Ciprofloxacin DPI

For reduction of exacerbations in non-cystic fibrosis bronchiectasis (NCFB) adult patients (≥18 years of age) with respiratory bacterial pathogens

FDA Antimicrobial Drugs Advisory Committee
November 16, 2017

Introduction

Jana Napolitano, M.Sc.

Vice President, Regulatory Affairs Strategy
Pulmonology, Anti-Infectives and Ophthalmology
Bayer

Agenda

Introduction	**Jana Napolitano, MSc** Vice President, Regulatory Affairs Strategy – Pulmonology, Anti-Infectives and Ophthalmology, Bayer
Medical Landscape in Non-Cystic Fibrosis Bronchiectasis	**Pamela McShane, MD** Assistant Professor of Medicine Section of Pulmonary and Critical Care Medicine University of Chicago
Efficacy and Microbiology	**Jeff Alder, PhD** Senior Director, Global Clinical Development, Bayer
Safety	**Gesa Schomakers, MD** Head of Therapeutic Area Anti-Infectives, Pharmacovigilance Benefit-Risk Management, Bayer
Clinical Perspective on Ciprofloxacin DPI Safety & Effectiveness	**Timothy Aksamit, MD** Associate Professor of Medicine Pulmonary Disease and Critical Care Medicine Mayo Clinic, Rochester
Conclusion	**Jeff Alder, PhD** Senior Director, Global Clinical Development, Bayer

Additional Experts Available to the Committee

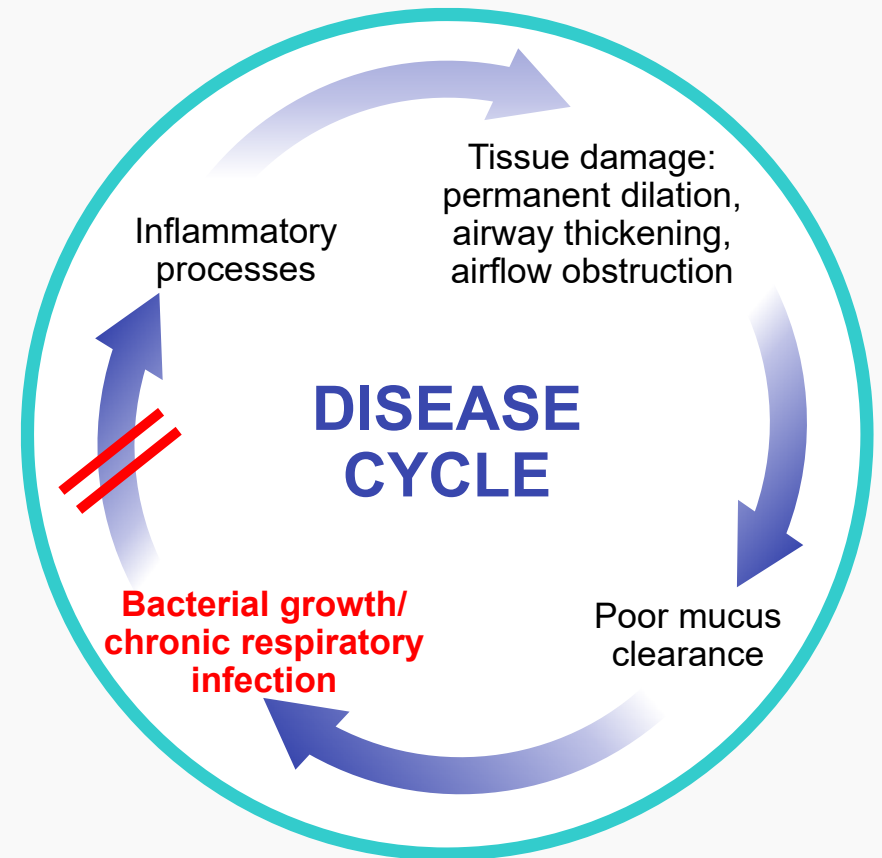|	
Anne O'Donnell, MD	Professor, Chief, Division of Pulmonary, Critical Care, and Sleep Medicine Medical Director, Sleep Disorders Center Georgetown University Medical Center
Kevin Winthrop, MD	Professor of Infectious Diseases, Ophthalmology, Public Health and Preventive Medicine Division of Infectious Diseases Oregon Health Science University
Tim Friede, PhD	Professor of Biostatistics University Medical Center Goettingen, Germany

Ciprofloxacin DPI – Proposed Indication

- **For reduction of exacerbations in non-cystic fibrosis bronchiectasis (NCFB) adult patients (≥18 years of age) with respiratory bacterial pathogens***

> ***There are no FDA approved therapies for this indication***

*Pseudomonas aeruginosa, Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Staphylococcus aureus, Stenotrophomonas maltophilia, Burkholderia cepacia

Ciprofloxacin DPI's Potential as an Important Treatment for NCFB

- **Non-cystic fibrosis bronchiectasis (NCFB)**
  - ‣ Severe, debilitating disease
  - ‣ Infections and exacerbations
  - ‣ Persistent disease cycle
- **Ciprofloxacin Dry Powder for Inhalation (DPI) aims to break cycle**
  - ‣ Reduced bacterial load
  - ‣ High antibiotic concentration at site of infection

DISEASE CYCLE

- Inflammatory processes
- Tissue damage: permanent dilation, airway thickening, airflow obstruction
- Poor mucus clearance
- Bacterial growth/ chronic respiratory infection

Ciprofloxacin is a Promising Antibiotic for NCFB

- **Systemically administered ciprofloxacin approved for multiple indications (US, 1987)**

- **Potent, broad spectrum bactericidal activity against Gram-negative and Gram-positive NCFB pathogens, including:**

  - *Pseudomonas aeruginosa*
  - *Haemophilus influenzae*
  - *Streptococcus pneumoniae*
  - *Moraxella catarrhalis*
  - *Staphylococcus aureus*

PulmoSphere™ Formulation Delivers High Targeted Concentrations of Ciprofloxacin

- **PulmoSphere™ small size and dispersion characteristics produces deep penetration into lung**

- **Achieves high ciprofloxacin concentrations in lung (site of infection) and low systemic levels**

- **Majority of the dose is deposited in lungs**

1 µm
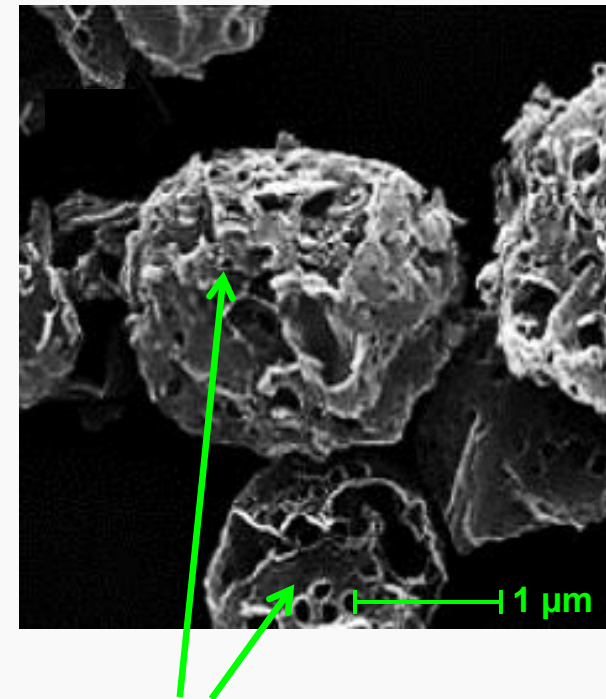
PulmoSphere™ ciprofloxacin particles

Inhaled Ciprofloxacin DPI

- **Dry powder formulation of ciprofloxacin in capsule for T-326 inhaler**

- **T-326 inhaler is component of FDA approved antibiotic drug-device combination, TOBI® Podhaler™**

puncture button

capsule chamber

mouthpiece

cap
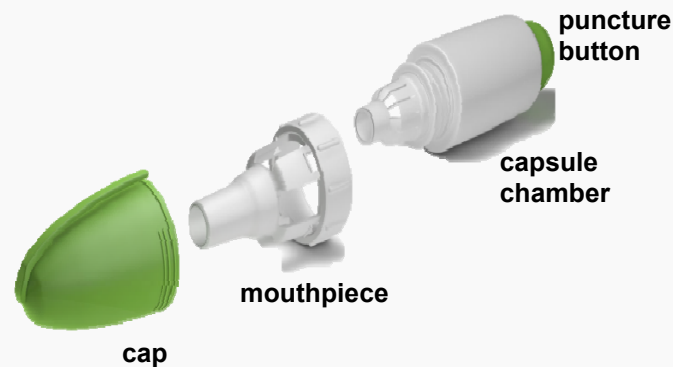
Ciprofloxacin DPI for NCFB Development Program for High Unmet Medical Need

- **Multiple FDA designations:**
  - ‣ Breakthrough Therapy
  - ‣ Fast Track
  - ‣ Orphan Drug
  - ‣ Qualified Infectious Disease Product
- **Phase 3 clinical program agreed with FDA:**
  - ‣ Primary endpoint
  - ‣ Duration
  - ‣ Dosing regimens
  - ‣ Patient population

Phase III RESPIRE Clinical Program

- **2 Phase III placebo-controlled trials, RESPIRE 1 and RESPIRE 2**
  - 2 dosing regimens of 32.5 mg ciprofloxacin DPI BID for 48 weeks
    - 14 days on/off
    - 28 days on/off

- **Total ciprofloxacin drug exposure by either regimen was the same**

- **RESPIRE 1 ciprofloxacin DPI 14 days on/off regimen showed statistically significant result (p = 0.005) for primary endpoint prior to the completion of RESPIRE 2**

- **Rolling NDA submission began with RESPIRE 1 based on 14 days on/off**

- **Totality of evidence supports consideration of both dosing regimens**

Medical Landscape in Non-Cystic Fibrosis Bronchiectasis
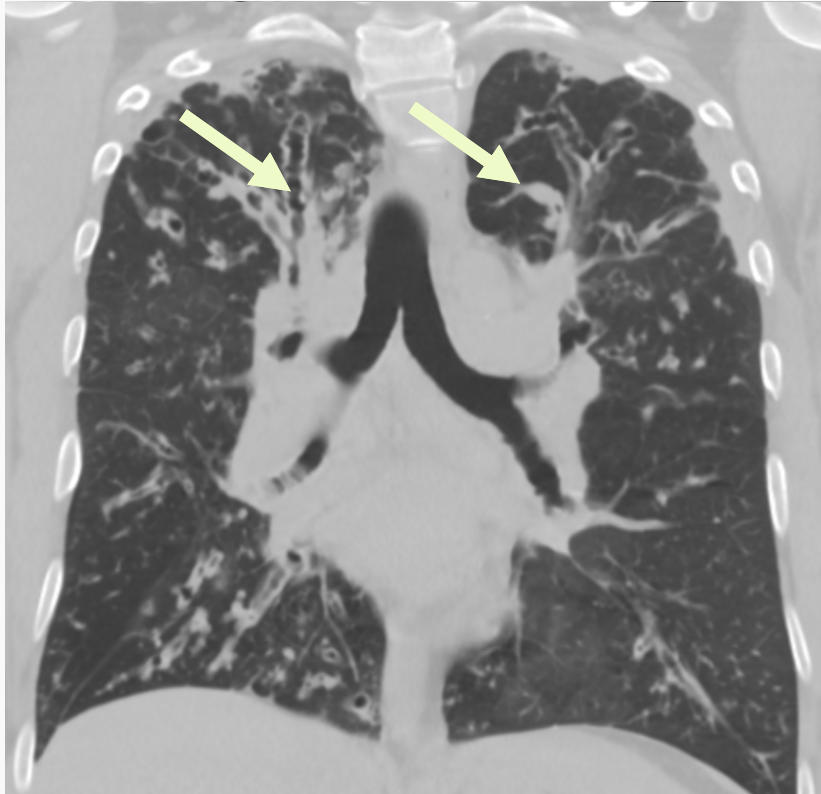
Dr. Pamela J McShane

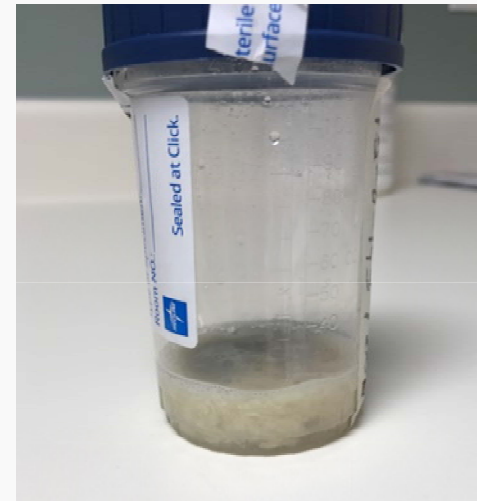Assistant Professor of Medicine

Section of Pulmonary and Critical Care

Department of Medicine

THE UNIVERSITY OF
CHICAGO
MEDICINE

CC-12

NCFB: Disease of Chronic Infection and Airway Destruction

- Chronic respiratory disease defined by abnormal widening of the bronchi and purulent sputum production[1–3]

- Ideal environment for growth of pathogens and further destruction of the bronchi[1–3]

1. McShane P, et al. *Am J Respir Crit Care Med* 2013;647.
2. King PT. *Int J COPD* 2009;4:411.
3. O'Donnell AE. *Chest* 2008;134:815.
4. Chalmers JD, et al. *Am J Respir Crit Care Med* 2014;189:576.
5. Aksamit TR, et al, *Am J Respir Crit Care Med* 2017;195:A7304

CT of the chest with coronal image, Dr. McShane; markings: mucus plug and dilated airways.

CC-13

NCFB: Disease of Chronic Infection and Airway Destruction

- **Chronic respiratory disease defined by abnormal widening of the bronchi and purulent sputum production[1–3]**

- **Ideal environment for growth of pathogens and further destruction of the bronchi[1–3]**

- **Substantial bronchiectasis morbidity robs sense of well-being[1–3]**

- **Exacerbations are a major driver of morbidity, future hospitalization and mortality**
  - ‣ 20-40% of patients experience ≥2 exacerbations/year[4,5]

> **There are no approved antibiotics to reduce the frequency of exacerbations in NCFB**

1. McShane P, et al. *Am J Respir Crit Care Med* 2013;647.
2. King PT. *Int J COPD* 2009;4:411.
3. O'Donnell AE. *Chest* 2008;134:815.
4. Chalmers JD, et al. *Am J Respir Crit Care Med* 2014;189:576.
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CT of the chest with coronal image, Dr. McShane; markings: mucus plug and dilated airways.

Major Obstacles to Treatment

- **Misdiagnosis**

**Myriam is a
57 y/o woman with a
cough that began
20 years ago[a]**

She was misdiagnosed
"asthma", "chronic
bronchitis" and "COPD"

**Appropriate work up
revealed that Myriam
had bronchiectasis
all along**

Chest imaging revealed
enlarged bronchi and
mucus plugging

**Most importantly,
Myriam's sputum grew
Pseudomonas
bacteria**

Major Obstacles to Treatment

- Misdiagnosis

- Extensive use of systemic antibiotics

Elizabeth is a 58 y/o woman with bronchiectasis[a]

- She suffers from frequent exacerbations
  - *H. influenzae*, *S. aureus*, and other Non-*Pseudomonas* bacteria

Hospitalizations

Systemic antibiotic side effects

- Gastrointestinal upset
- Dizziness
- Malaise

Major Obstacles to Treatment

- Misdiagnosis

- Extensive use of systemic antibiotics

- No inhaled antibiotics approved for NCFB

- **Anwar is a 39 y/o husband and father with NCFB[a]**
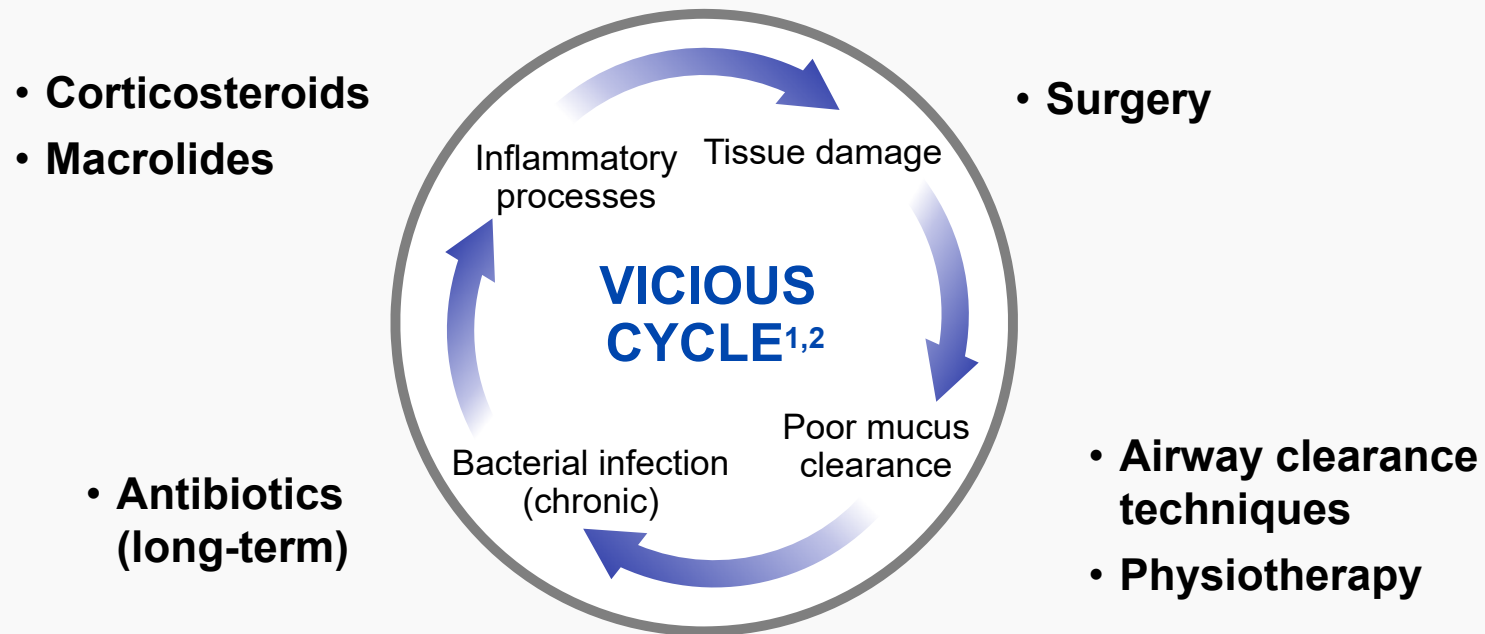
- **After years of misdiagnosis he was finally diagnosed at age 33**

- **Delay of diagnosis and frequent exacerbations lead to significant disease progression**

- **Today he suffers from chronic _Pseudomonas_ infection and repeated exacerbations**

- **As a result he requires supplemental oxygen, is listed for transplantation and can no longer work**

Anwar's Last Resort

NCFB is Perpetuated by a Vicious Cycle of Inflammation, Infection, and Lung Tissue Damage

- **Corticosteroids**
- **Macrolides**

- **Surgery**

VICIOUS CYCLE[1,2]

Inflammatory processes

Tissue damage

Poor mucus clearance

Bacterial infection (chronic)

- **Antibiotics (long-term)**
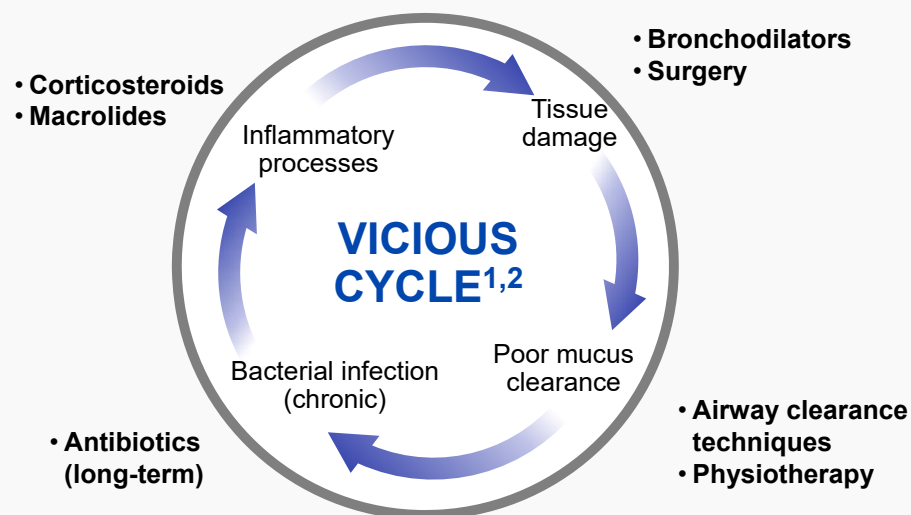
- **Airway clearance techniques**
- **Physiotherapy**

1. Cole PJ. *Eur J Respir Dis.* 1986;69:6.
2. King PT. *Int J Chron Obstruct Pulmon Dis.* 2009;4:411.

NCFB is Perpetuated by a Vicious Cycle of Inflammation, Infection, and Lung Tissue Damage

Therapy	Data available from patients (No.)[3]	Overall use No. (%)[a]
Antibiotic use		
Any suppressive antibiotic	1775	694 (39)
Inhaled suppressive antibiotics	1759	178 (10)
Use of other therapies		
Inhaled steroid	1794	696 (39)
Inhaled bronchodilator	1798	1098 (61)
Mucus active agent	1784	424 (24)
Measure to improve bronchial hygiene YES	1730	965 (56)

Percentages and other descriptive statistics calculated after excluding participants with missing data from the column total

- **Corticosteroids**
- **Macrolides**

Inflammatory processes

Tissue damage

- **Bronchodilators**
- **Surgery**

VICIOUS CYCLE[1,2]

Bacterial infection (chronic)

Poor mucus clearance

- **Antibiotics (long-term)**

- **Airway clearance techniques**
- **Physiotherapy**

1. Cole PJ. *Eur J Respir Dis.* 1986;69:6.
2. King PT. *Int J Chron Obstruct Pulmon Dis.* 2009;4:411.
3. Aksamit TR, et al. *CHEST* 2017;151:982..

