doses
- AEs associated with quinolone class effects were not observed to a significant extent in the Phase 3 trials
  - For example, the 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
- Of note, a subject in RESPIRE 1 who received the Cipro 14-day regimen, and who had no prior history of tendon disorder, experienced left Achilles heel tendinopathy of moderate intensity which the study investigator deemed related to study therapy

Number of subjects with treatment-emergent ciprofloxacin-resistant pathogens at any point post-baseline in RESPIRE 1 and 2

Organism	RESPIRE 1			RESPIRE 2		
	Cipro DPI 28 on/off	**Cipro DPI 14 on/off**	**Pooled Placebo**	**Cipro DPI 28 on/off**	**Cipro DPI 14 on/off**	**Pooled Placebo**
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
P. aeruginosa	**30/61 (49.2%)**	**23/62 (37.1%)**	**15/66 (22.7%)**	**23/76 (30.3%)**	**34/83 (40.9%)**	**7/86 (8.1%)**
H. influenzae	4 /34 (11.8%)	2/34 (5.9%)	0/42 (0)	3/38 (7.9%)	1/24 (4.2%)	0/27 (0)
S. aureus	3/26 (11.5%)	1/18 (5.6%)	2/26 (7.7%)	2/40 (5%)	0/40 (0)	3/45 (6.6%)

n=number of subjects with the indicated pathogen susceptible at baseline who then had a resistant isolate cultured at any point post baseline

N=number of subjects with the indicated pathogen susceptible at baseline

Number of subjects with treatment-emergent ciprofloxacin-resistant *P. aeruginosa* at the End of Study Visit in RESPIRE 1 and 2

Organism	RESPIRE 1			RESPIRE 2		
	Cipro DPI 28 on/off	Cipro DPI 14 on/off	Pooled Placebo	Cipro DPI 28 on/off	Cipro DPI 14 on/off	Pooled Placebo
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
P. aeruginosa	**4/61 (6.6%)**	**5/62 (8.1%)**	**2/66 (3%)**	**6/76 (7.9%)**	**8/83 (9.6%)**	**2/86 (2.3%)**

n=number of subjects with *P. aeruginosa* susceptible at baseline who then had a resistant *P. aeruginosa* at the End of Study visit

N=number of subjects with *P. aeruginosa* susceptible at baseline

*The End of Study visit occurred 8 weeks after the last dose of study medication

Revised 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%)~~ 1 (0.6%)	0
M. catarrhalis	0	0	0	0	0	0
P. aeruginosa	30 (21.3)	23 (16.8)	15 (10.9)	~~53 (30.9)~~ 23 (13.5)	~~76 (43.2)~~ 34 (19.3)	~~38 (21.8)~~ 7 (4.0)
S. maltophilia	0	1 (0.7)	0	~~9 (5.2)~~ 0	~~11 (62.5)~~ 1 (0.6)	~~5 (2.9)~~ 0
B. cepacia	0	0	0	~~1 (0.6)~~ 0	~~1 (0.6)~~ 0	~~3 (1.7)~~ 0
S. aureus	3 (2.1)	1 (0.7)	2 (1.4)	~~5 (2.9)~~ 2 (1.2)	~~6 (3.4)~~ 0	~~7 (4.0)~~ 3 (1.7)
S. pneumoniae	1 (0.7)	1 (0.7)	0	~~1 (0.6)~~ 0	~~5 (2.8)~~ 1 (0.6%)	~~1 (0.6)~~ 0

Safety Conclusions

- In Phase 3 trials, there were similar rates of TEAEs resulting in death, TEAEs leading to premature treatment discontinuation, nonfatal SAEs, and common TEAEs in Cipro DPI and placebo groups
- Majority of TEAEs appeared to be related to local effects of Cipro DPI: taste disorders, dyspnea, bronchospasm, hemoptysis, cough, etc.
- Low incidence of systemic effects
- 2 to 4 fold more subjects treated with Cipro DPI vs. pooled placebo had treatment-emergent ciprofloxacin-resistant *P. aeruginosa* cultured at any point post-baseline and notably at 2 months after the last dose of study medication
- Unknown whether exposure beyond one year may lead to additional safety concerns, increased resistance to fluoroquinolones, or result in reduced treatment effect
- Without a comparator arm that did not receive any dry powder, it is difficult to ascertain incidence of adverse reactions due solely to inhaling the dry powder


FDA
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Summary Presentation

Thomas Smith, MD
Division of Anti-Infective Products

Antimicrobial Drugs Advisory Committee Meeting
November 16, 2017

NCFB Clinical Trials

- There are no approved therapies for prevention or management of NCFB exacerbations.
- We recognize the need for safe and effective therapies for patients with NCFB.
- Studies of other 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.*
- There are uncertainties regarding the duration of treatment, frequency of administration, and appropriate endpoints to use in clinical trials of NCFB.

*Publications referenced in FDA briefing document

Overall Observations

- In RESPIRE 1, only the ciprofloxacin 14-day regimen had a statistically significant finding for the primary endpoint of time to first exacerbation; this treatment effect was not replicated in RESPIRE 2
- The ciprofloxacin 28-day regimen did not meet the pre-specified primary endpoint in either trial
- Pooled analyses of primary and secondary endpoints are exploratory
- Lack of consistency of findings within and across trials
- Limitation of endpoints
  - TFE may not be the most appropriate endpoint for assessing long-term success (potentially lifelong use)
- Safety of Cipro DPI appears to be similar to pooled placebo powder
- Patients treated with Cipro DPI more likely to have treatment-emergent ciprofloxacin-resistant *P. aeruginosa* cultured at any point post-baseline

Uncertainties

- Clinical relevance of the observed treatment effects when risks such as adverse reactions and development of resistance are considered
- Durability of efficacy and safety findings over time (e.g., development of resistance)
- Long-term use of inhaled ciprofloxacin could limit the utility of systemic fluoroquinolones for treatment of severe bacterial exacerbations and pneumonia in NCFB patients

Question 1

- Has the applicant provided substantial evidence of the safety and effectiveness for the ciprofloxacin dry powder inhaler (DPI) 14-day regimen in delaying the time to first exacerbation after starting treatment?

a. If yes, please provide any recommendations concerning labeling.

b. If no, what additional studies/analyses are needed? Please discuss appropriate endpoints, drug regimens and trial duration.

Question 2

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

a. If yes, please provide any recommendations concerning labeling.

b. If no, what additional studies/analyses are needed? Please discuss endpoints, drug regimens and trial duration.