Exacerbations Require Physician Intervention and Can Result in Emergency Room Visits or Hospitalization

- In general, an exacerbation is the worsening of symptoms compared with those present most of the time[1]

- Recently, a consensus definition for clinical research was proposed by world experts from around the globe[2]

Deterioration in ≥3 of the following key symptoms for at least 48 h	1. Cough 2. Sputum volume and/or consistency 3. Sputum purulence 4. Breathlessness and/or exercise tolerance 5. Fatigue and/or malaise 6. Hemoptysis

AND

A clinician determines that a change in bronchiectasis treatment is required	**Other potential causes of clinical deterioration have been discounted**

1. Pasteur MC, et al. *Thorax* 2010;65.
2. Hill AT, et al. *Eur Respir J* 2017;49.

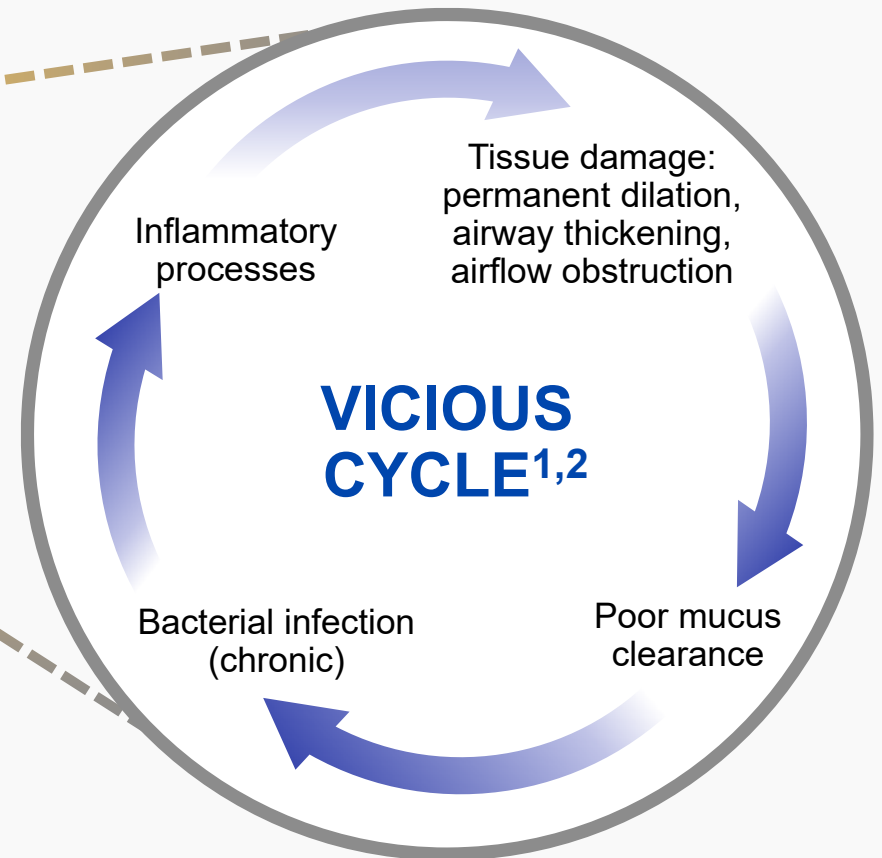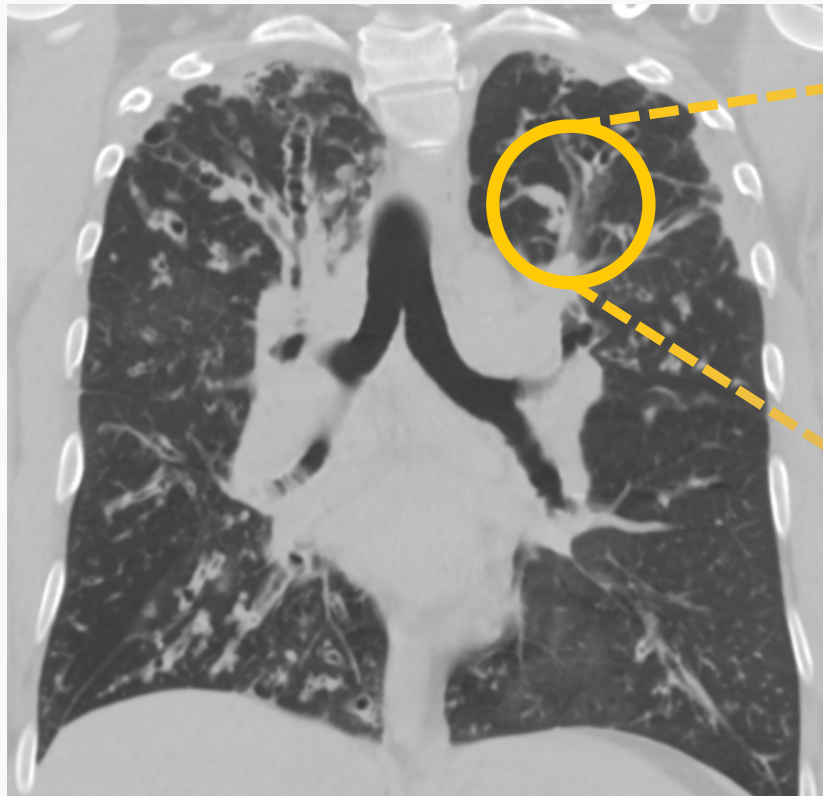# Exacerbations are Associated with Worsening of Baseline Symptoms That Can Persist for Weeks

Exacerbation Duration Before and After Start of Antibiotic Therapy
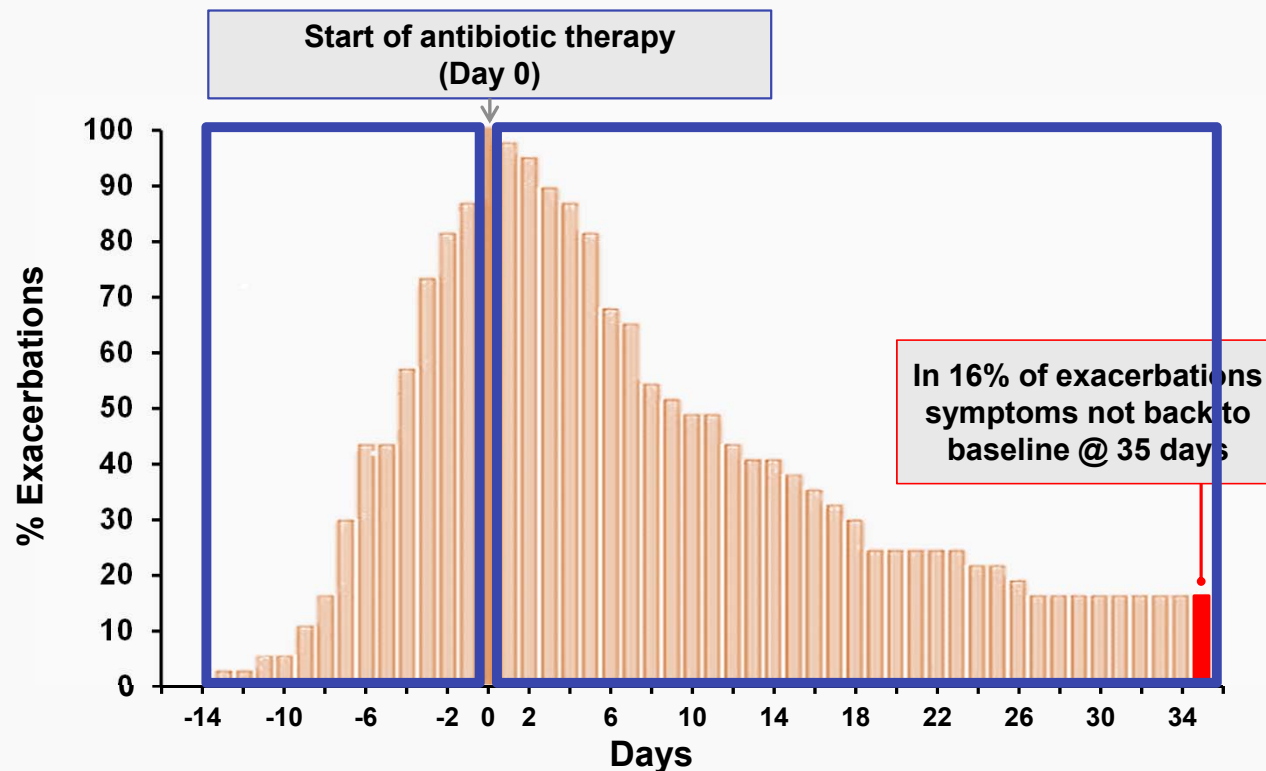
- **During exacerbation**
  - Inflammation markers increase
  - Impaired lung function

In 16% of exacerbations symptoms not back to baseline @ 35 days

The Role of Bacteria in the Pathophysiological Model

VICIOUS CYCLE[1,2]

- Tissue damage: permanent dilation, airway thickening, airflow obstruction
- Poor mucus clearance
- Bacterial infection (chronic)
- Inflammatory processes

1. Cole PJ. *Eur J Respir Dis.* 1986;69:6.
2. King PT. *Int J Chron Obstruct Pulmon Dis.* 2009;4:411.
CT of the chest with coronal image, Dr. McShane; markings: mucus plug and dilated airways.

Bacterial Load is Associated with Inflammation, Exacerbations, and Reduced Quality of Life

- **In patients with stable NCFB, a higher bacterial load was associated with**

  - ‣ Elevated levels of inflammatory markers in sputum

- **After 1 year of follow-up, there was a significant correlation between bacterial load and:**

  - ‣ Number of exacerbations
  - ‣ Number of unscheduled hospitalizations
  - ‣ Severity of cough symptoms
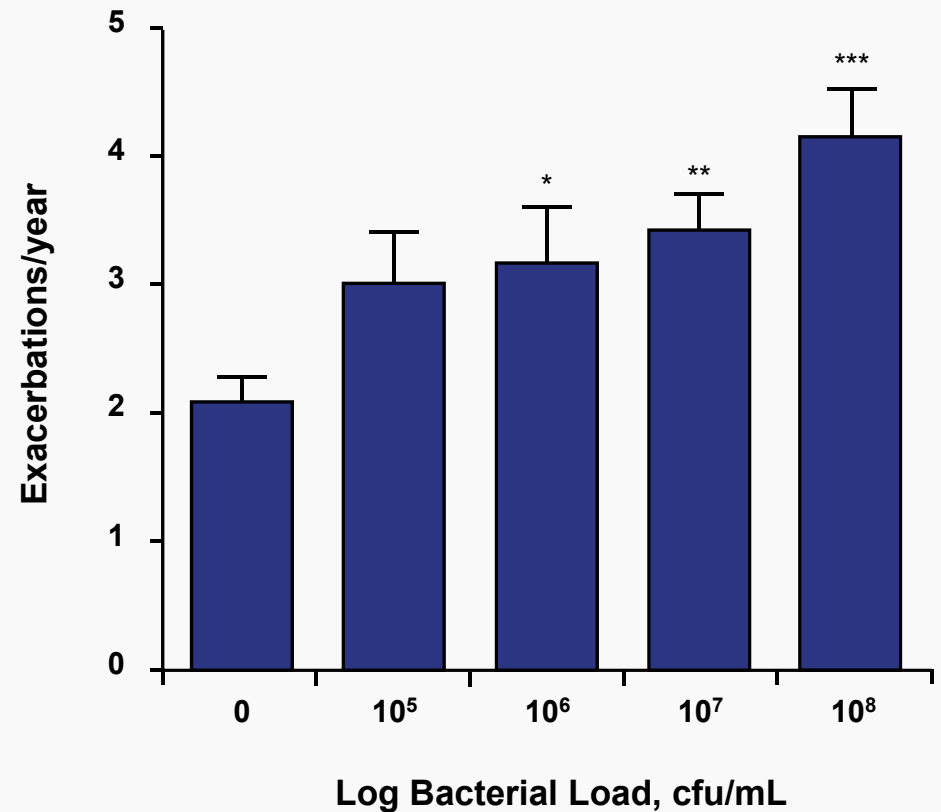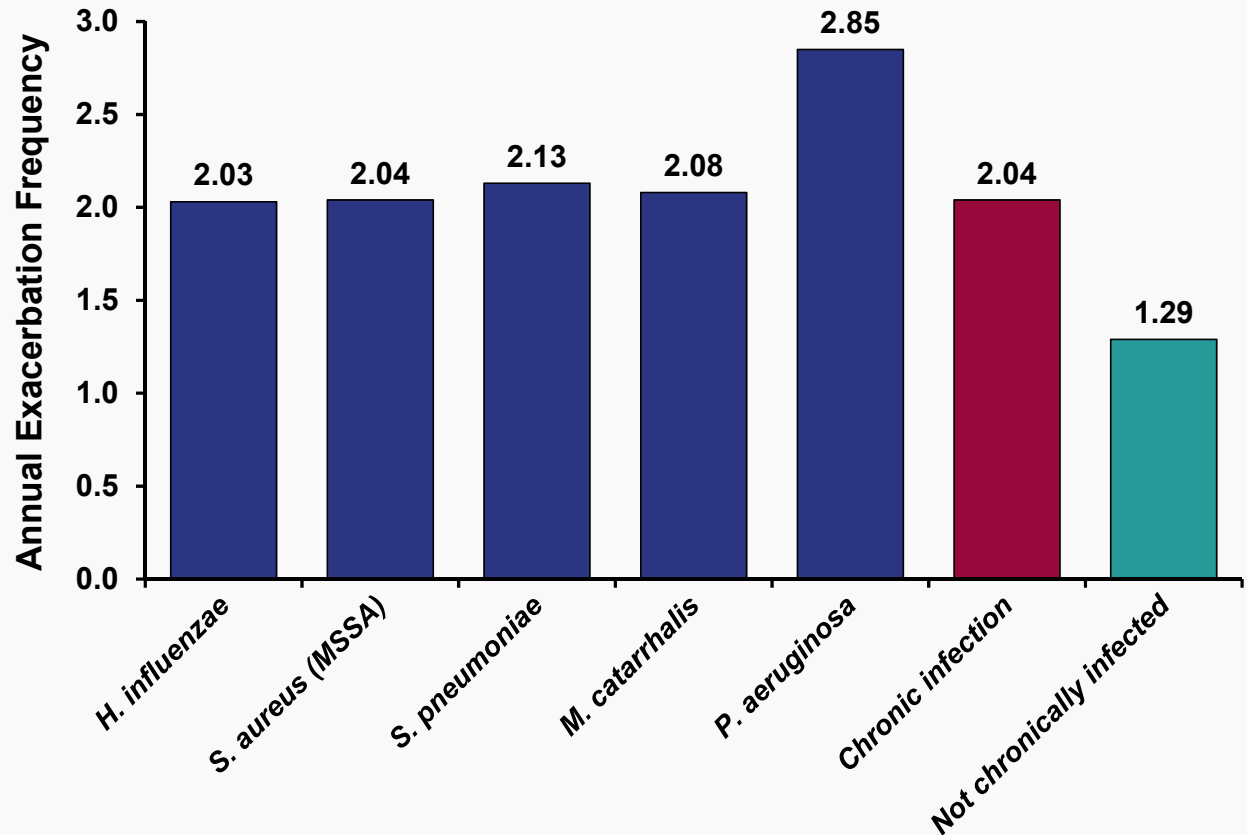

*P<0.05 **P<0.01 ***P<0.0001.
cfu: Colony-Forming Units.
Chalmers JD, et al. *Am J Respir Crit Care Med.* 2012;186:657.

The chart y-axis is "Exacerbations/year" and x-axis is "Log Bacterial Load, cfu/mL" with values 0, 10^5, 10^6, 10^7, 10^8

Pathogenic Bacteria in Patients with NCFB

- **Common pathogenic bacteria detected by sputum culture include[1-3]**

  - *Haemophilus influenzae*
  - *Pseudomonas aeruginosa*
  - *Streptococcus pneumoniae*
  - *Moraxella catarrhalis*
  - *Staphylococcus aureus*
  - *Stenotrophomonas*
  - *Burkholderia*

- **Patients can have multiple pathogens[1-3]**

Chart — Annual Exacerbation Frequency:

| Category	Annual Exacerbation Frequency
H. influenzae	2.03
S. aureus (MSSA)	2.04
S. pneumoniae	2.13
M. catarrhalis	2.08
P. aeruginosa	2.85
Chronic infection	2.04
Not chronically infected	1.29

1. Angrill J, et al. *Thorax.* 2002;57:15.
2. King PT, et al. *Respir Med.* 2007;101:1633.
3. Chalmers JD, et al. *Am J Respir Crit Care Med.* 2014;189:576.

More Frequent Exacerbations are Associated with Worse Outcomes

Prospective Cohort Study
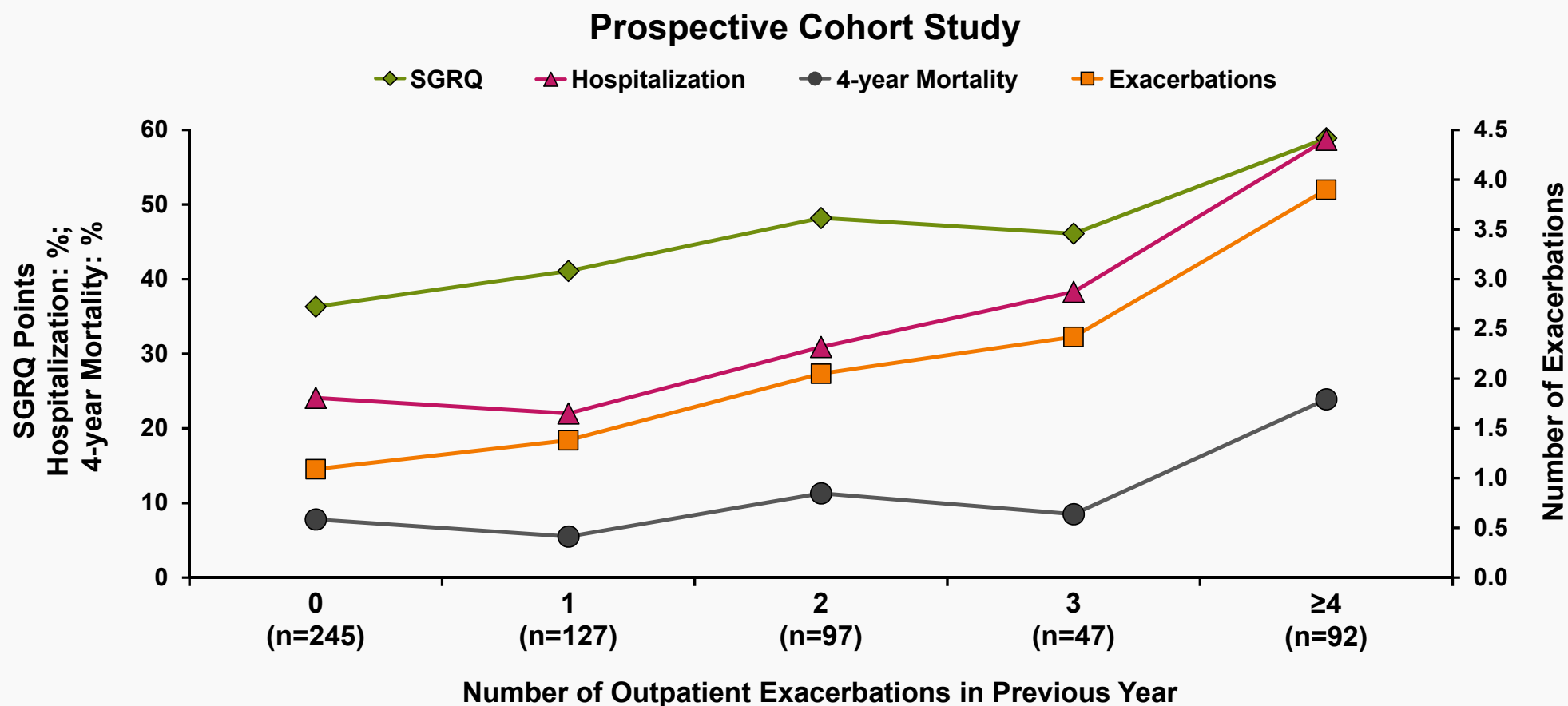
SGRQ: St. George's Respiratory Questionnaire
Chalmers JD, et al. *Am J Respir Crit Care Med.* 2014;189:576.

General Treatment Goals in NCFB[1-3]

- **Reduce exacerbations**

- **Improve daily symptoms**

- **Maintain pulmonary function**

- **Identify and treat the underlying cause, if possible**

> **Reducing bacterial load in the lungs is an important strategy
> to reduce exacerbations in NCFB**

1. Chang AB, et al. *Med J Aust.* 2015;202:130.
2. Pasteur MC, et al. *Thorax* 2010;65:1.
3. Polverino E, et al. *Eur Respir J* 2017;50.

Efficacy and Microbiology

Jeff Alder, PhD

Senior Director, Global Clinical Development
Bayer

Ciprofloxacin DPI – Clinical Development

1. **Built on the extensive ciprofloxacin legacy**

   ‣ Ciprofloxacin approved for RTI with similar pathogen array as in NCFB

2. **Goal: Reduce exacerbations in NCFB patients by directly treating respiratory pathogens**

3. **Achieve targeted drug concentrations directly in lung**

   ‣ Dry powder drug + inhaler device are portable and simple to use
   ‣ Multiple advantages over existing nebulizers
   ‣ Device approved (with tobramycin) for CF patients

RTI=Respiratory Tract Infections

Ciprofloxacin DPI PulmoSpheres™: Lung Deposition in Phase 1 Scintigraphy Study

^{99m}Tc Scans

^{99m}Tc Scans

Healthy volunteer

Oropharyngeal region

Lungs

Stomach

100%

0%

1 µm
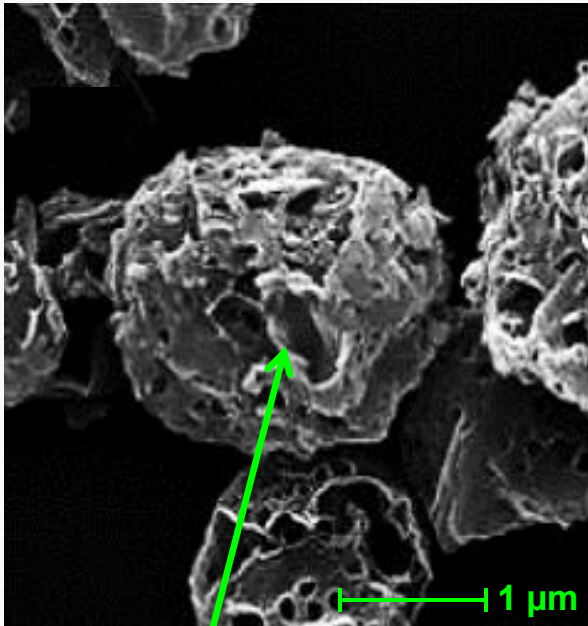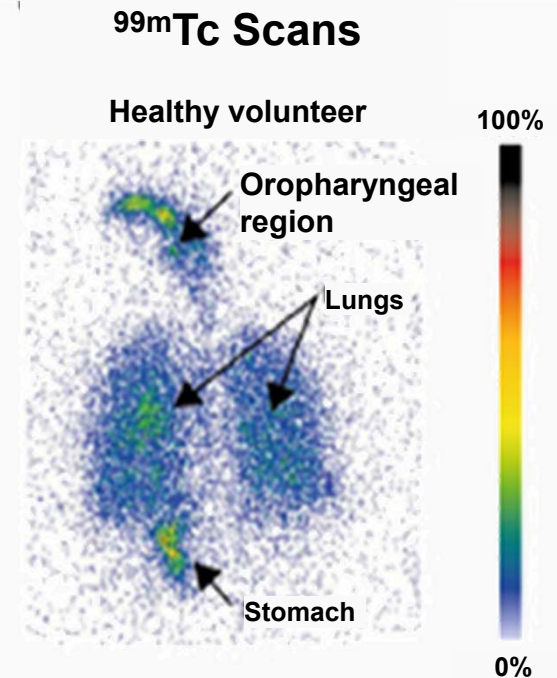
- **PulmoSphere™: small size and dispersion characteristics produce deep penetration into lung**
- **Achieves high ciprofloxacin concentrations in lung (site of infection) and low systemic levels**
- **>50% of the dose is deposited in the lung**

Ciprofloxacin DPI Yields High Sputum and Low Systemic Exposure in NFCB Patients

Ciprofloxacin DPI Sputum
$C_{max,u}$ = 120 mg/L (median)

Oral ciprofloxacin [500 mg BID] Plasma (Healthy subjects)
$C_{max,ss,u}$ = 2.08 mg/L

Ciprofloxacin DPI Plasma
$C_{max,ss,u}$ = 0.086 mg/L (median)

~ 58 x

~ 24 x

~ 1400 x

fraction unbound in plasma = 0.7

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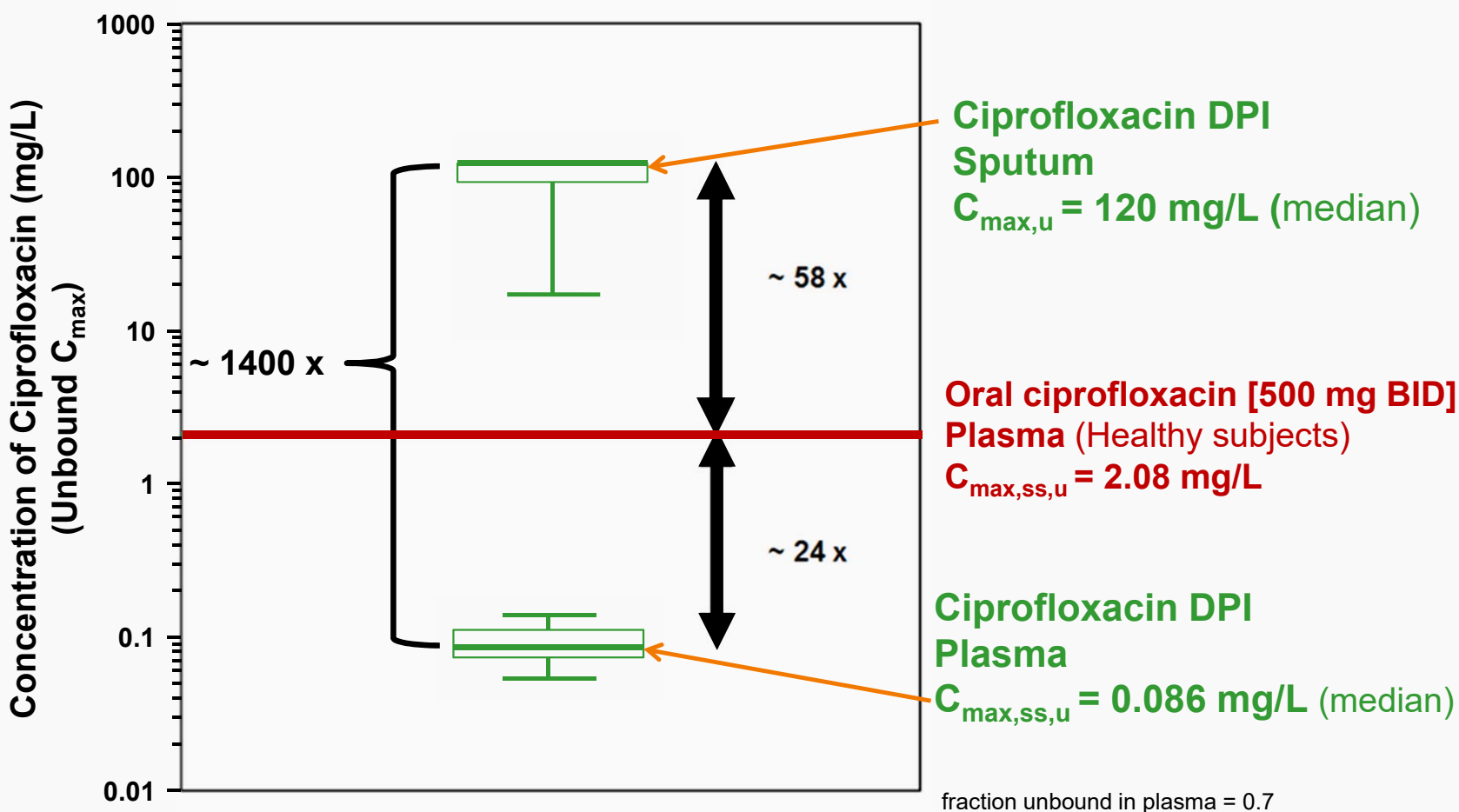
Ciprofloxacin DPI 28 Bacterial Reduction Achieved in First 10 Days of Dosing Cycle in Phase 2 Study in NCFB
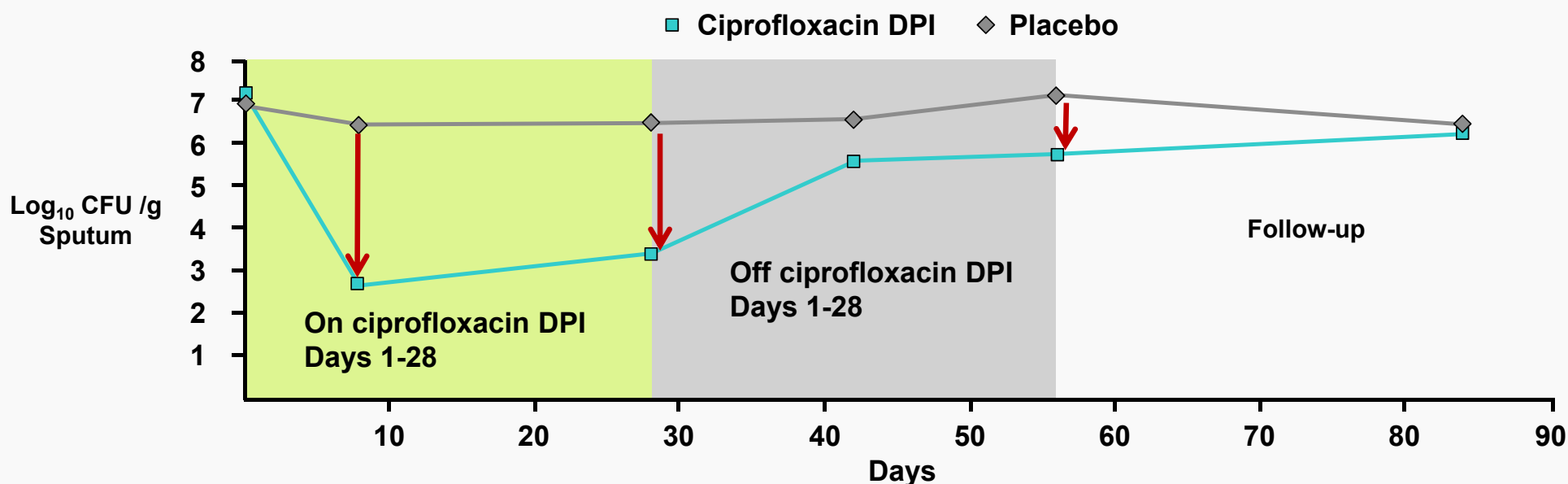
- **Reduction in total bacterial burden**
  - ‣ Peaked within 10 days of dosing initiation
  - ‣ Maintained during rest of on cycle (Days 8-28)
- **Regrowth of bacterial burden during off cycle (Days 29-56)**
- **Shorter Ciprofloxacin DPI 14 on/off cycle to maximize bacterial reduction & minimize regrowth**

There were 124 patients randomized (60 ciprofloxacin DPI; 64 placebo) who comprised the safety and modified intent to treat (mITT) population

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Study Design RESPIRE 1 and RESPIRE 2

12 active cycles **over 48 weeks**: **14 days on/14 days off therapy**

| Ciprofloxacin DPI 14 | OFF | Ciprofloxacin DPI 14 | OFF |
| Placebo | OFF | Placebo | OFF |

6 active cycles **over 48 weeks**: **28 days on/28 days off therapy**

| Ciprofloxacin DPI 28 | OFF |
| Placebo | OFF |

8 week f/u after last dose
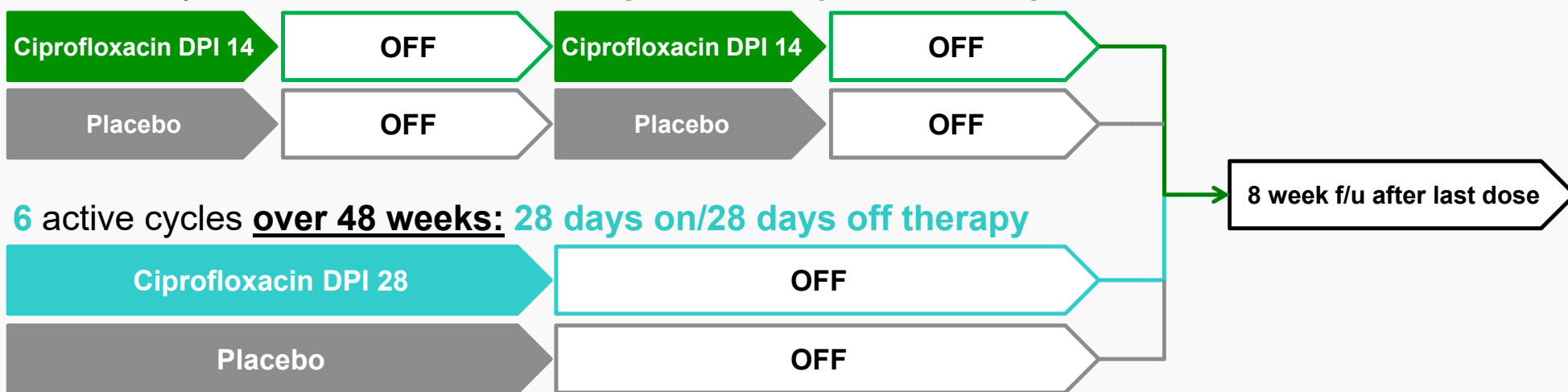
- **Equal drug exposures** for Ciprofloxacin DPI 14 and Ciprofloxacin DPI 28
- **Equal doses** (32.5 mg active drug) for both regimens
- Largest, most comprehensive clinical development program in NCFB patients
- Two global trials; **937** patients randomized in Phase 3

CC-36

RESPIRE 1 and 2: Inclusion Criteria

- Age ≥18 years
- Proven/documented diagnosis of idiopathic or post-infectious NCFB by CT scan
- Positive culture for 1+ of 7 pathogens[a]
- Stable pulmonary status
- Stable regimen of standard treatments

- History ≥2 documented exacerbations in past 12 months
- Sputum production majority of days
- Able to follow inhaler device instructions
- Able to complete questionnaires
- Written informed consent
- Negative urine pregnancy test before first dose of study drug

a. *Pseudomonas aeruginosa, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Streptococcus pneumoniae, Stenotrophomonas maltophilia* or *Burkholderia cepacia* obtained at screening

RESPIRE 1 and 2: Efficacy Evaluations in Hierarchy

Exacerbations

1 Time to first exacerbation event (Primary)

2 Frequency of exacerbation events (≥3 signs)

3 Frequency of exacerbation events (≥1 sign)

4 Pathogen eradication

5 St. George's Respiratory Questionnaire (SGRQ; Symptoms component score)

6 Occurrence of new pathogens

7 Quality of Life (QoL-B) Respiratory symptoms domain

8 Lung function (FEV$_1$)

Exacerbation Definitions for RESPIRE 1 and 2: Criteria of Clinical Relevance

A <u>qualifying</u> exacerbation requires that:

≥**3** signs or symptoms have worsened for at least 2 consecutive days:

Dyspnea	None	Mild	Moderate	Severe
Wheezing	No		Yes	
Cough	None	Mild	Moderate	Severe
Sputum Volume	24 hour volume (mL)			
Sputum Purulence	Clear	Pale yellow/green	Dark yellow/green	± Rusty spots

<u>And</u> presence of

- **Fever** (body temperature ><u>38.0°C</u>) or **malaise / fatigue** (<u>No, Yes</u>)

<u>And</u>

- **Systemic antibiotic treatment**

Subject Disposition in RESPIRE 1 and 2

Disposition, n (%)	Ciprofloxacin DPI 14		Ciprofloxacin DPI 28		Pooled Placebo	
	RESPIRE 1	RESPIRE 2	RESPIRE 1	RESPIRE 2	RESPIRE 1	RESPIRE 2
Randomized (FAS)	137 (100%)	176 (100%)	141 (100%)	171 (100%)	138 (100%)	174 (100%)
Completing Trial*	111 (81.0%)	151 (85.8%)	118 (83.7%)	148 (86.5%)	105 (76.1%)	143 (82.2%)
Not Completing Trial*	26 (19.0%)	25 (14.2%)	23 (16.3%)	23 (13.5%)	33 (23.9%)	31 (17.8%)

*Follow-up visit

Baseline Pathogens in Ciprofloxacin DPI Phase 3 Program

RESPIRE 1

Legend: ■ Cipro 14   ■ Cipro 28   ■ Pooled Placebo

Percentage of Patients (y-axis: 0–70)

Categories: P. aeruginosa, S. aureus, H. influenzae, Four pathogens*

RESPIRE 2

Legend: ■ Cipro 14   ■ Cipro 28   ■ Pooled Placebo

Percentage of Patients (y-axis: 0–70)

Categories: P. aeruginosa, S. aureus, H. influenzae, Four pathogens*

* S. pneumoniae, M. catarrhalis, S. maltophilia, or B. cepacia

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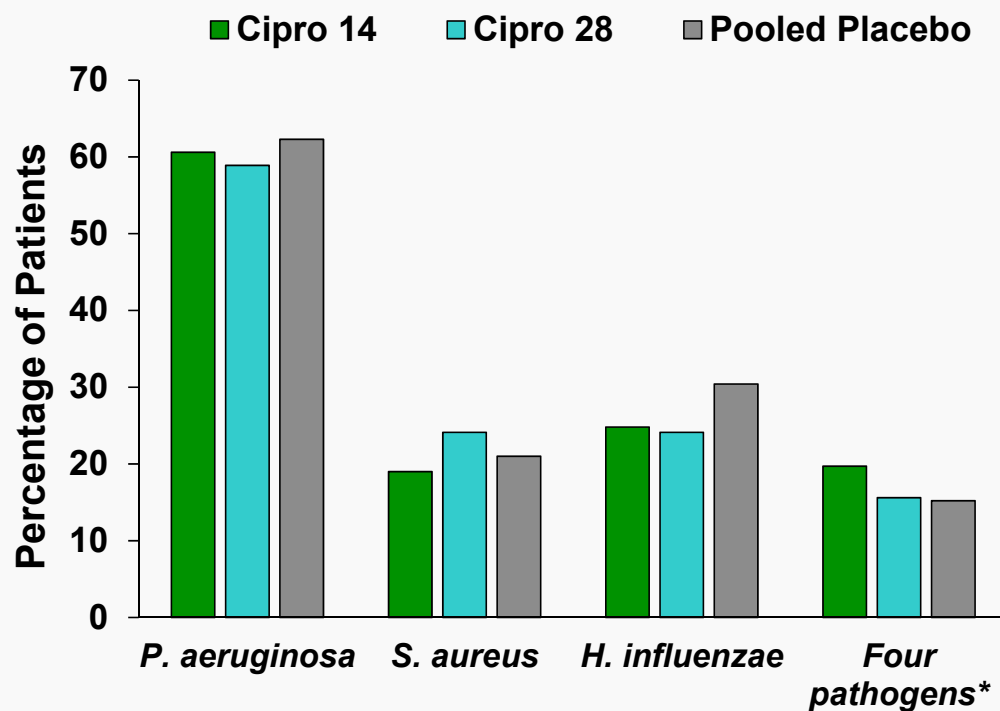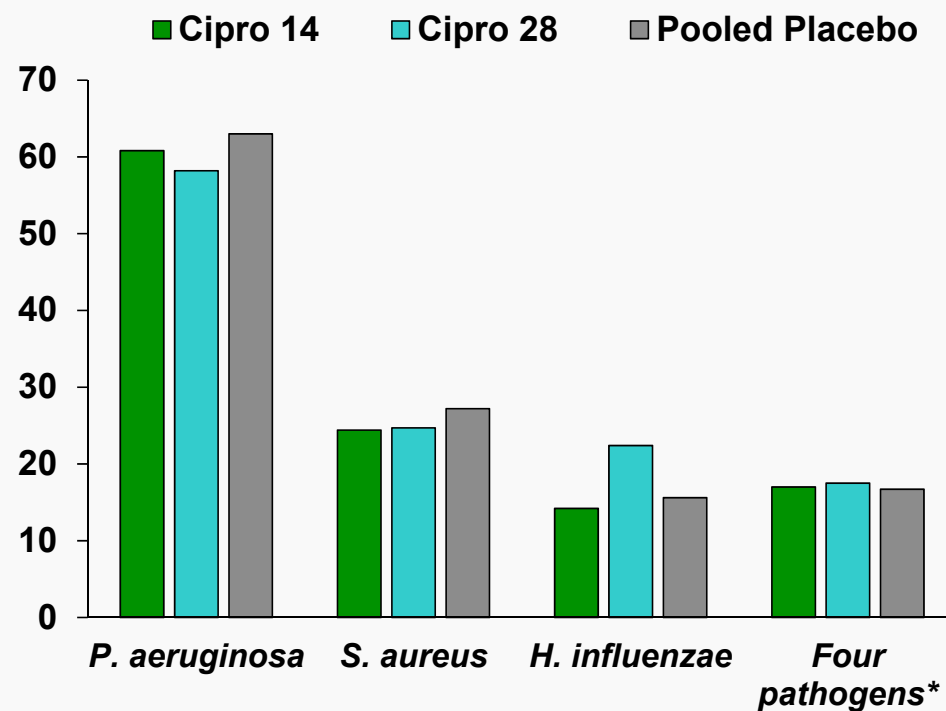
RESPIRE 1: Time to First Exacerbation Event Kaplan-Meier Plot and Weibull Survival Fit
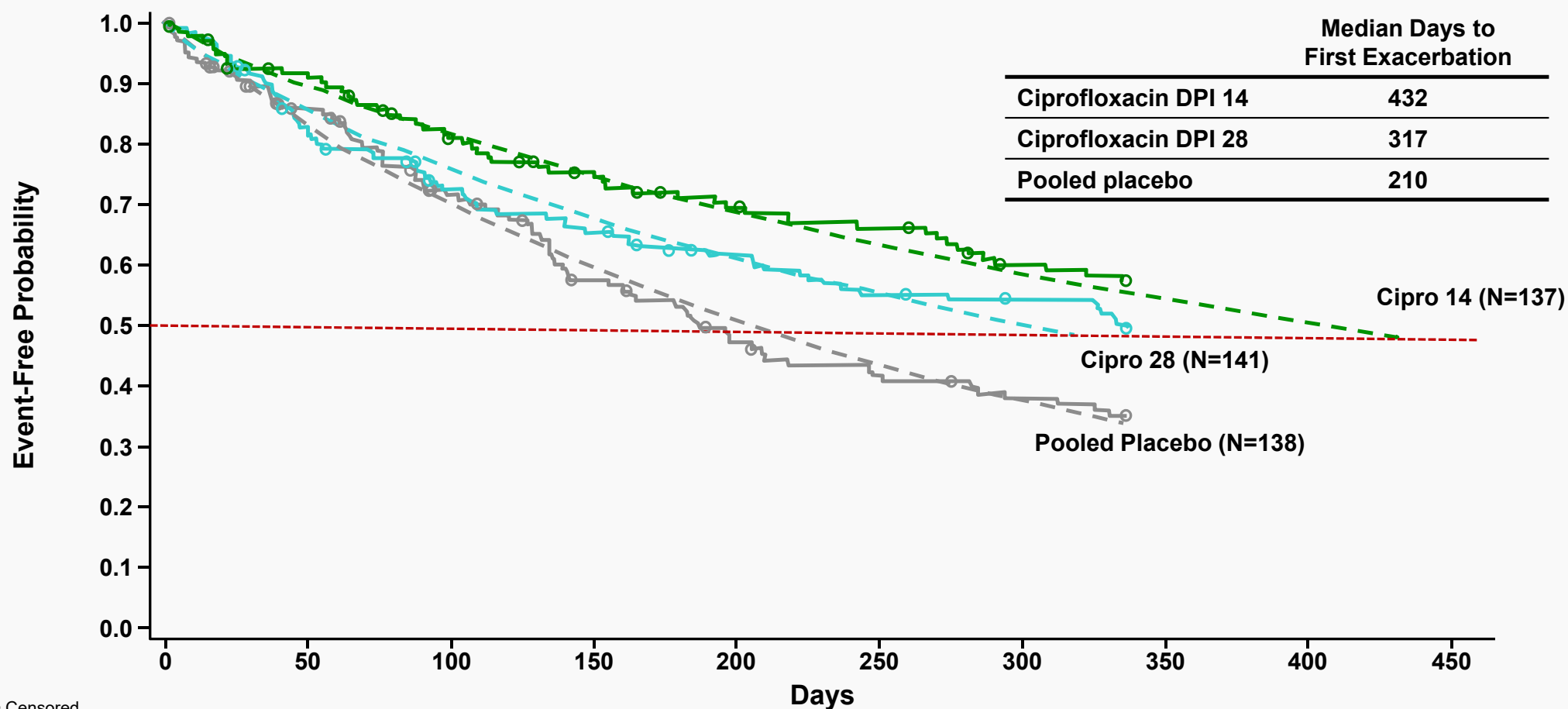
	Median Days to First Exacerbation
Ciprofloxacin DPI 14	432
Ciprofloxacin DPI 28	317
Pooled placebo	210

Cipro 14 (N=137)

Cipro 28 (N=141)

Pooled Placebo (N=138)

○ Censored

Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution. Kaplan Meier plots are solid lines, Weibull survival fits are dashed.

CC-42

RESPIRE 1 Primary and Secondary Efficacy Analyses: Exacerbations

	Ciprofloxacin DPI 14 N=137	Ciprofloxacin DPI 28 N=141	Pooled Placebo N=138
Time to first exacerbation			
Estimated median time [days][a]	432	317	210
Patients with Exacerbation n (%)	53 (**38.7%**)	67 (**47.5%**)	79 (**57.2%**)
Primary (time to 1st exacerbation)			
Hazard ratio (HR)[b]	0.53	0.73	---
97.5%-CI for HR	[0.36, 0.80]	[0.50, 1.07]	
p-value[c]	**0.0005**	**0.0650**	---
Frequency of exacerbations (≥3 signs)			
Mean number ± SD	0.85 ± 1.24	1.01 ± 1.41	1.17 ± 1.27
Incidence rate ratio (IRR)[d]	0.73	0.86	---
97.5%-CI for IRR[d]	[0.52; 1.03]	[0.63; 1.18]	
p-value[c]	**0.0382**	**0.2944**	---

Ciprofloxacin DPI 14 significantly (p=0.0005) increased time to first exacerbation

a. Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution
b: Hazard ratio (HR) based on Cox Proportional Hazards model; HR for the comparison of active treatment vs. pooled placebo (HRs <1 indicate better outcome on active treatment).
c: Wald-type test
d: Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment vs. pooled placebo (IRRs <1 indicate better outcome on active treatment).

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RESPIRE 1: Analysis of 8 Pre-Specified Endpoints

		HR/IRR/OR (97.5% CI)
Time to first exacerbation (Hazard Ratio)	Cipro 14	0.53 (0.36, 0.80)
	Cipro 28	0.73 (0.50, 1.07)
Frequency of exacerbations (≥3 signs) (Incidence Rate Ratio)	Cipro 14	0.73 (0.52, 1.03)
	Cipro 28	0.86 (0.63, 1.18)
Frequency of exacerbations (≥1 sign) (Incidence Rate Ratio)	Cipro 14	0.74 (0.55, 1.00)
	Cipro 28	0.87 (0.66, 1.16)
Pathogen eradication (Odds Ratio)	Cipro 14	0.43 (0.18, 1.01)
	Cipro 28	0.86 (0.39, 1.92)
Occurrence of new pathogens (Odds Ratio)	Cipro 14	0.56 (0.17, 1.79)
	Cipro 28	0.36 (0.10, 1.31)

0.1 ← Favors Ciprofloxacin DPI   1   Favors Placebo → 10

		LS Mean Difference (97.5% CI)
Changes (units) in SGRQ-SCS	Cipro 14	-7.59 (-14.04, -1.14)
	Cipro 28	-5.21 (-11.53, 1.10)
Changes (units) in QOL-B-RSDS	Cipro 14	-2.47 (-8.07, 3.14)
	Cipro 28	-1.18 (-6.53, 4.17)
Changes (L) in FEV$_1$	Cipro 14	0.05 (-0.03, 0.13)
	Cipro 28	0.03 (-0.05, 0.11)

-16   -12   -8   -4   0   4   8   12   16

Smaller values favor Cipro DPI. Some endpoints have been re-scaled for this purpose.

CC-44

RESPIRE 2: Time to First Exacerbation Event Kaplan-Meier Plot and Weibull Survival Fit

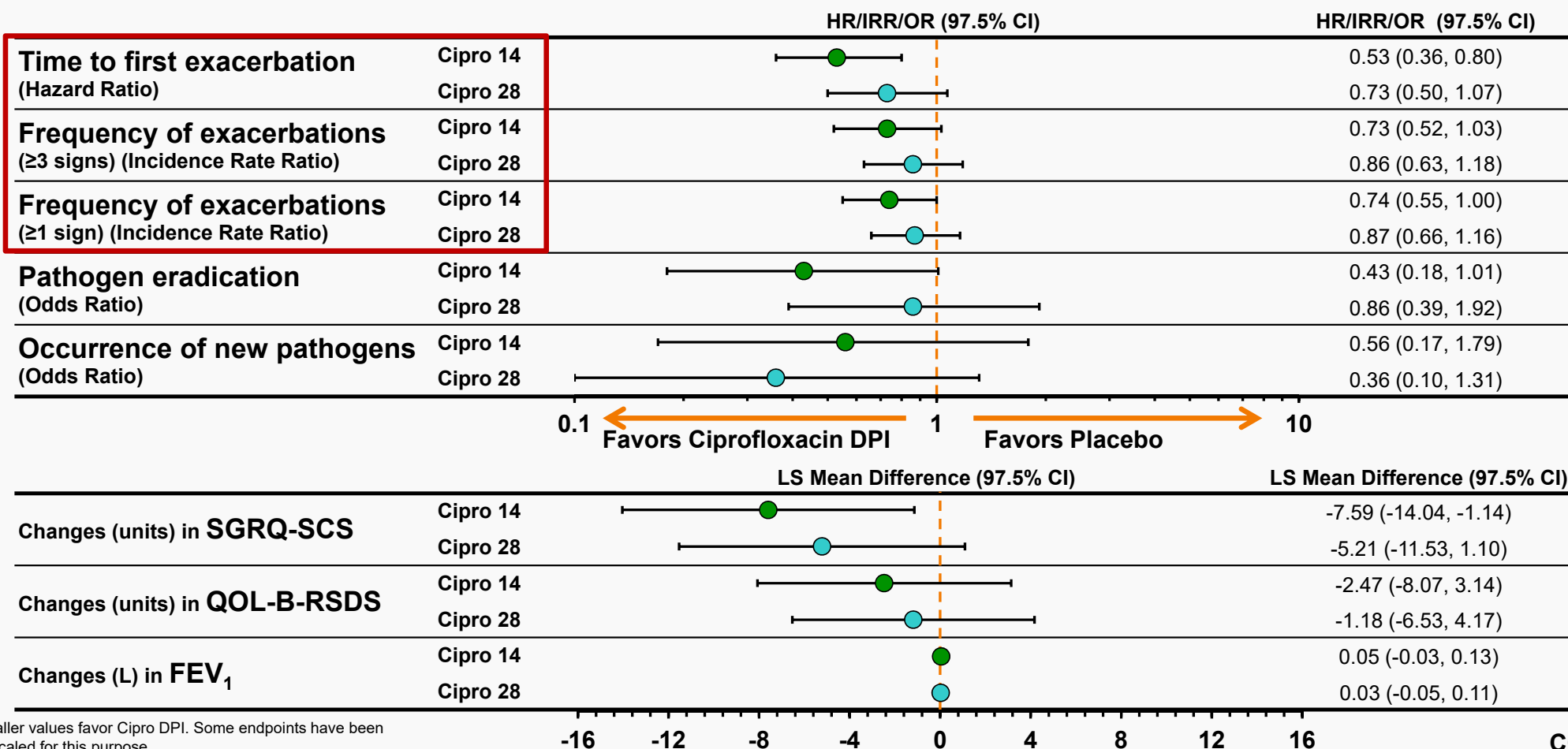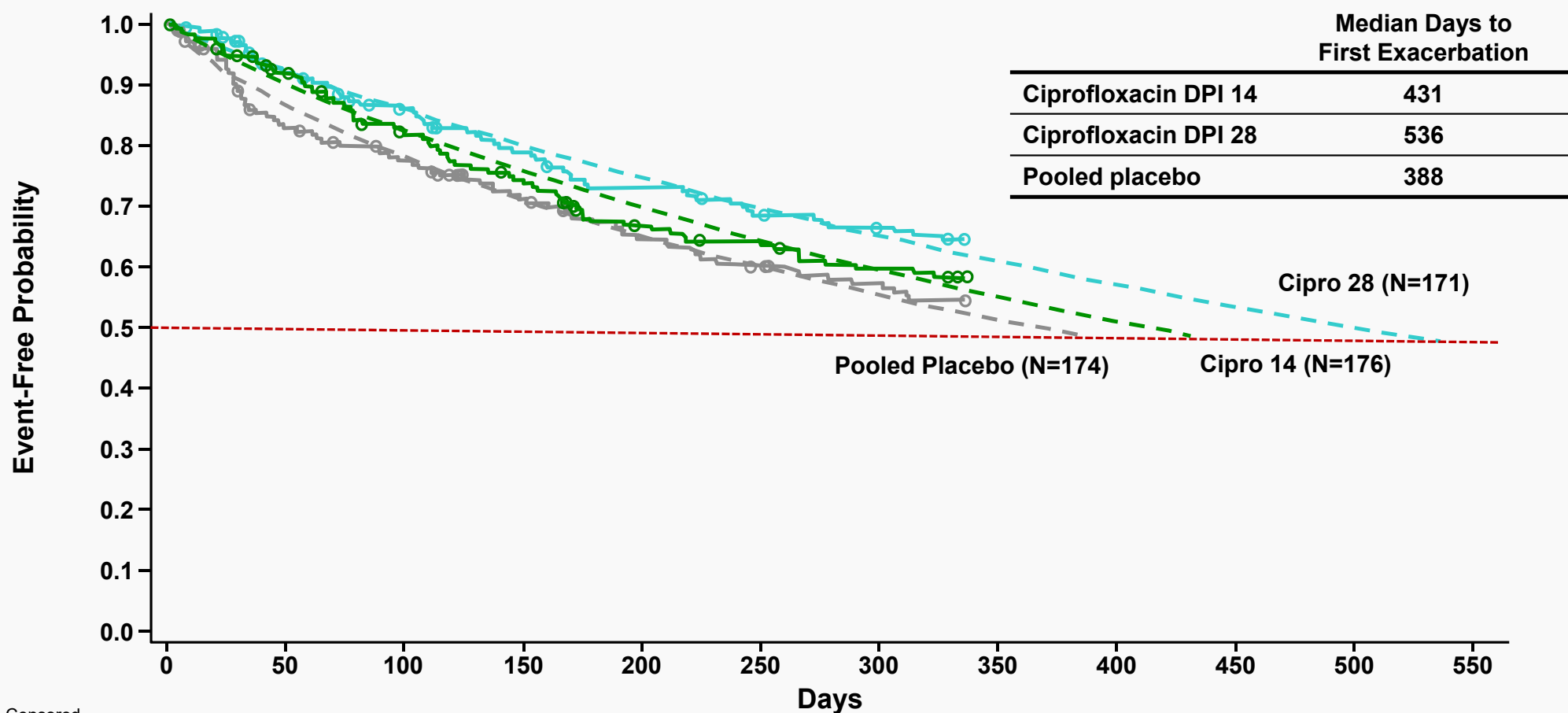|	Median Days to First Exacerbation
Ciprofloxacin DPI 14	431
Ciprofloxacin DPI 28	536
Pooled placebo	388

Cipro 28 (N=171)

Pooled Placebo (N=174)

Cipro 14 (N=176)

O Censored

Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution. Kaplan Meier plots are solid lines, Weibull survival fits are dashed.

RESPIRE 2 Primary and Secondary Efficacy Analyses: Exacerbations

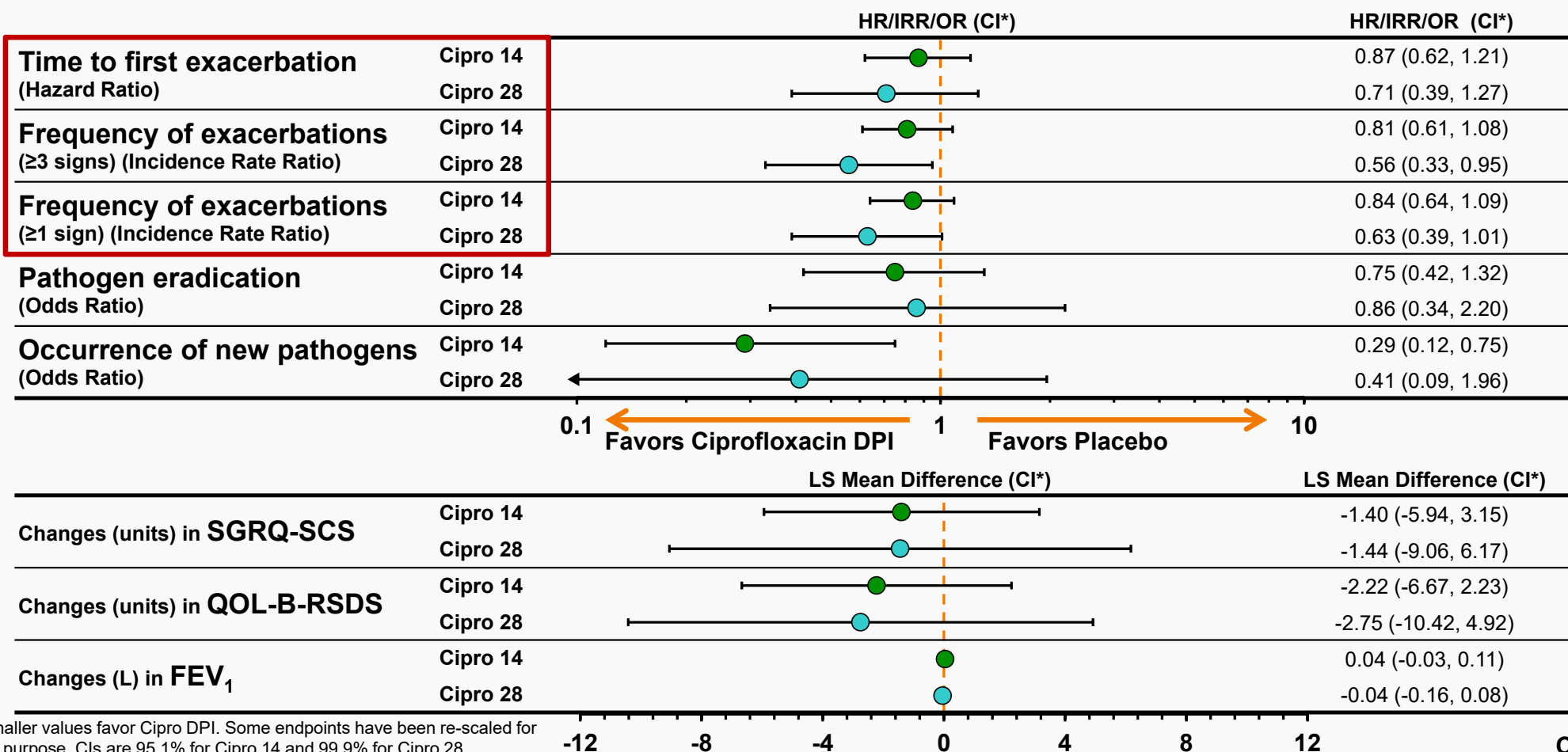|	Ciprofloxacin DPI 14 N=176	Ciprofloxacin DPI 28 N=171	Pooled Placebo N=174
Time to first exacerbation			
Median time [days][a]	431	536	388
Patients with exacerbation	68 (**38.6%**)	56 (**32.7%**)	73 (**42.0%**)
Pre-specified analysis			
Hazard ratio (HR)[b]	0.87	0.71	----
99.9 CI for HR	---	(0.39, 1.27)	----
95.1 CI for HR	(0.61, 1.21)	---	----
p-value[c]	**0.3965**	**0.0511**	----
No. of exacerbations (≥3 signs)			
Mean number ± SD	0.58 ± 0.84	0.40 ± 0.64	0.70 ± 1.02
Incidence rate ratio (IRR)[d]	0.81	0.56	----
p-value[c]	**0.1471**	**0.0003**	----

a. Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution
b: Hazard ratio (HR) based on Cox Proportional Hazards model; HR for the comparison of active treatment vs. pooled placebo (HRs <1 indicate better outcome on active treatment).
c Wald-type test.
d: Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment vs. pooled placebo (IRRs <1 indicate better outcome on active treatment).
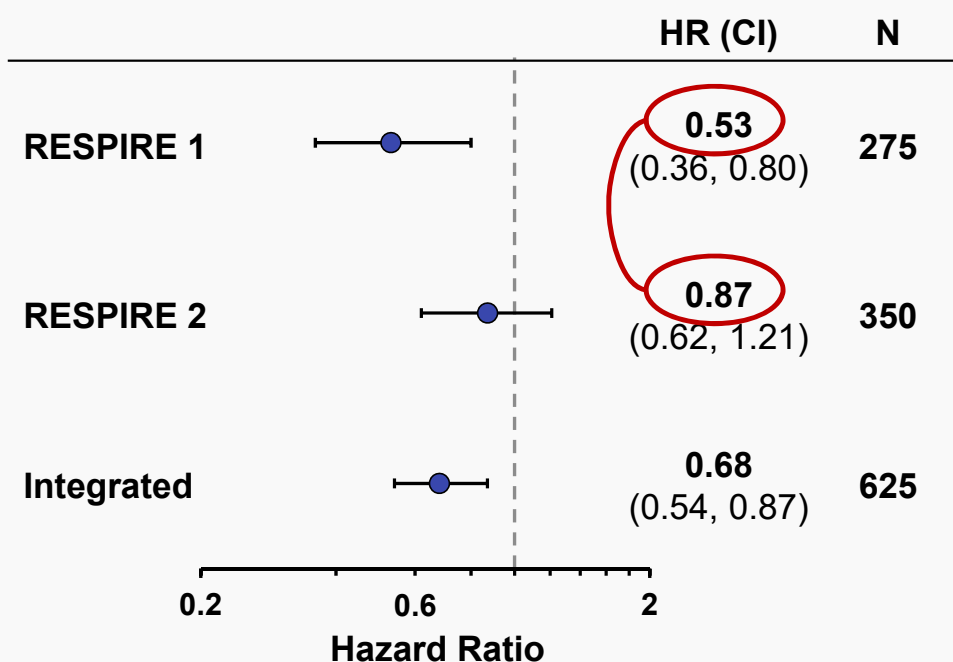
RESPIRE 2: Analysis of 8 Pre-Specified Endpoints

			HR/IRR/OR (CI*)
Time to first exacerbation (Hazard Ratio)	Cipro 14		0.87 (0.62, 1.21)
	Cipro 28		0.71 (0.39, 1.27)
Frequency of exacerbations (≥3 signs) (Incidence Rate Ratio)	Cipro 14		0.81 (0.61, 1.08)
	Cipro 28		0.56 (0.33, 0.95)
Frequency of exacerbations (≥1 sign) (Incidence Rate Ratio)	Cipro 14		0.84 (0.64, 1.09)
	Cipro 28		0.63 (0.39, 1.01)
Pathogen eradication (Odds Ratio)	Cipro 14		0.75 (0.42, 1.32)
	Cipro 28		0.86 (0.34, 2.20)
Occurrence of new pathogens (Odds Ratio)	Cipro 14		0.29 (0.12, 0.75)
	Cipro 28		0.41 (0.09, 1.96)

0.1 ← Favors Ciprofloxacin DPI   1   Favors Placebo → 10

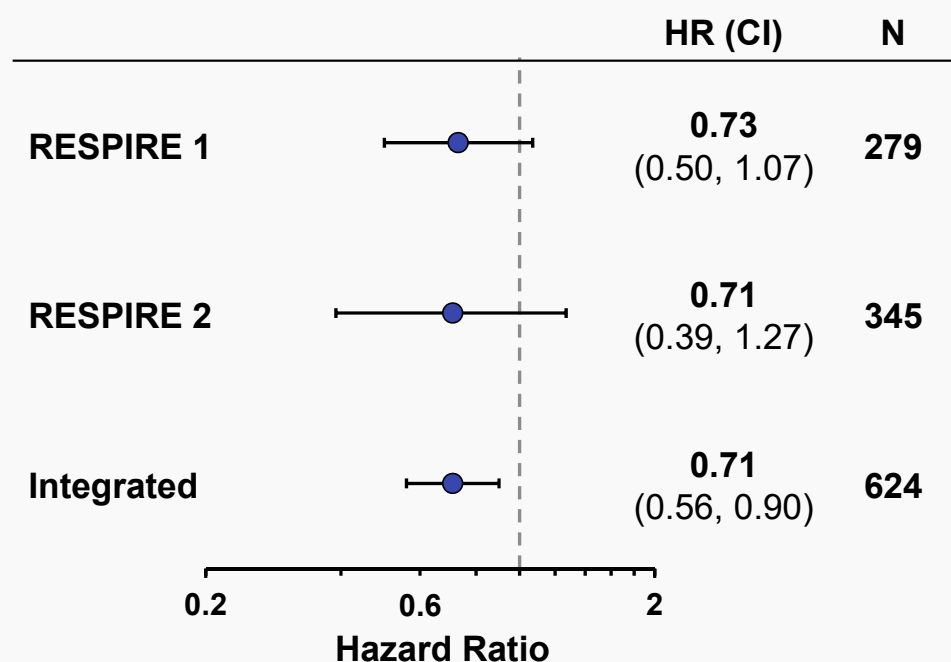|			LS Mean Difference (CI*)
Changes (units) in SGRQ-SCS	Cipro 14		-1.40 (-5.94, 3.15)
	Cipro 28		-1.44 (-9.06, 6.17)
Changes (units) in QOL-B-RSDS	Cipro 14		-2.22 (-6.67, 2.23)
	Cipro 28		-2.75 (-10.42, 4.92)
Changes (L) in FEV$_1$	Cipro 14		0.04 (-0.03, 0.11)
	Cipro 28		-0.04 (-0.16, 0.08)

-12   -8   -4   0   4   8   12

*Smaller values favor Cipro DPI. Some endpoints have been re-scaled for this purpose. CIs are 95.1% for Cipro 14 and 99.9% for Cipro 28

Time to First Exacerbation by Single Study and in an Integrated Analysis of RESPIRE 1 and 2
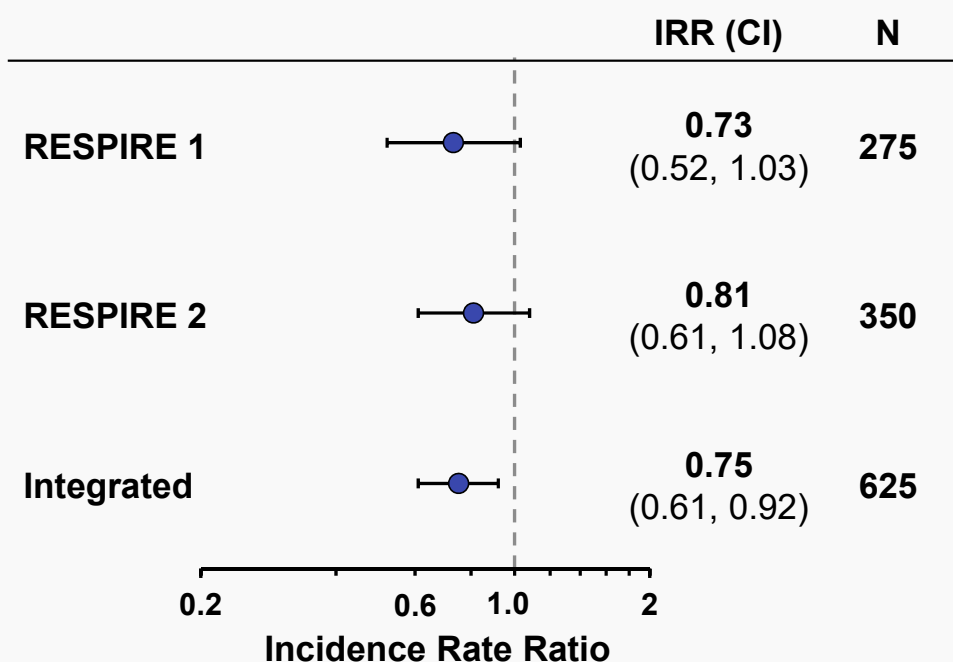

Cipro 14 vs Pooled Placebo

	HR (CI)	N
RESPIRE 1	**0.53** (0.36, 0.80)	275
RESPIRE 2	**0.87** (0.62, 1.21)	350
Integrated	**0.68** (0.54, 0.87)	625

Hazard Ratio

Cipro 28 vs Pooled Placebo

|	HR (CI)	N
RESPIRE 1	**0.73** (0.50, 1.07)	279
RESPIRE 2	**0.71** (0.39, 1.27)	345
Integrated	**0.71** (0.56, 0.90)	624

Hazard Ratio

Confidence intervals are 97.5% for RESPIRE 1 and 95.1% (Ciprofloxacin DPI 14) / 99.9% (Ciprofloxacin DPI 28) for RESPIRE 2. Confidence interval are 95.0% for integrated
HRs are based on Cox Proportional Hazards model for the comparison of active treatment vs. pooled placebo (HRs <1 indicate better outcome on active treatment).

Frequency of Exacerbations by Single Study and in an Integrated Analysis of RESPIRE 1 and 2

Cipro 14 vs Pooled Placebo

	IRR (CI)	N
RESPIRE 1	0.73 (0.52, 1.03)	275
RESPIRE 2	0.81 (0.61, 1.08)	350
Integrated	0.75 (0.61, 0.92)	625

Incidence Rate Ratio: 0.2 0.6 1.0 2

Cipro 28 vs Pooled Placebo

	IRR (CI)	N
RESPIRE 1	0.86 (0.63, 1.18)	279
RESPIRE 2	0.56 (0.33, 0.95)	345
Integrated	0.72 (0.58, 0.88)	624

Incidence Rate Ratio: 0.2 0.6 1.0 2

Confidence intervals are 97.5% for RESPIRE 1 and 95.1% (Ciprofloxacin DPI 14) / 99.9% (Ciprofloxacin DPI 28) for RESPIRE 2. Confidence interval are 95.0% for integrated.
Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment vs. pooled placebo (IRRs <1 indicate better outcome on active treatment).

CC-49
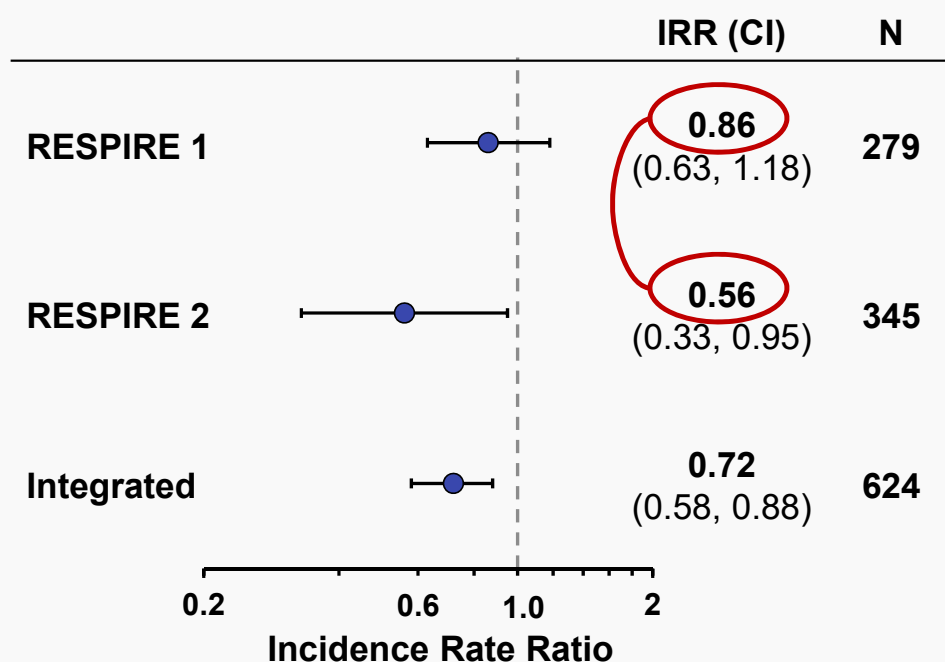
Analyses Conducted to Investigate the Differences Between RESPIRE 1 and RESPIRE 2
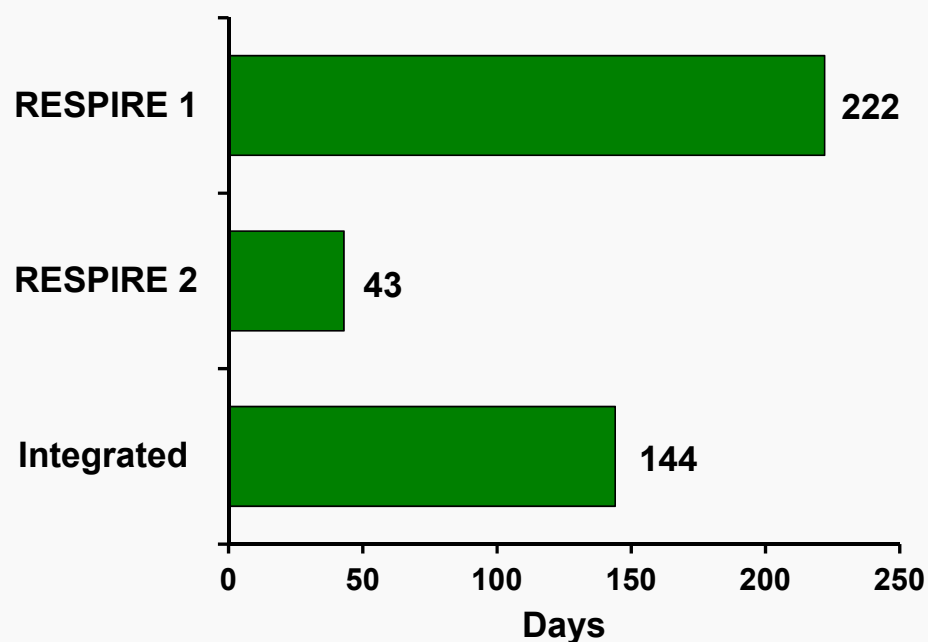
- **Geographical / Regional Effects**

- **Disease history / Severity of Disease / Comorbidities**

- **Demographic Factors (Age, Gender, Race)**

- **Time/ Seasonal Effects**

- **Influence of Resistance / MIC values**

- **Screening of subgroups individually and in combination**

- **None of these analyses produced meaningful explanations:**
  - ‣ Different exacerbation rates observed in placebo groups between studies
  - ‣ Range of Ciprofloxacin DPI treatment effects observed between studies and treatment regimens

CC-50

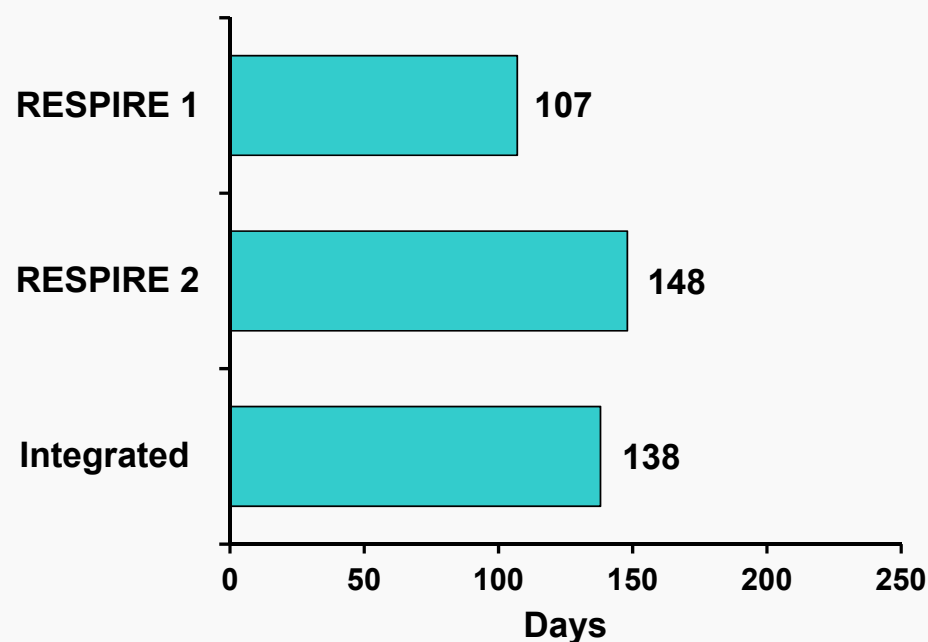# RESPIRE 1 and 2: Time to First Exacerbation Event for Placebo Groups

RESPIRE 2, Pooled Placebo (N=174)

RESPIRE 1, Pooled Placebo (N=138)

O Censored
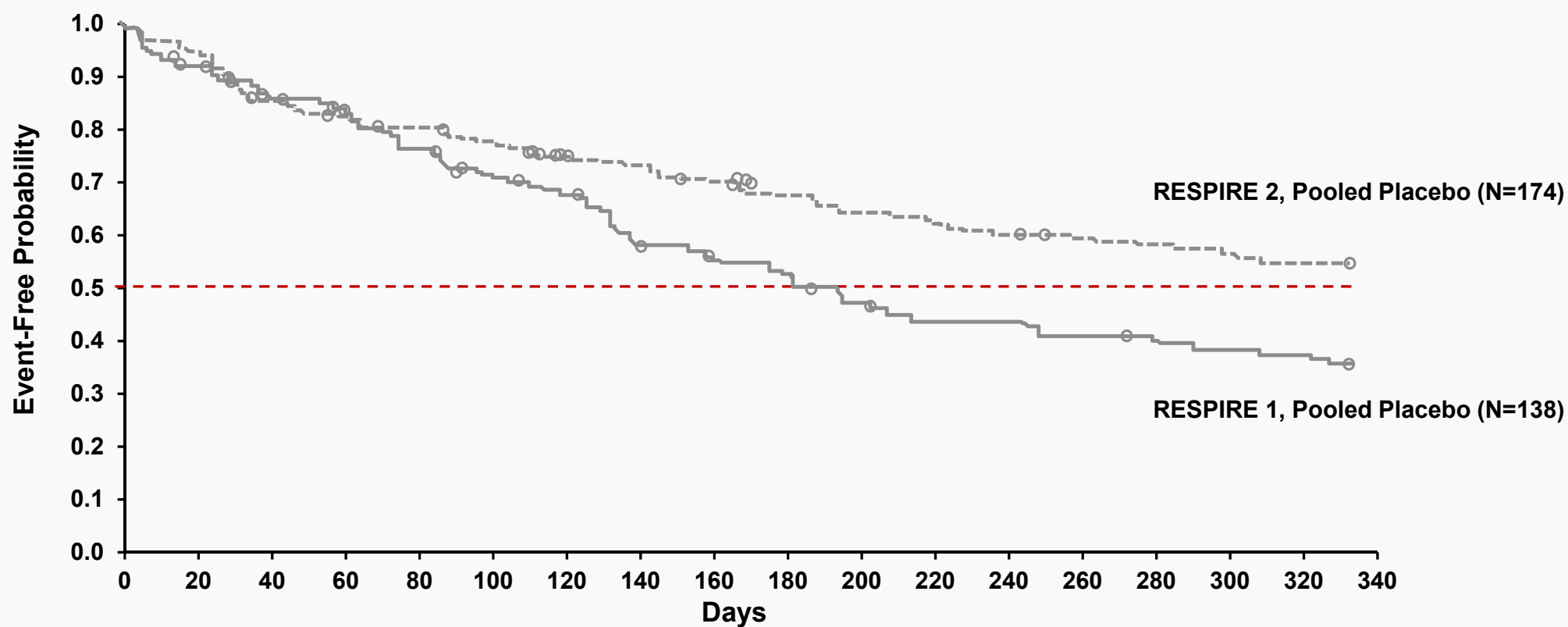
Integrated Analysis: Increase in Median Time to First Exacerbation by Single Study and in the Integrated Analysis

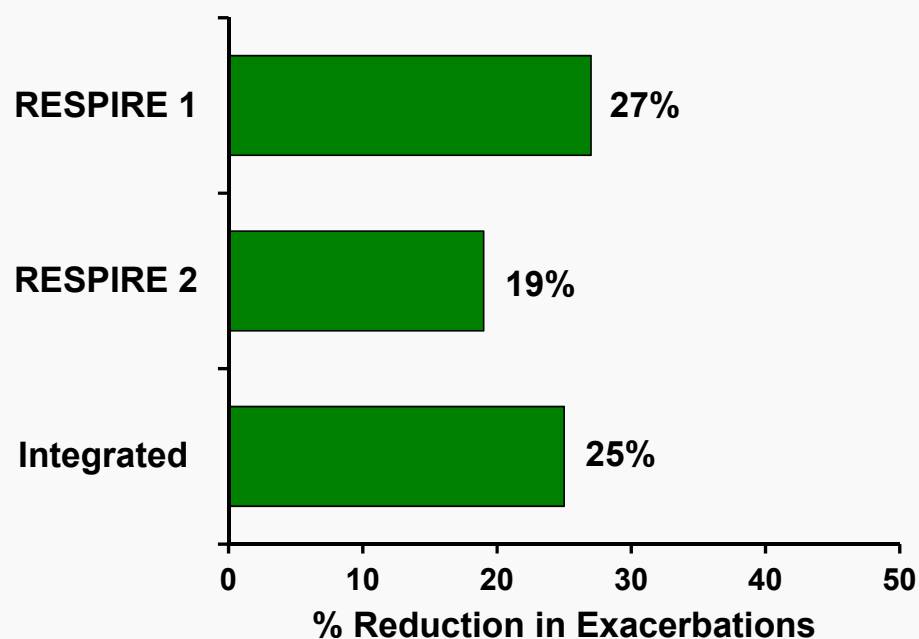Model (Weibull regression) based estimates of mean survival time (in days) until first exacerbation

CC-52

Integrated Analysis: Decrease in Frequency of Exacerbations by Single Study and in the Integrated Analysis

Ciprofloxacin DPI 14
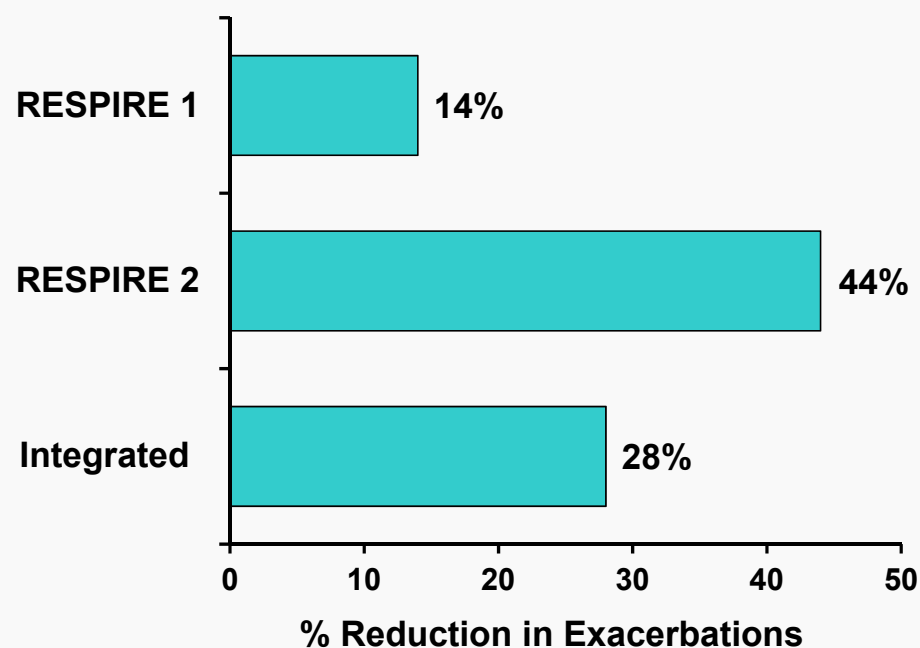
Study	% Reduction in Exacerbations
RESPIRE 1	27%
RESPIRE 2	19%
Integrated	25%

% Reduction in Exacerbations

Ciprofloxacin DPI 28

Study	% Reduction in Exacerbations
RESPIRE 1	14%
RESPIRE 2	44%
Integrated	28%

% Reduction in Exacerbations

Decrease in frequency from Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment vs. pooled placebo

CC-53

Resistance Rates per Patient at Baseline and EOT RESPIRE 1 and 2

Group	Baseline Resistance		Resistance at End of Treatment	
	n/N	Percentage	n/N	Percentage
Ciprofloxacin DPI 14	71/313	**22.7%**	50/241	**20.7%**
Ciprofloxacin DPI 28	67/312	**21.5%**	48/245	**19.6%**
Pooled placebo	62/312	**19.9%**	26/232	**11.2%**

EOT: End of Treatment
Resistance n/N based on patients with ≥ 1 resistant isolate/total numbers of patients with a sputum sample
Systemic breakpoints used.

Integrated Analysis: Frequency of Exacerbations by Baseline Pathogen for RESPIRE 1 and 2

	Baseline Pathogen							
	P. aeruginosa		*S. aureus*		*H. influenzae*		*S. pneumoniae, M. catarrhalis, S. maltophilia, or B. cepacia*	
Group	N	Exacerbation Frequency[1]	N	Exacerbation Frequency[1]	N	Exacerbation Frequency[1]	N	Exacerbation Frequency[1]
Ciprofloxacin DPI 14	190	0.58	69	0.51	59	0.64	55	0.71
Ciprofloxacin DPI 28	182	0.57	76	0.45	72	0.75	48	0.69
Pooled placebo	195	0.78	76	0.79	69	0.71	47	0.89

1. Frequency of exacerbations during the 48 week course of the study.

Total Number of Exacerbations During RESPIRE 1 and RESPIRE 2
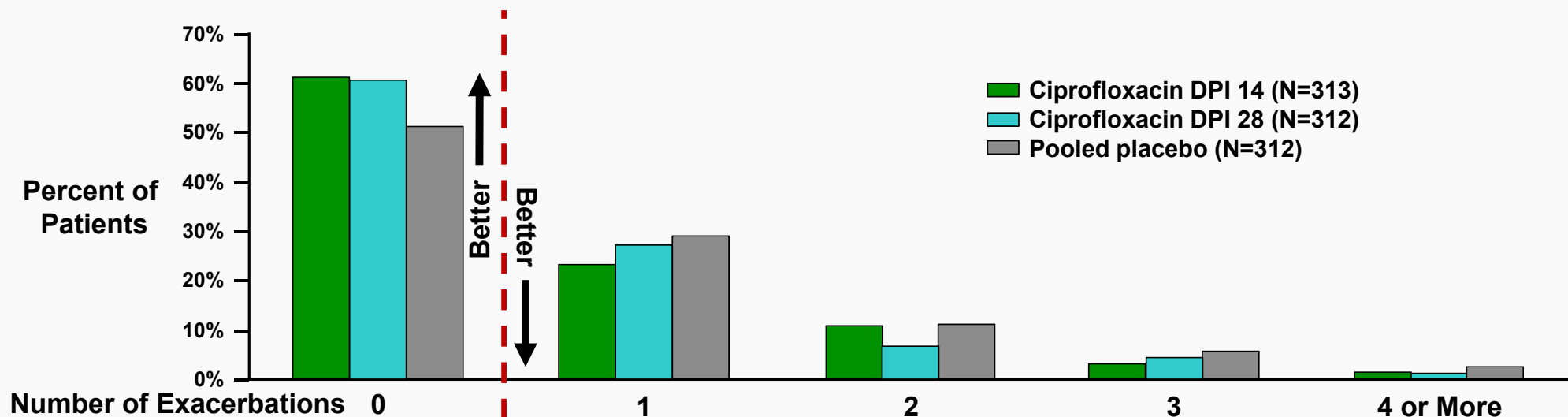
Treatment Group	Total Patients	Exacerbations	
		Total	Mean/Patient
Ciprofloxacin DPI 14	313	188	0.60
Ciprofloxacin DPI 28	312	184	0.59
Pooled placebo	312	248	0.79

Note: Given is the absolute number of exacerbations (≥3 signs) and the arithmetic mean (related to patients in FAS).
Source: Integrated analysis, data on file

CC-56

Integrated Analysis, RESPIRE 1 and 2: Time to First Exacerbation
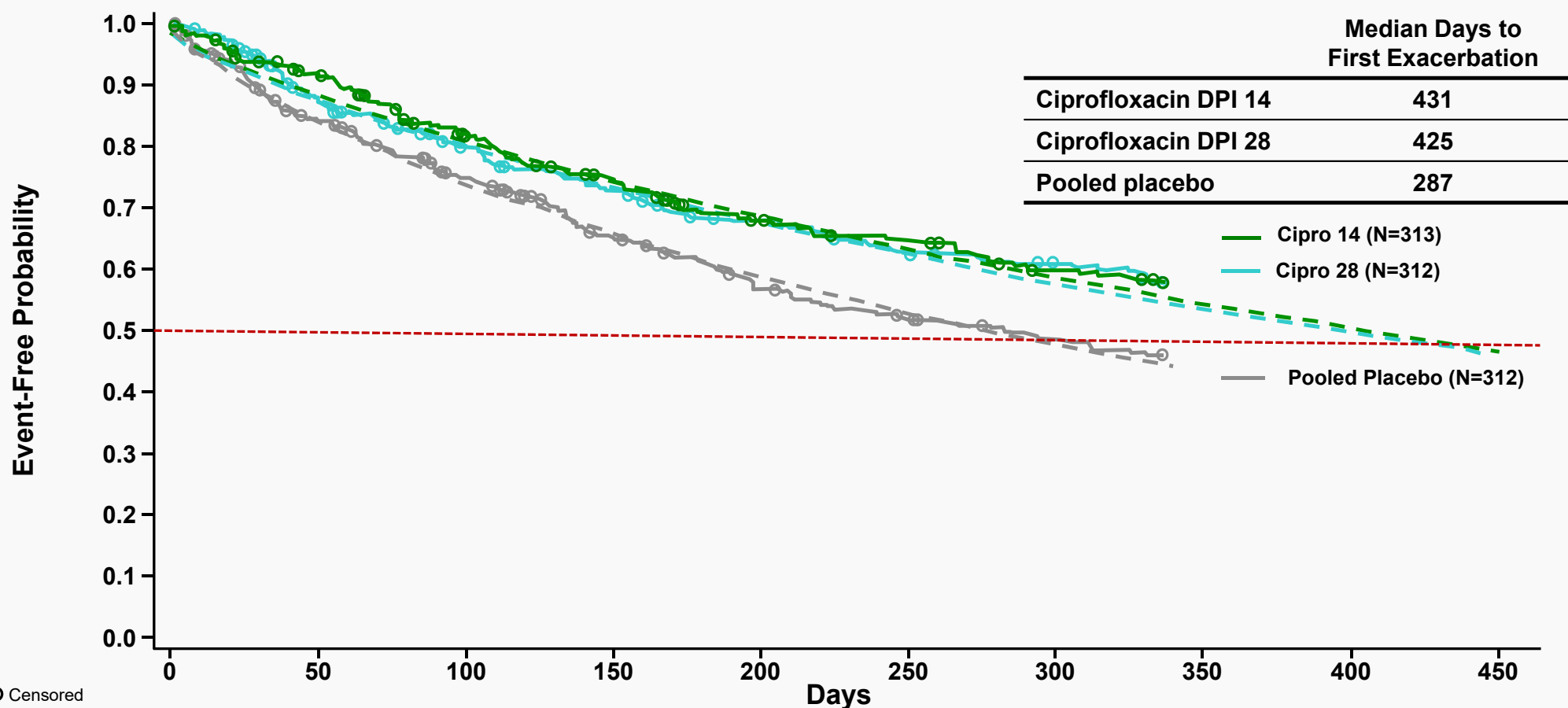
	Median Days to First Exacerbation
Ciprofloxacin DPI 14	431
Ciprofloxacin DPI 28	425
Pooled placebo	287

Cipro 14 (N=313)
Cipro 28 (N=312)
Pooled Placebo (N=312)

O Censored

*Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution. Kaplan Meier plots are solid lines, Weibull survival fits are dashed.
See figure 4c, FDA Briefing Document

Summary of Treatment Effects

- **Two global Phase III trials; 937 patients enrolled**

- **Two dosing regimens tested (identical dose)**

- **Range of treatment estimates favoring ciprofloxacin DPI**

  ‣ Ciprofloxacin DPI 14 and 28

  ‣ RESPIRE 1 and 2

- **Overall favorable treatment effect: exacerbations & other endpoints**

Ciprofloxacin DPI 14	Ciprofloxacin DPI 28
• **144 Day** delay time to first exacerbation	• **138 Day** delay time to first exacerbation
• **25%** reduction frequency of exacerbations	• **28%** reduction frequency of exacerbations

CC-58

Safety

Gesa Schomakers, MD
Head of Therapeutic Area Anti-Infectives
Pharmacovigilance Benefit-Risk Management
Bayer

Introduction to Safety Assessment

- **Ciprofloxacin is a well established antibiotic drug for oral and intravenous use with 30 years post-marketing experience**

- **Nonclinical safety evaluation of ciprofloxacin DPI was performed in agreement with FDA and according to FDA/ICH guidelines for drug products administered chronically by inhalation**

- **Clinical safety evaluation was performed in agreement with FDA according to FDA/ICH guidelines for drug products intended for long term use**

Pooled Analysis of Phase III Safety Data

- Improves ability to detect safety signals

- Consistent adverse event profiles in the individual studies (RESPIRE 1 and RESPIRE 2)

- Safety presentation focuses on all AEs from first administration of study medication to 30 days after last dose (TEAE – treatment emergent AEs)

Composition of Integrated Safety Pool

- **Respective treatment arms from RESPIRE 1 and RESPIRE 2 were pooled**

- **Safety population consists of:**
  - 310 patients ciprofloxacin DPI 14
  - 312 patients ciprofloxacin DPI 28
  - 311 patients pooled placebo

- **More female patients (62.6%)**

- **Mean age 62.1 yrs. (18-91 yrs.)**

- **Pooled population representative of NCFB population with regards to demographic factors and medical history**

No Increase in Incidence for AE, SAE, Death and Discontinuations
Pooled Safety Data

	Cipro 14 N=310 n (%)	Cipro 28 N=312 n (%)	Pooled Placebo N=311 n (%)
Any TEAE	239 (77.1)	205 (65.7)	230 (74.0)
Any serious TEAE	68 (21.9)	57 (18.3)	73 (23.5)
Discontinuation due to TEAE	27 (8.7)	20 (6.4)	29 (9.3)
TEAE with outcome death	4 (1.3)	6 (1.9)	5 (1.6)

Most Frequent Adverse Events – Preferred Term
Pooled Safety Data

	Cipro 14 N=310 n (%)	Cipro 28 N=312 n (%)	Pooled Placebo N=311 n (%)
Any TEAE	**239 (77.1)**	**205 (65.7)**	**230 (74.0)**
Hemoptysis	33 (10.6)	27 (8.7)	32 (10.3)
Bronchiectasis	32 (10.3)	33 (10.6)	38 (12.2)
Nasopharyngitis	32 (10.3)	25 (8.0)	24 (7.7)
Dyspnea	26 (8.4)	20 (6.4)	12 (3.9)
Headache	24 (7.7)	21 (6.7)	9 (2.9)
Cough	20 (6.5)	20 (6.4)	20 (6.4)
Upper respiratory tract infection	17 (5.5)	14 (4.5)	15 (4.8)
Diarrhea	16 (5.2)	8 (2.6)	10 (3.2)
Bronchospasm	14 (4.5)	10 (3.2)	19 (6.1)

The incidence cut of ≥5% was applied to any of the treatment groups (active treatment groups or pooled placebo group)

SAEs by System Organ Class
Pooled Safety Data

	Cipro 14 N=310 n (%)	Cipro 28 N=312 n (%)	Pooled Placebo N=311 n (%)
Any serious TEAE	**68 (21.9)**	**57 (18.3)**	**73 (23.5)**
Respiratory, thoracic and mediastinal disorders	40 (12.9)	38 (12.2)	44 (14.1)
Infections and infestations	10 (3.2)	15 (4.8)	18 (5.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0)	2 (0.6)	6 (1.9)
Cardiac disorders	3 (1.0)	4 (1.3)	3 (1.0)
Gastrointestinal disorders	3 (1.0)	2 (0.6)	4 (1.3)
Injury, poisoning and procedural complication	4 (1.3)	1 (0.3)	3 (1.0)
Nervous system disorders	2 (0.6)	3 (1.0)	3 (1.0)
Musculoskeletal and connective tissue disorders	2 (0.6)	1 (0.3)	3 (1.0)

SOC with more than 2 patients are displayed.

Adverse Events With Fatal Outcome
Pooled Safety Data

	Cipro 14 N=310 n (%)	Cipro 28 N=312 n (%)	Pooled Placebo N=311 n (%)
Any TEAE with fatal outcome	**4 (1.3)**	**6 (1.9)**	**5 (1.6)**
Bronchiectasis	1 (0.3)	2 (0.6)	2 (0.6)
Cor pulmonale	0	2 (0.6)	0
Pneumonia	0	1 (0.3)	1 (0.3)
Esophageal carcinoma	1 (0.3)	0	0
Gastrointestinal hemorrhage	1 (0.3)	0	0
Pneumonia aspiration	1 (0.3)	0	0
Congestive cardiomyopathy	0	1 (0.3)	0
Complications of transplant surgery	0	0	1 (0.3)
Pulmonary hemorrhage	0	0	1 (0.3)

CC-66

Selected Events of Interest (TEAEs)
Pooled Safety Data

	Cipro 14 N=310 n (%)	Cipro 28 N=312 n (%)	Pooled Placebo N=311 n (%)
Bronchospasm	14 (4.5)	10 (3.2)	19 (6.1)
Hemoptysis	33 (10.6)	27 (8.7)	32 (10.3)
Positive Aspergillus tests	8 (2.6)	7 (2.2)	2 (0.6)

Selected Adverse Events of Interest: Bronchospasm
Pooled Safety Data

	Cipro 14 N=310 n (%)	Cipro 28 N=312 n (%)	Pooled Placebo N=311 n (%)
Number of patients with event			
TEAEs	14 (4.5)	10 (3.2)	19 (6.1)
Serious TEAEs	0	1 (0.3)	0
Number of patients with event			
On cycle	14 (4.5)	9 (2.9)	17 (5.5)
Off cycle	0	1 (0.3)	2 (0.6)

Patients can have both on- and off-cycle events

Selected Adverse Events of Interest: Hemoptysis
Pooled Safety Data

	Cipro 14 N=310 n (%)	Cipro 28 N=312 n (%)	Pooled Placebo N=311 n (%)
Number of patients with event			
TEAEs	33 (10.6)	27 (8.7)	32 (10.3)
Serious TEAEs	4 (1.3)	4 (1.3)	6 (1.9)
Number of patients with event			
On cycle	21 (6.8)	16 (5.1)	18 (5.8)
Off cycle	21 (6.8)	18 (5.8)	22 (7.1)

Patients can have both on- and off-cycle events

CC-69

Ciprofloxacin DPI Yields Low Systemic Exposure in NCFB Patients

Chart axis: Concentration of Ciprofloxacin (mg/L) (Unbound C_{max})

Y-axis values: 1000, 100, 10, 1, 0.1, 0.01

Ciprofloxacin DPI Sputum $C_{max,u}$ = 120 mg/L (median)

~ 58 x

~ 1400 x

Oral ciprofloxacin [500 mg BID] Plasma (Healthy subjects) $C_{max,ss,u}$ = 2.08 mg/L

~ 24 x

Ciprofloxacin DPI Plasma $C_{max,ss,u}$ = 0.086 mg/L (median)

fraction unbound in plasma = 0.7

CC-70
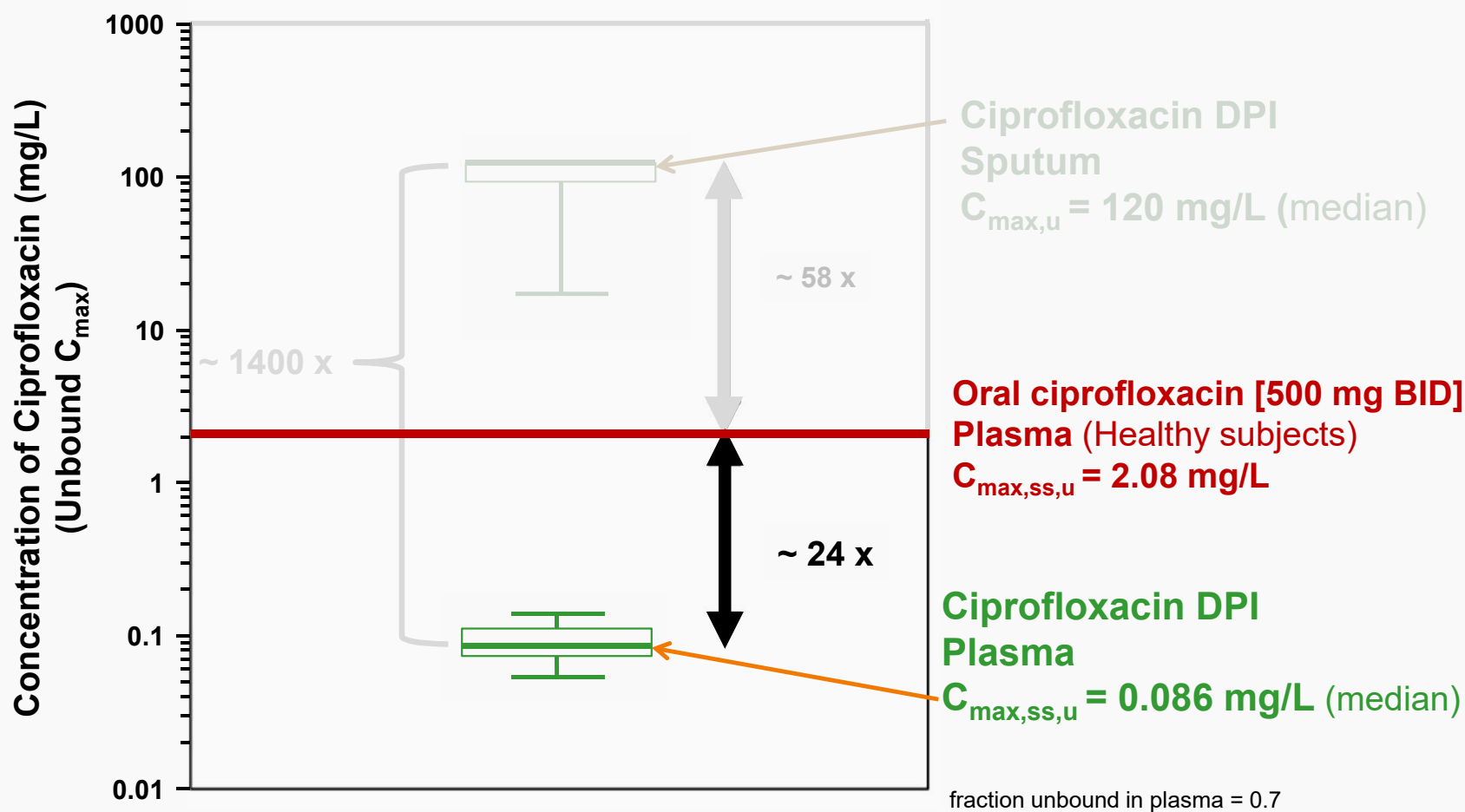
No Increased Risk for Systemic Fluoroquinolone Class Effects

	Cipro 14 N=310 n (%)	Cipro 28 N=312 n (%)	Pooled Placebo N=311 n (%)
Hypersensitivity	32 (10.3)	21 (6.7)	40 (12.9)
Hepatic disorders	7 (2.3)	4 (1.3)	4 (1.3)
Tendon disorder	5 (1.6)	3 (1.0)	3 (1.0)
Psychiatric reactions	3 (1.0)	0	2 (0.6)
Peripheral neuropathy	1 (0.3)	0	1 (0.3)
Prolongation of QTc interval	0	1 (0.3)	0
Seizure	0	1 (0.3)	0
Clostridial gastroenteritis	0	0	1 (0.3)

CC-71

Safety Summary

- **Adverse event profile consistent across studies and treatment regimens**

  - Most AEs mild to moderate, no relevant differences between treatment arms

  - No increased rate for deaths; SAEs, and discontinuations in ciprofloxacin DPI treated patients

  - No increased risk for class effects associated with systemic fluoroquinolones

- **Ciprofloxacin DPI has a favorable safety profile**

Clinical Perspective on Ciprofloxacin DPI Safety & Effectiveness

Timothy R. Aksamit, MD
Pulmonary Disease and Critical Care Medicine
Mayo Clinic
Rochester, MN

Division of
**PULMONARY &
CRITICAL CARE MEDICINE**

CC-73

Inhaled Antibiotics for Bronchiectasis

MAYO CLINIC ▮▮▮▮▮▮▮▮▮
ROCHESTER, MINNESOTA

▮▮▮▮▮▮

February 12, 1951

Dr. E. H. Littig
Mechanicsville, Iowa

Dear Dr. Littig:

We wish to thank you very much for referring little ▮▮▮▮▮▮▮▮
to the Clinic. I saw her in consultation with Dr. Keith and am glad to send you
a report of our findings.

Our studies, which included bronchoscopic and bronchographic studies,
revealed that ▮▮▮▮▮ has bilateral bronchiectasis. There is involvement of
the left lower lobe, the lingula of the left upper lobe, and some involvement of
all three lobes on the right side. The major involvement is in the left lower
lobe. The situation was discussed at some length with the ▮▮▮▮▮▮▮, and Dr.
Clagett of the department of thoracic surgery saw ▮▮▮▮ in consultation with me.
It is obvious that surgical treatment would require bilateral operations, and,
even so, it would be impossible to remove all of her trouble. I instructed her
in the technique of nebulization therapy. I recommended the use of a DeVilbiss
#40 nebulizer and suggested that they obtain an electric motor and air compressor
from the Jordan Pump Company at Kansas City, Missouri. As a matter of fact, the
DeVilbiss nebulizer comes with this equipment. Soluble penicillin tablets are
made by both Lilly and Sharp and Dohme in 50,000 and 100,000-unit sizes. These
can be put directly into the nebulizer and can be dissolved in either sterile
saline or distilled water. I think a concentration of 50,000 units would be most
desirable and would suggest that she try to use 400,000 to 500,000 units daily.
We suggested to the ▮▮▮▮▮▮ that they try a conservative program for three or
four months and perhaps return here in July for re-evaluation. At that time we
might consider the desirability of doing a left lower lobectomy and lingulectomy.
Other factors in treatment, such as postural drainage and climate change, were
discussed.

There were no other significant findings in the course of ▮▮▮▮ exam-
ination. She was 55 inches tall and weighed 74½ pounds. The blood pressure was
110/80. Laboratory studies were as follows: urinalysis was normal, hemoglobin
determination was 13.7 gm. per cent, and leukocyte count was 5,700. Differential
count showed 28 per cent lymphocytes, 2.5 per cent monocytes, 65.5 per cent
neutrophils, 3.5 per cent eosinophils, and 0.5 per cent basophils. Sedimentation
rate was 10 mm. in one hour (Westergren). Bronchial material was negative for
acid-fast bacilli on smear. Sinus x-rays showed thickened membrane in the right
antrum and a moderate amount of adenoid tissue; the frontal sinuses were undeveloped.

We shall be glad to cooperate in this patient's further care.

Sincerely yours,

A. M. Olsen, M. D.

AMO:DM

P. S. Cultures of sputum have just been reported and show the presence of
Hemophilus influenzae. If her response to penicillin inhalation treatment is not
satisfactory, one might try using streptomycin or dihydrostreptomycin by inhalation.
Usually we recommend 1 gm. daily, using a concentration of 200 mg. ▮▮▮▮▮▮▮▮

CC-74

Inhaled Antibiotics for Bronchiectasis

MAYO CLINIC ▓▓▓▓▓▓▓▓▓▓
ROCHESTER, MINNESOTA

▓▓▓▓▓▓▓

February 12, 1951

Dr. E. H. Littig
Mechanicsville, Iowa

Dear Dr. Littig:

We wish to thank you very much for referring little ▓▓▓▓▓▓▓▓▓ to the Clinic. I saw her in consultation with Dr. Keith and am glad to send you a report of our findings.

Our studies, which included bronchoscopic and bronchographic studies, revealed that ▓▓▓▓▓ has bilateral bronchiectasis. There is involvement of the left lower lobe, the lingula of the left upper lobe, and some involvement of all three lobes on the right side. The major involvement is in the left lower lobe. The situation was discussed at some length with the ▓▓▓▓▓▓, and Dr. Clagett of the department of thoracic surgery saw ▓▓▓▓ in consultation with me. It is obvious that surgical treatment would require bilateral operations, and, even so, it would be impossible to remove all of her trouble. I instructed her in the technique of nebulization therapy. I recommended the use of a DeVilbiss #40 nebulizer and suggested that they obtain an electric motor and air compressor from the Jordan Pump Company at Kansas City, Missouri. As a matter of fact, the DeVilbiss nebulizer comes with this equipment. Soluble penicillin tablets are made by both Lilly and Sharp and Dohme in 50,000 and 100,000-unit sizes. These can be put directly into the nebulizer and can be dissolved in either sterile saline or distilled water. I think a concentration of 50,000 units would be most desirable and would suggest that she try to use 400,000 to 500,000 units daily. We suggested to the ▓▓▓▓ that they try a conservative program for three or four months and perhaps return here in July for re-evaluation. At that time we might consider the desirability of doing a left lower lobectomy and lingulectomy. Other factors in treatment, such as postural drainage and climate change, were discussed.

There were no other significant findings in the course of ▓▓▓▓ examination. She was 55 inches tall and weighed 74½ pounds. The blood pressure was 110/80. Laboratory studies were as follows: urinalysis was normal, hemoglobin determination was 13.7 gm. per cent, and leukocyte count was 5,700. Differential count showed 28 per cent lymphocytes, 2.5 per cent monocytes, 65.5 per cent neutrophils, 3.5 per cent eosinophils, and 0.5 per cent basophils. Sedimentation rate was 10 mm. in one hour (Westergren). Bronchial material was negative for acid-fast bacilli on smear. Sinus x-rays showed thickened membrane in the right antrum and a moderate amount of adenoid tissue; the frontal sinuses were undeveloped.

We shall be glad to cooperate in this patient's further care.

Sincerely yours,

A. M. Olsen, M. D.

AMO:DM

P. S. Cultures of sputum have just been reported and show the presence of Hemophilus influenzae. If her response to penicillin inhalation treatment is not satisfactory, one might try using streptomycin or dihydrostreptomycin by inhalation. Usually we recommend 1 gm. daily, using a concentration of 200 mg. ▓▓▓▓

CC-75

Inhaled Antibiotics for Bronchiectasis

MAYO CLINIC
ROCHESTER, MINNESOTA

February 12, 1951

Dr. E. H. Littig
Mechanicsville, Iowa

Dear Dr. Littig:

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There were no other significant findings in the course of ▮▮▮▮ examination. She was 55 inches tall and weighed 74½ pounds. The blood pressure was 110/80. Laboratory studies were as follows: urinalysis was normal, hemoglobin determination was 13.7 gm. per cent, and leukocyte count was 5,700. Differential count showed 28 per cent lymphocytes, 2.5 per cent monocytes, 65.5 per cent neutrophils, 3.5 per cent eosinophils, and 0.5 per cent basophils. Sedimentation rate was 10 mm. in one hour (Westergren). Bronchial material was negative for acid-fast bacilli on smear. Sinus x-rays showed thickened membrane in the right antrum and a moderate amount of adenoid tissue; the frontal sinuses were undeveloped.

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NCFB Today: Data from US Bronchiectasis Research Registry

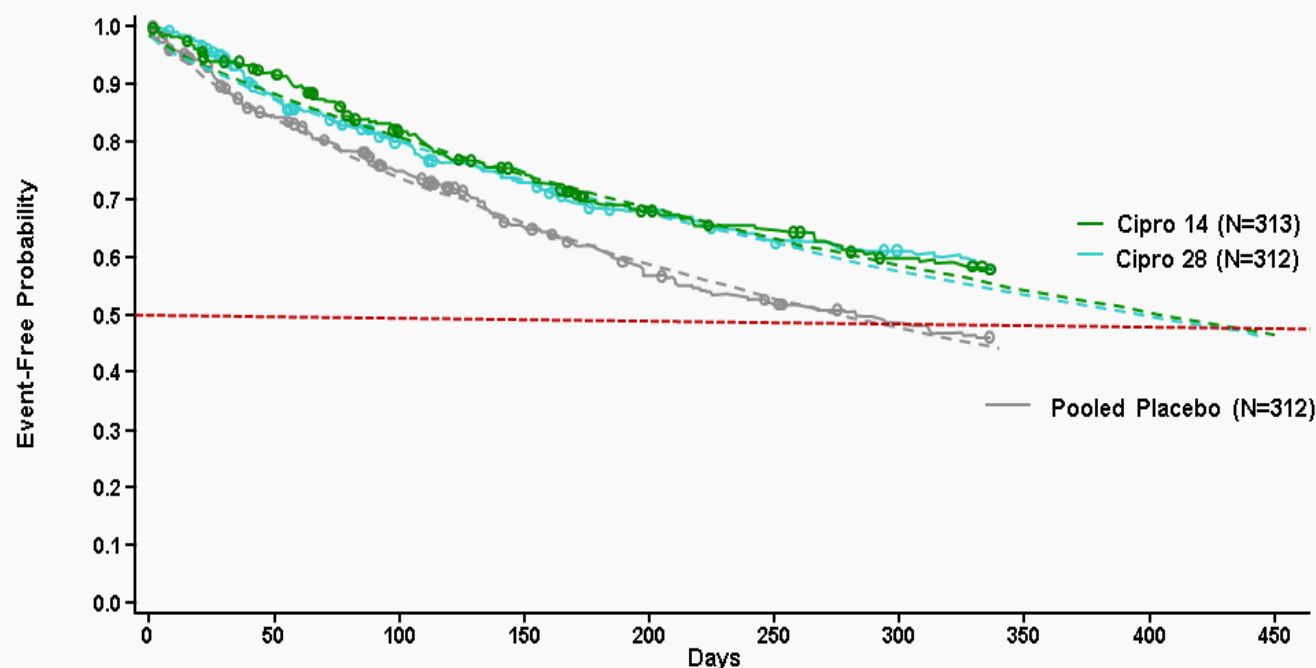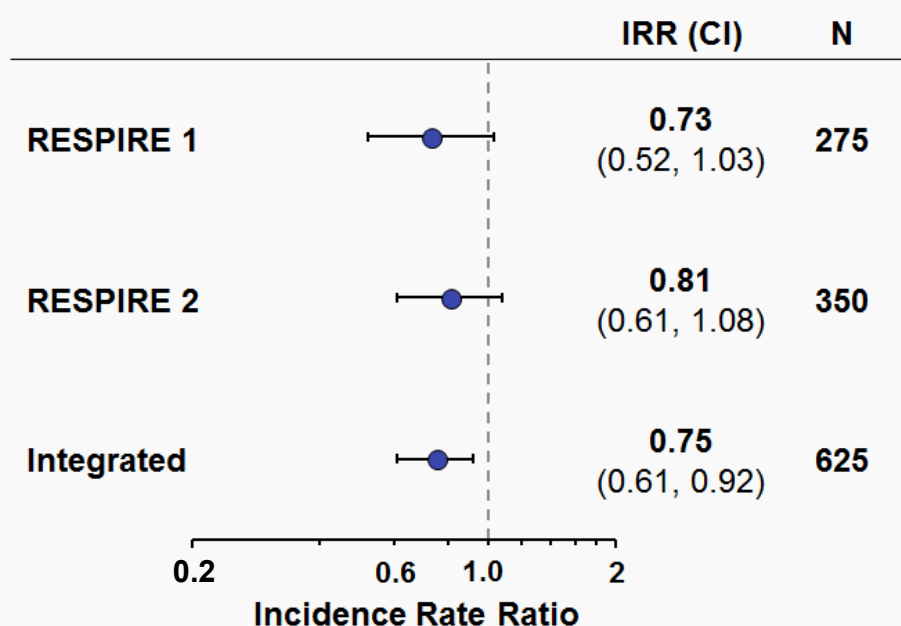|	Patients with ≥2 exacerbations/year n=198 (18.9%)	Patients with <2 exacerbations/year n=851 (81.1%)
Baseline*		
Pseudomonas sputum isolation (% of patients)	50%	35%
Inhaled antibiotic (% of patients)	29%	13%
History of hospitalization (% of patients)	29.7%	17.2%
for exacerbation (% of patients)	79.2%	56.0%
During 2-year follow-up period:		
Average exacerbations (in 2 years) +/- SD	2.58 +/-0.97	0.32 +/-0.47
Hospital admissions per year (mean)	0.39	0.05

CC-77

Large Unmet Need for NCFB Patients

- Gap in knowledge about science of NCFB

- Lack of any FDA approved therapeutics for NCFB

- An exacerbation has a big impact[3,4] on
  - the patient
  - the physician
  - healthcare utilization
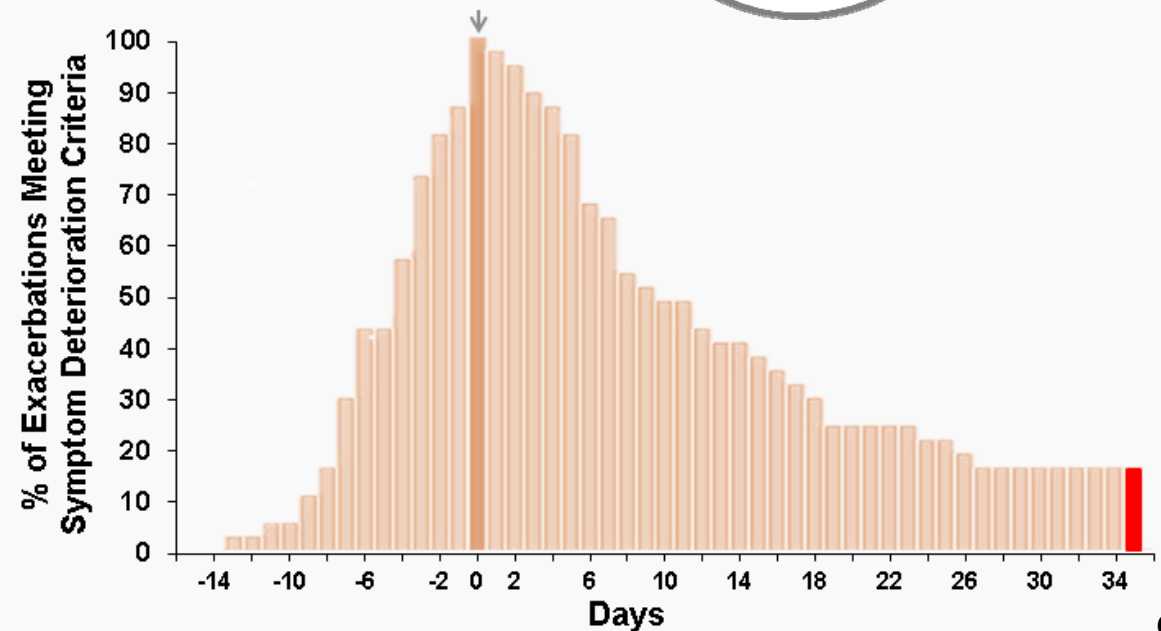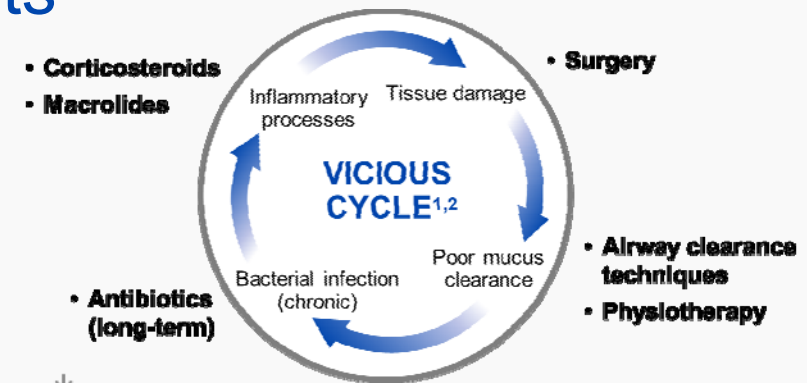
1. Cole PJ. *Eur J Respir Dis.* 1986;69:6.
2. King PT. *Int J Chron Obstruct Pulmon Dis.* 2009;4:411.
3. Brill SE, et al. *Respir Res.* 2015;16:16.
4. de la Rosa D, et al. *Chron Respir Dis.* 2016; 13:361

CC-78

Large Unmet Need for NCFB Patients: the Opportunity at Hand

- Gap in knowledge about science of NCFB

- Lack of any FDA approved therapeutics for NCFB

- An exacerbation has a big impact[1,2] on
  - the patient
  - the physician
  - healthcare utilization

Legend:
- Cipro 14 (N=313)
- Cipro 28 (N=312)
- Pooled Placebo (N=312)
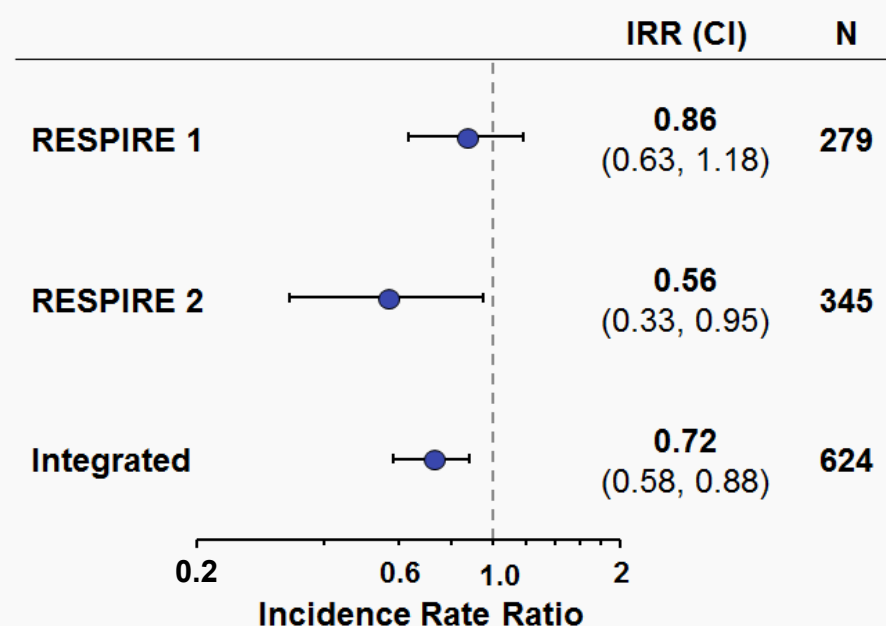
Y-axis: Event-Free Probability
X-axis: Days

1. Brill SE, et al. *Respir Res.* 2015;16:16.
2. de la Rosa D, et al. *Chron Respir Dis.* 2016; 13:361

Frequency of Exacerbations in RESPIRE 1, RESPIRE 2 and Integrated Analysis

Cipro 14 vs Pooled Placebo

	IRR (CI)	N
RESPIRE 1	0.73 (0.52, 1.03)	275
RESPIRE 2	0.81 (0.61, 1.08)	350
Integrated	0.75 (0.61, 0.92)	625

Incidence Rate Ratio

Cipro 28 vs Pooled Placebo

	IRR (CI)	N
RESPIRE 1	0.86 (0.63, 1.18)	279
RESPIRE 2	0.56 (0.33, 0.95)	345
Integrated	0.72 (0.58, 0.88)	624

Incidence Rate Ratio

Confidence intervals are 97.5% for RESPIRE 1 and 95.1% (Ciprofloxacin DPI 14) / 99.9% (Ciprofloxacin DPI 28) for RESPIRE 2. Confidence interval are 95.0% for integrated.
Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment vs. pooled placebo (IRRs <1 indicate better outcome on active treatment).

CC-80

Ciprofloxacin DPI: Unprecedented Opportunity for NCFB Patients

- Well characterized drug with new way of administration

- Increases in time to first exacerbation for patients

- Safe and convenient
  - Minimal systemic absorption
  - Adverse event rates similar to placebo
  - Dry powder inhaler

Hope for NCFB Patients Exists Now

What: Ciprofloxacin DPI 14-day on/off and 28-day on/off regimen

- The two regimens showed comparable, meaningful treatment effect
- More tools in the toolbox allow for better individualized approach

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Who: Not everyone

- Frequent exacerbators i.e. ≥2 exacerbations/yr
- Respiratory pathogens, not just *P. aeruginosa*

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- Respiratory pathogens, not just *P. aeruginosa*

Why: Suboptimal care will improve to best care for NCFB patients

- Don't have to use off-label or compounded non-approved products
- Lower number of exacerbations, which do have big impact on life
- Less systemic antibiotic exposure
- Safety and tolerability profile
- Approval would allow for structured data collection through registry
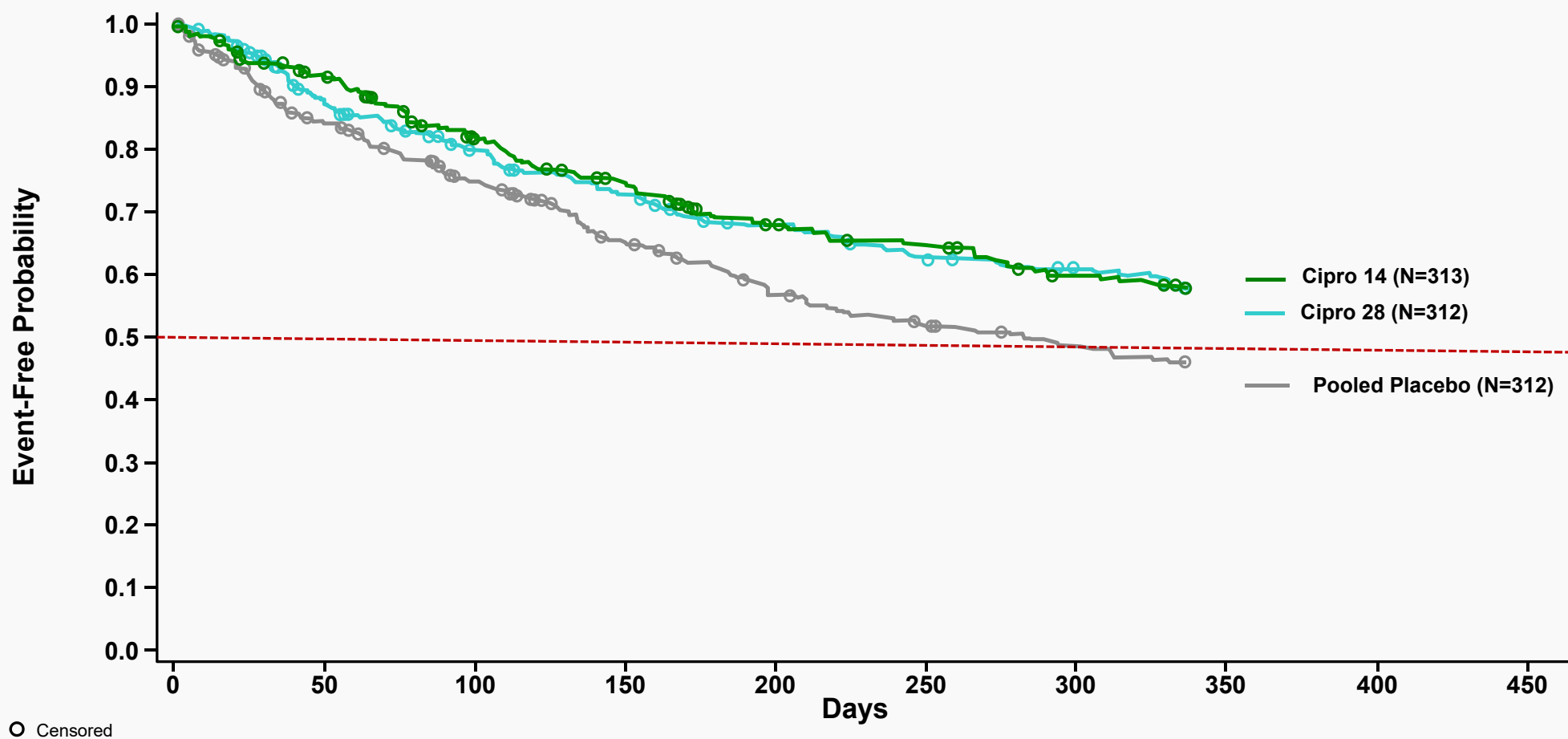
Conclusion

Jeff Alder, PhD

Senior Director, Global Clinical Development
Bayer

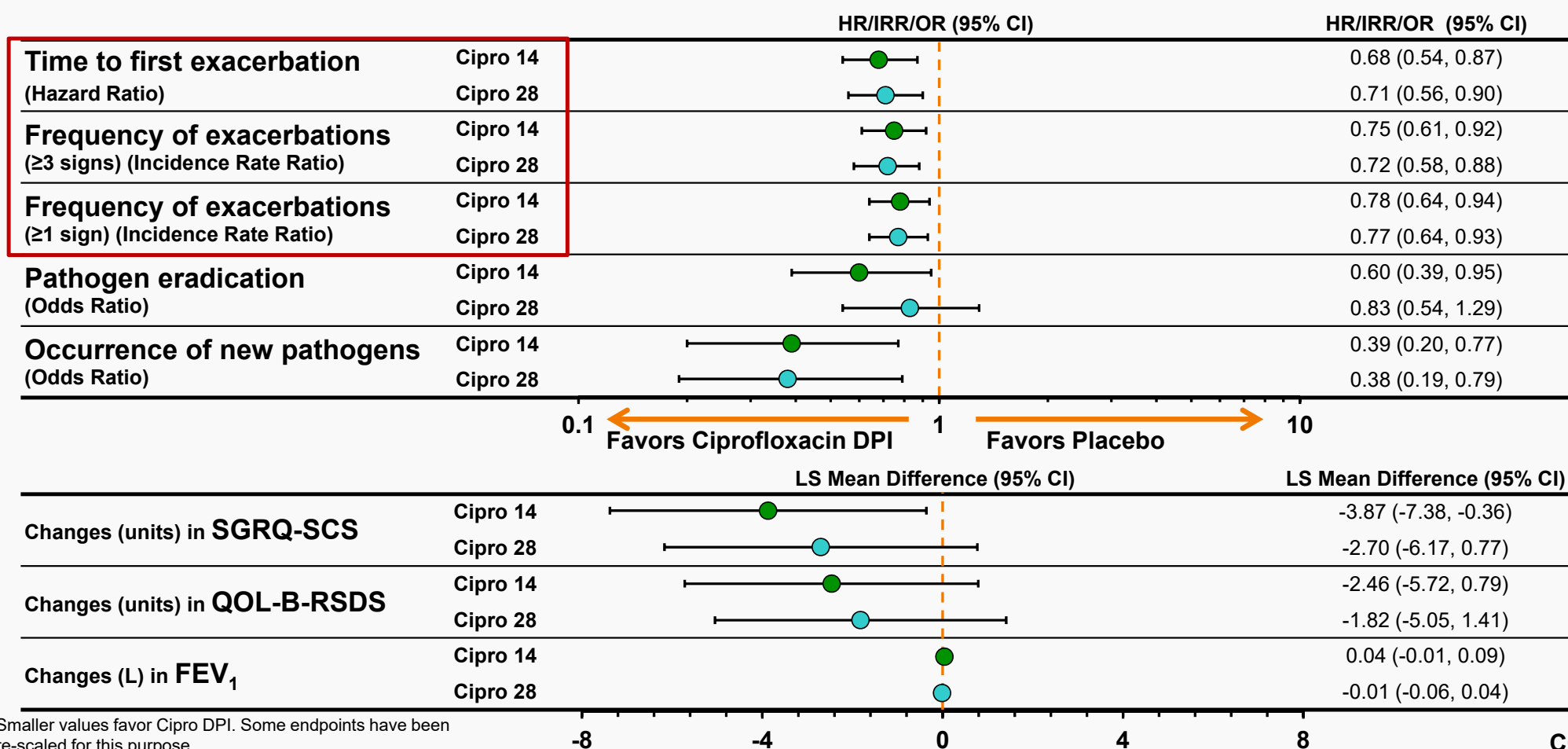# Proposed Indication for Ciprofloxacin DPI 14 and 28

INDICATIONS AND USAGE:

- *CIPROFLOXACIN DPI is indicated for reduction of exacerbations in non-cystic fibrosis bronchiectasis (NCFB) adult patients (≥18 years of age) with P. aeruginosa, H. influenzae, S. aureus, M. catarrhalis, S. pneumoniae, or S. maltophilia*

Integrated Analysis:
Time to First Exacerbation

Cipro 14 (N=313)
Cipro 28 (N=312)
Pooled Placebo (N=312)

O Censored

CC-87

Integrated Analysis: Consistency of Overall Treatment Effects

		HR/IRR/OR (95% CI)	HR/IRR/OR (95% CI)
Time to first exacerbation (Hazard Ratio)	Cipro 14		0.68 (0.54, 0.87)
	Cipro 28		0.71 (0.56, 0.90)
Frequency of exacerbations (≥3 signs) (Incidence Rate Ratio)	Cipro 14		0.75 (0.61, 0.92)
	Cipro 28		0.72 (0.58, 0.88)
Frequency of exacerbations (≥1 sign) (Incidence Rate Ratio)	Cipro 14		0.78 (0.64, 0.94)
	Cipro 28		0.77 (0.64, 0.93)
Pathogen eradication (Odds Ratio)	Cipro 14		0.60 (0.39, 0.95)
	Cipro 28		0.83 (0.54, 1.29)
Occurrence of new pathogens (Odds Ratio)	Cipro 14		0.39 (0.20, 0.77)
	Cipro 28		0.38 (0.19, 0.79)

0.1 ← Favors Ciprofloxacin DPI   1   Favors Placebo → 10

		LS Mean Difference (95% CI)	LS Mean Difference (95% CI)
Changes (units) in SGRQ-SCS	Cipro 14		-3.87 (-7.38, -0.36)
	Cipro 28		-2.70 (-6.17, 0.77)
Changes (units) in QOL-B-RSDS	Cipro 14		-2.46 (-5.72, 0.79)
	Cipro 28		-1.82 (-5.05, 1.41)
Changes (L) in FEV$_1$	Cipro 14		0.04 (-0.01, 0.09)
	Cipro 28		-0.01 (-0.06, 0.04)

-8   -4   0   4   8

Smaller values favor Cipro DPI. Some endpoints have been re-scaled for this purpose

CC-88

Rationale for Ciprofloxacin DPI in NCFB

- NCFB has a high unmet medical need and no approved therapies for reduction of exacerbations in this orphan disease

- Ciprofloxacin DPI demonstrated favorable treatment effects, especially in reduction of exacerbations

- Ciprofloxacin DPI demonstrated a favorable safety profile, consistent with long-term treatment

Ciprofloxacin DPI can help fulfill critical unmet medical need in NCFB patients
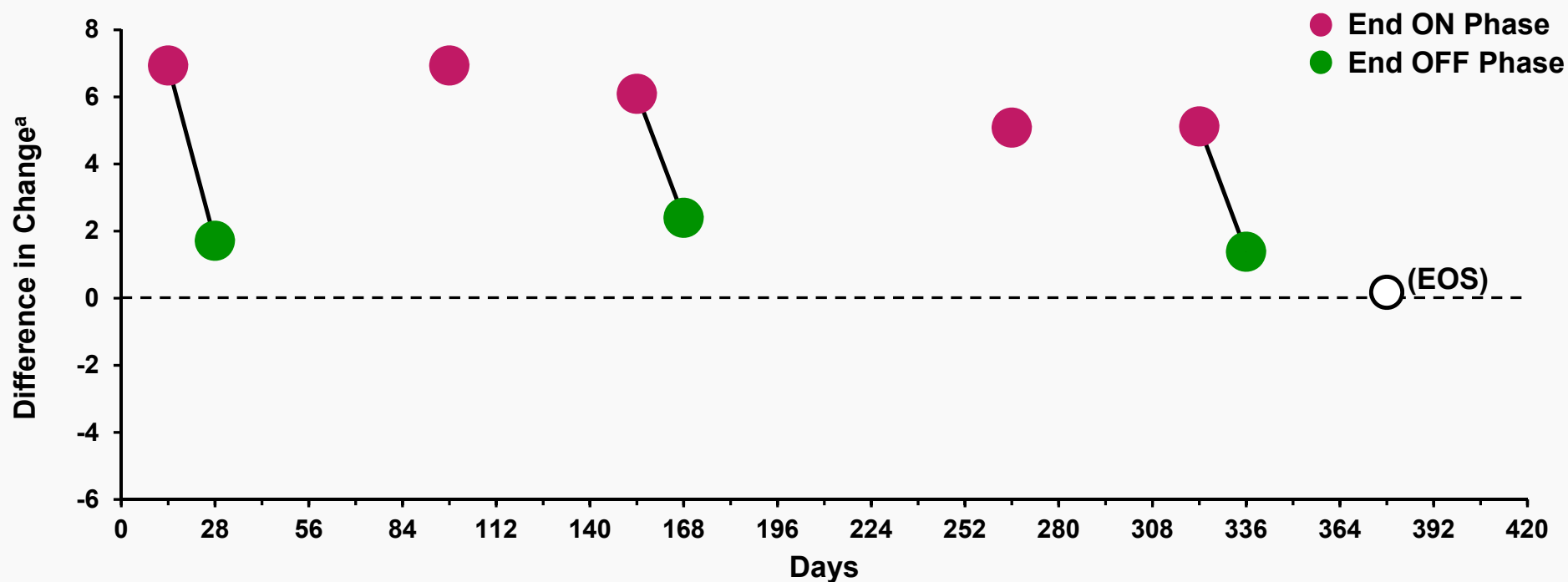
Backup Slides Shown

RESPIRE 1: Baseline, EOT, and Mean Changes in QOL-B RSDS
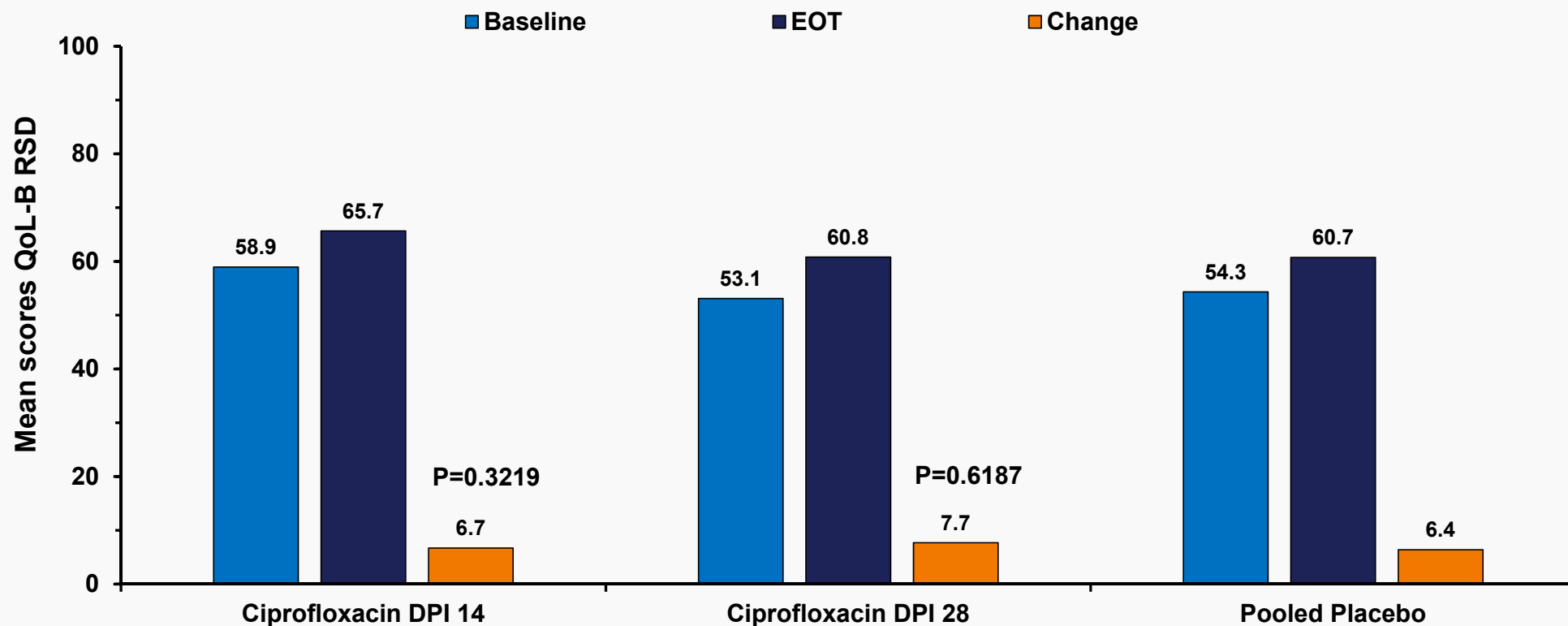
Positive change indicates improvement in health (respiratory symptoms)

EF-104

RESPIRE 1: Improvement in Respiratory Quality of Life (QOL-B RSDS) Observed During the ON-treatment Phase with Ciprofloxacin DPI 14 (FAS)

Change in QoL-B RSDS: Ciprofloxacin DPI 14 Days on/off vs Matching Placebo

QoL- B= Quality of Life-Bronchiectasis respiratory symptom score; EOT=end of treatment; EOS= end of study
Differences >0 indicate outcomes in favor of ciprofloxacin DPI.
a. Adjusted for geographic region, pre-therapy positive culture for P. aeruginosa, and chronic macrolide use

EF-202

Improvement in Respiratory Quality of Life (QoL-B RSDS) Observed During the ON-treatment Phase with Ciprofloxacin DPI 14 and 28 in RESPIRE 1 and 2
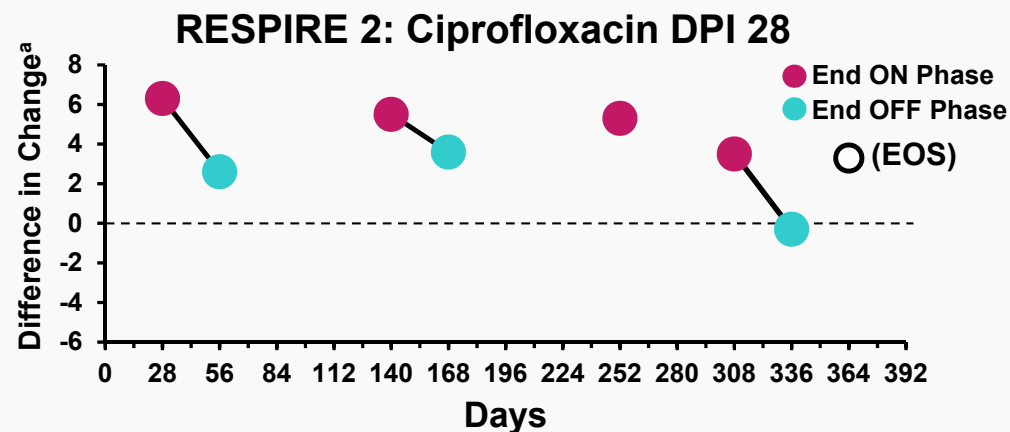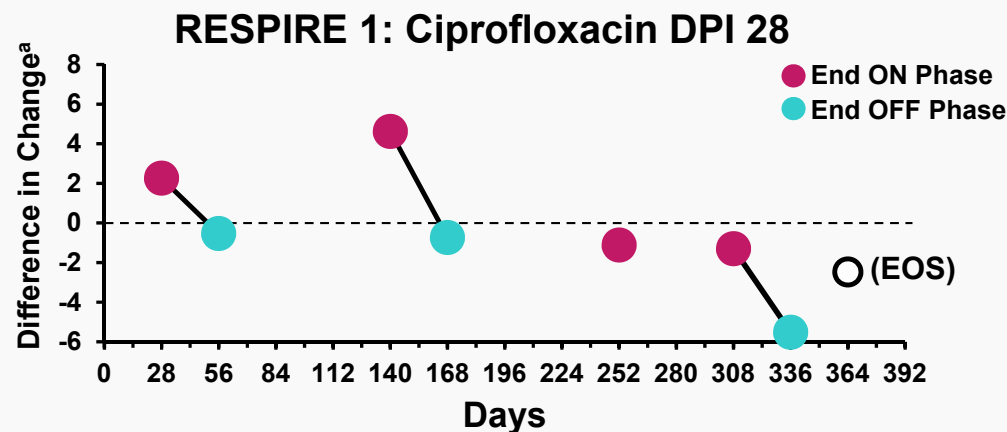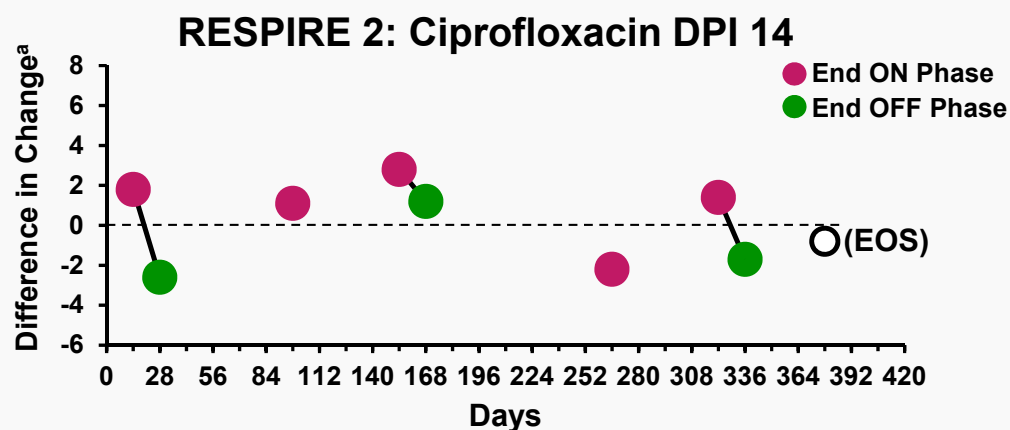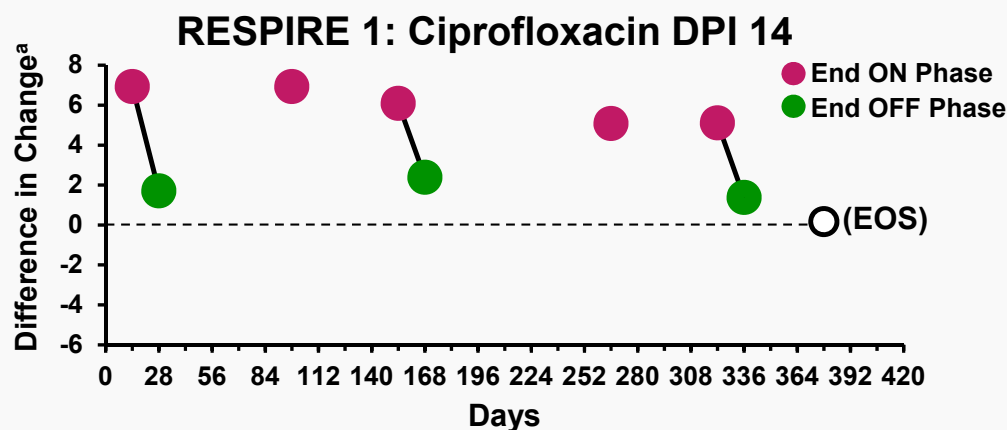
QoL-B RSDS = Quality of Life-Bronchiectasis respiratory symptom domain score; EOS= end of study; Differences >0 indicate superiority of active treatment.
a. ANCOVA adjusted for geographic region, pre-therapy positive culture for *P. aeruginosa*, and chronic macrolide use

EF-233

RESPIRE 1 and 2: Development of Ciprofloxacin-Resistant Pathogens by Patient in Sputum

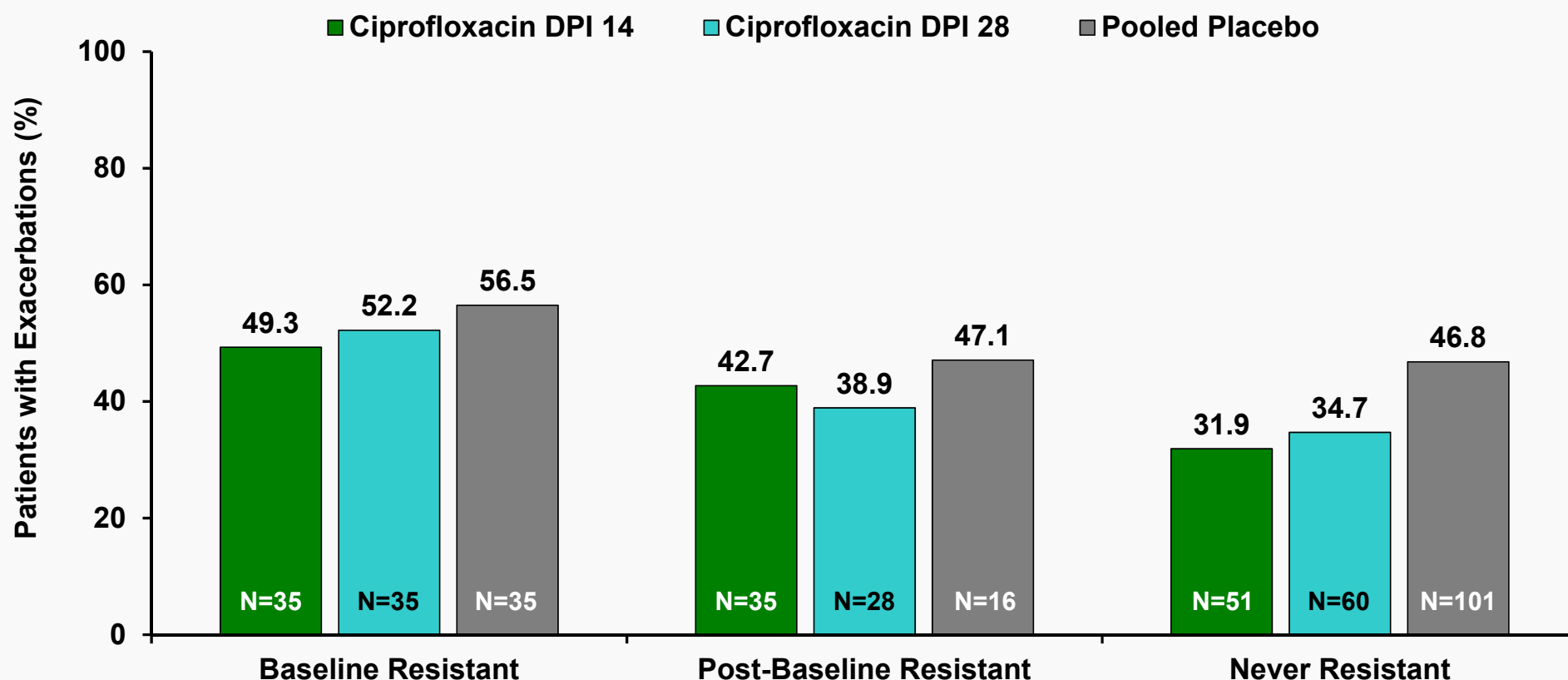|	Ciprofloxacin DPI 14 N=313 n (%)	Ciprofloxacin DPI 28 N=312 n (%)	Pooled Placebo N=312 n (%)
Resistance at baseline			
No	242 (77.3)	245 (78.5)	250 (80.1)
Yes	71 (22.7)	67 (21.5)	62 (19.9)
Development of resistance: from pre-treatment at any time			
No	248 (79.2)	247 (79.2)	285 (91.3)
Yes	65 (20.8)	65 (20.8)	27 (8.7)
Development of resistance: from pre-treatment at end of study			
No	199 (63.6)	180 (57.7)	196 (62.8)
Yes	22 (7.0)	23 (7.4)	7 (2.2)

Note: All frequency data are subject-based (denominator [N] is the number of all randomized subjects within the respective population).

EF-122

Anwar's Sputum Culture Susceptibility Testing[a]

Susceptibility	Mucoid *Pseudomonas aeruginosa*		*Pseudomonas aeruginosa*	
	August 10, 2017	September 28, 2017	August 10, 2017	October 26, 2017
AMIKACIN	--	SUSCEPTIBLE	SUSCEPTIBLE	--
AZTREONAM	SUSCEPTIBLE	SUSCEPTIBLE	SUSCEPTIBLE	SUSCEPTIBLE
CEFEPIME	SUSCEPTIBLE	SUSCEPTIBLE	SUSCEPTIBLE	SUSCEPTIBLE
CEFTAZIDIME	SUSCEPTIBLE	SUSCEPTIBLE	SUSCEPTIBLE	SUSCEPTIBLE
CIPROFLOXACIN	INTERMEDIATE	INTERMEDIATE	SUSCEPTIBLE	SUSCEPTIBLE
GENTAMICIN	SUSCEPTIBLE	SUSCEPTIBLE	RESISTANT	SUSCEPTIBLE
MEROPENEM	SUSCEPTIBLE	SUSCEPTIBLE	SUSCEPTIBLE	SUSCEPTIBLE
PIPERACILLIN	SUSCEPTIBLE	RESISTANT	SUSCEPTIBLE	SUSCEPTIBLE
TOBRAMYCIN	SUSCEPTIBLE	INTERMEDIATE	RESISTANT	SUSCEPTIBLE

Red text indicates change from previous test

RESPIRE 1 and 2: Percent of Patients with Exacerbations Over 48 Weeks by Resistance Status

EF-246

# RESPIRE 1: Resistance at Baseline and EOT - Ciprofloxacin DPI 14

Pathogen	Baseline		Cycle 12 (end of OFF)	
	N	% Resistant	N	% Resistant
Haemophilus influenzae	57	0	4	0
Moraxella catarrhalis	9	0	2	0
Pseudomonas aeruginosa	146	30 (20.5%)	35	17 (48.6%)
Staphylococcus aureus	46	13 (23.8%)	8	4 (50%)
Stenotrophomonas maltophilia	14	9 (64.3%)	0	0
Streptococcus pneumoniae	17	8 (47.1%)	7	2 (28.6%)
Total	**289**	**60 (20.8%)**	**56**	**23 (41.1%)**

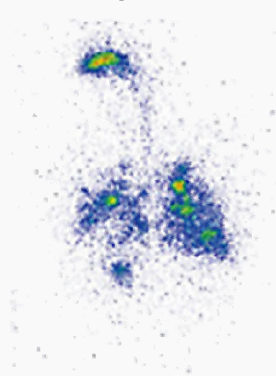# Ventilated Areas Reached Independent from Lung Disease State

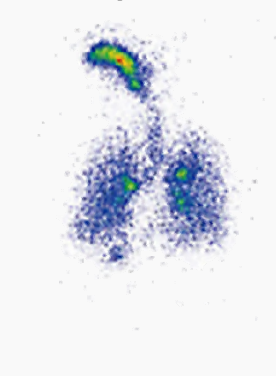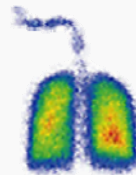**Particle deposition in the ventilated lung** — ^{99m}Tc Scans
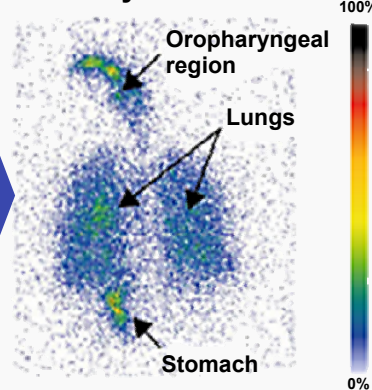
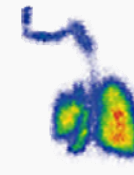Healthy Volunteer | NCFB patient | COPD patient

Oropharyngeal region
Lungs
Stomach

100%
0%

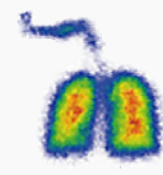**Lung contours using ^{89m}Kr** — ^{89m}Kr Scans
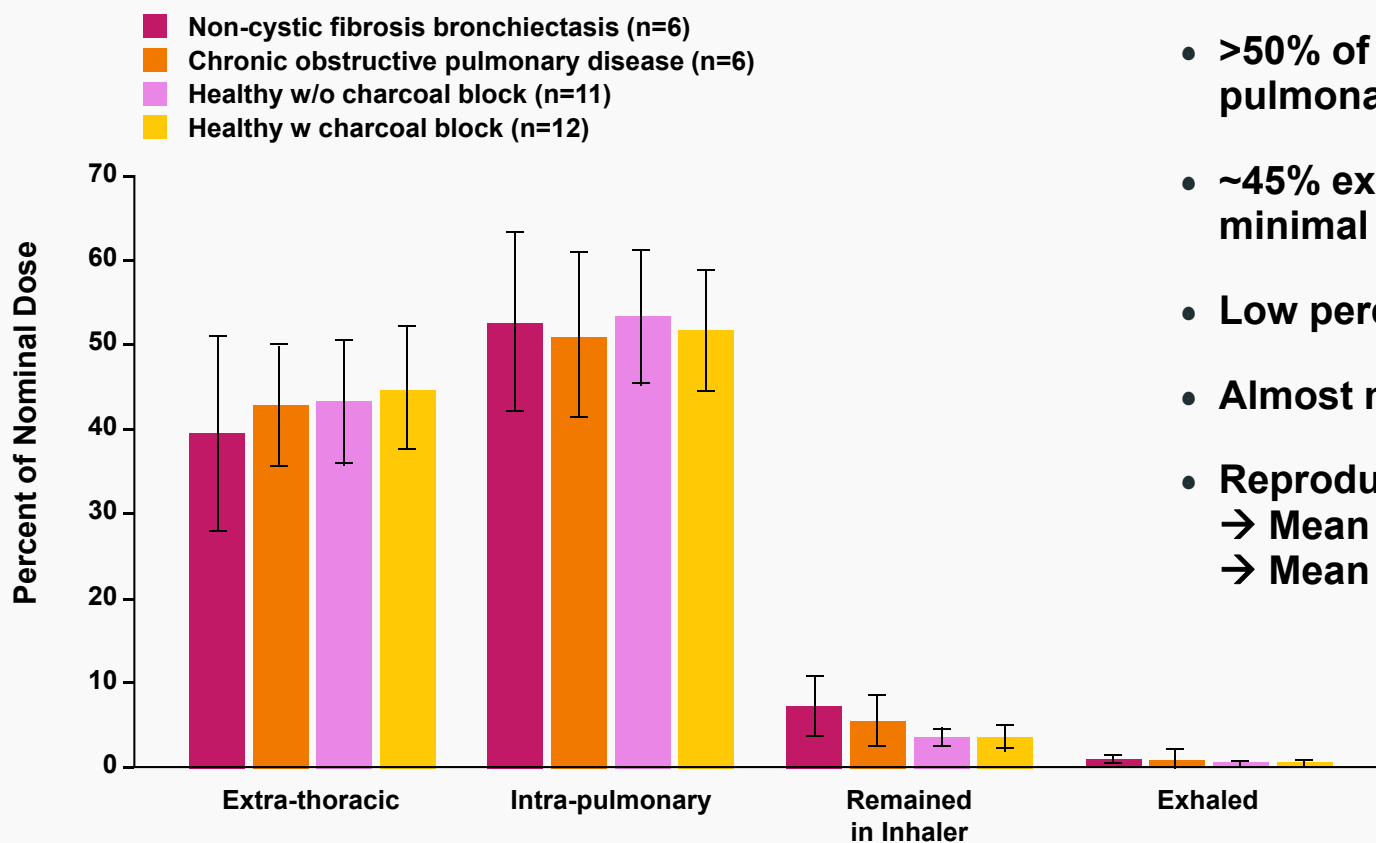
FEV$_1$ (% predicted) 96
FVC (% predicted) 88

FEV$_1$ (% predicted) 53
FVC (% predicted) 60

FEV$_1$ (% predicted) 25
FVC (% predicted) 32

Effective and Reproducible Intra-pulmonary Drug Deposition

Legend:
- Non-cystic fibrosis bronchiectasis (n=6)
- Chronic obstructive pulmonary disease (n=6)
- Healthy w/o charcoal block (n=11)
- Healthy w charcoal block (n=12)

Y-axis: Percent of Nominal Dose

X-axis categories: Extra-thoracic, Intra-pulmonary, Remained in Inhaler, Exhaled

- >50% of the dose deposited intra-pulmonary

- ~45% extrathoracic deposition causes minimal systemic exposure

- Low percentage left in the device

- Almost no drug exhaled

- Reproducible lung deposition
  → Mean inter-subject variability ~12%
  → Mean intra-subject variability ~15%

RESPIRE 1 Subgroup Analyses: Time to First Exacerbation for Ciprofloxacin DPI 14 vs. Pooled Placebo

		N	HR (97.5% CI)	Hazard ratio (97.5% CI)
Overall		275		0.53 (0.36, 0.80)
Baseline culture of *P. aeruginosa*	Positive	169		0.39 (0.22, 0.67)
	Negative	106		0.85 (0.46, 1.57)
Baseline FEV$_1$ (% predicted) <50	Yes	81		0.68 (0.34, 1.37)
	No	194		0.48 (0.29, 0.79)
Hospitalization or >2 exacerbations in the previous year	Yes	146		0.47 (0.28, 0.80)
	No	128		0.59 (0.31, 1.11)
Positive repeat culture	Yes	208		0.62 (0.39, 0.97)
	No	67		0.28 (0.11, 0.74)
Chronic macrolide use	Yes	46		0.27 (0.08, 0.85)
	No	229		0.61 (0.39, 0.94)
Ciprofloxacin resistant pathogen at baseline	Yes	66		0.65 (0.30, 1.41)
	No	207		0.50 (0.31, 0.81)

Positive point estimate in 12/12 subgroups.

EF-101

Encouraging Data from Single Center Experience with Off-label Use of Inhaled Antibiotics in NCFB

- Retrospective case series of NCFB patients treated with inhaled antibiotics, between 2006 and 2014

  - Inhaled antibiotics :
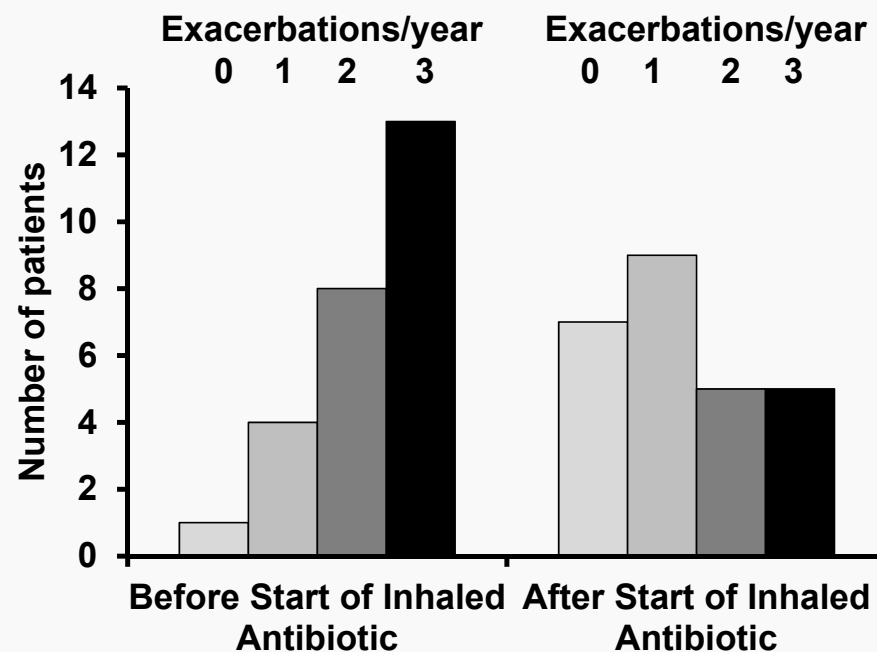   tobramycin   23 patients
    aztreonam   3 patients
    amikacin   5 patients

  - Significant reduction in number of exacerbations after initiation of inhaled antibiotics (p=0.003)

Number of Exacerbations in the Year Before and After Initiation of Inhaled Antibiotic

Nadig TR, Flume P. *Am J Respir Crit Care Med* 2016; 193:108

RESPIRE 1 and RESPIRE 2: Patients with Antibiotics Follow-up Prescription and Multiple Therapies After Antibiotic Treatment for Treating Acute Exacerbation Events
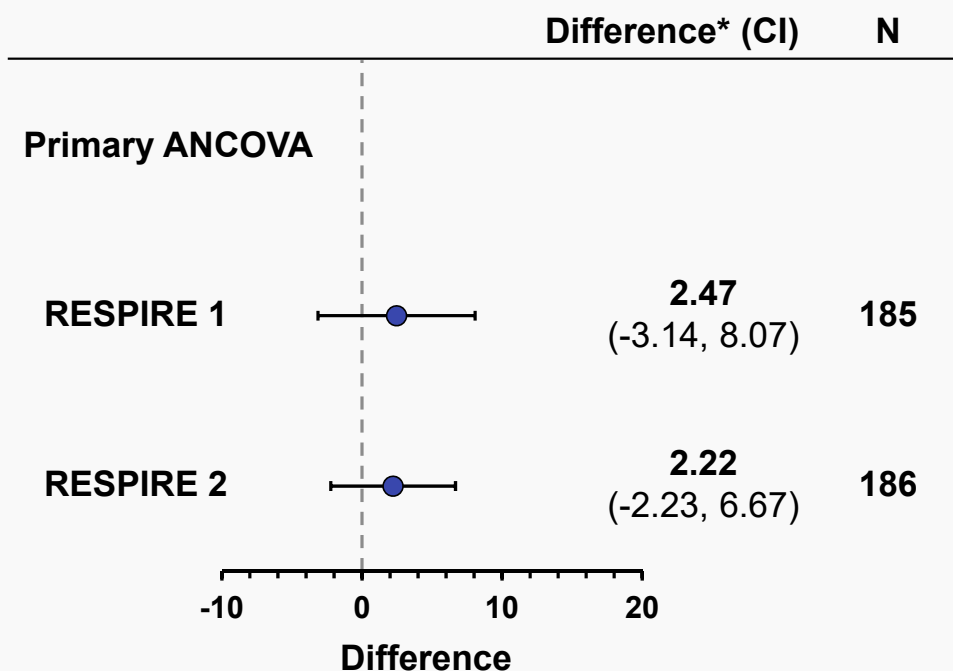
	Cipro 14 N=313 n (%)	Cipro 28 N=312 n (%)	Pooled Placebo N=312 n (%)
Follow-up prescription			
Missing	149 (47.6)	147 (47.1)	130 (41.7)
No	143 (45.7)	149 (47.8)	153 (49.0)
Yes	21 (6.7)	16 (5.1)	29 (9.3)
Multiple therapies			
Missing	149 (47.6)	147 (47.1)	130 (41.7)
No	119 (38.0)	119 (38.1)	117 (37.5)
Yes	45 (14.4)	46 (14.7)	65 (20.8)

SA-162

Number of Qualifying Exacerbations Treated with Ciprofloxacin or Levofloxacin

	Cipro 14 n/N (%)	Cipro 28 n/N (%)	Pooled Placebo n/N (%)	Total n/N (%)
RESPIRE 1	29/86 (33.7)	34/116 (29.3)	45/126 (35.7)	108/328 (32.9)
RESPIRE 2	40/102 (39.2)	20/68 (29.4)	46/122 (37.7)	106/292 (36.3)
Integrated	69/188 (36.7)	54/184 (29.3)	91/248 (36.7)	214/620 (34.5)

SA-186

Change from Baseline in QOL-B RSDS at EOT for Ciprofloxacin DPI 14 and 28 vs. Pooled Placebo (Full Analysis Set)

Ciprofloxacin DPI 14 vs. Pooled Placebo

	Difference* (CI)	N
Primary ANCOVA		
RESPIRE 1	2.47 (-3.14, 8.07)	185
RESPIRE 2	2.22 (-2.23, 6.67)	186

Ciprofloxacin DPI 28 vs. Pooled Placebo
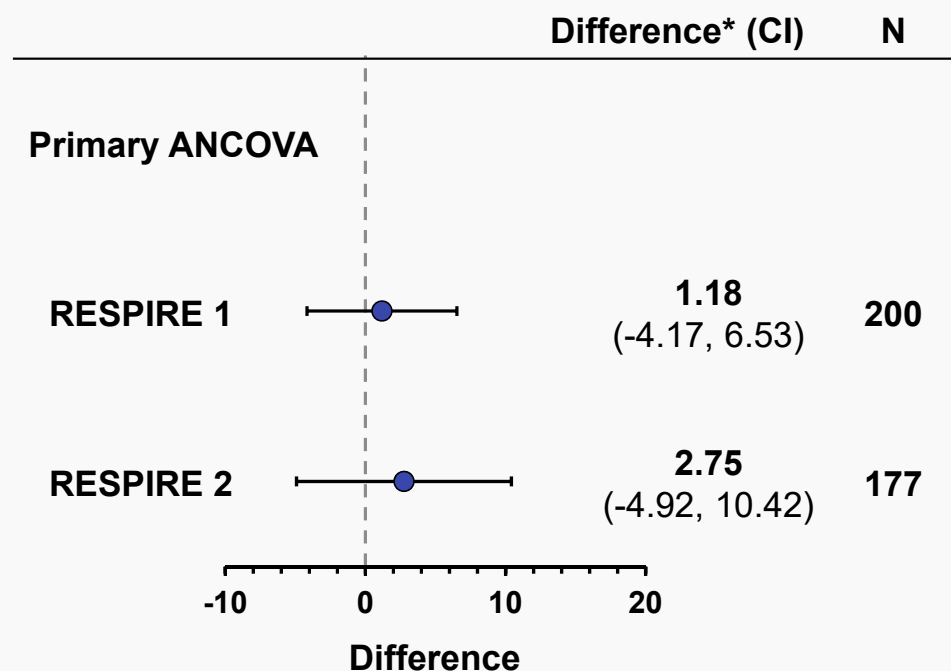
	Difference* (CI)	N
Primary ANCOVA		
RESPIRE 1	1.18 (-4.17, 6.53)	200
RESPIRE 2	2.75 (-4.92, 10.42)	177

*Confidence intervals are 97.5% for RESPIRE 1 and 95.1% (Ciprofloxacin DPI 14) / 99.9% (Ciprofloxacin DPI 28) for RESPIRE 2.
Differences > 0 indicate superiority of active treatment%. N based on patients with evaluable QoL data.
EOT = End of Treatment (week 44/46)
RSDS = Respiratory Symptoms Domain Score

EF-231

Success of Systemic Ciprofloxacin or Levofloxacin for Treatment of Acute Exacerbations

		Pooled Placebo	Pooled Cipro
Pooled Studies	n	75	97
	Success (%)	60 (80.0%)	74 (76.0%)

Only exacerbations where Ciprofloxacin or Levofloxacin was used as first-line treatment are considered.
Failure: any antibiotics treatment is accompanying or following the Ciprofloxacin or Levofloxacin treatment within 28 days after the start of an exacerbation.
Success: no antibiotics treatment is accompanying or following the Ciprofloxacin or Levofloxacin treatment within 28 days after the start of an exacerbation.

Resistance Rates per Patient at Baseline and EOT RESPIRE 1 and 2

Group	Baseline Resistance		Resistance at End of Treatment	
	n/N	Percentage	n/N	Percentage
Ciprofloxacin DPI 14	71/313	22.7%	50/241	20.7%
Ciprofloxacin DPI 28	67/312	21.5%	48/245	19.6%

EOT: End of Treatment
Resistance n/N based on patients with ≥ 1 resistant isolate/total numbers of patients with a sputum sample
Systemic breakpoints used.