

# Anti-infective Drugs Advisory Committee (CABP)

**Ceftaroline fosamil**

*Cerexa, Inc.*

*A subsidiary of Forest Laboratories, Inc.*

*07 September 2010*

# Introduction

## Ceftaroline fosamil

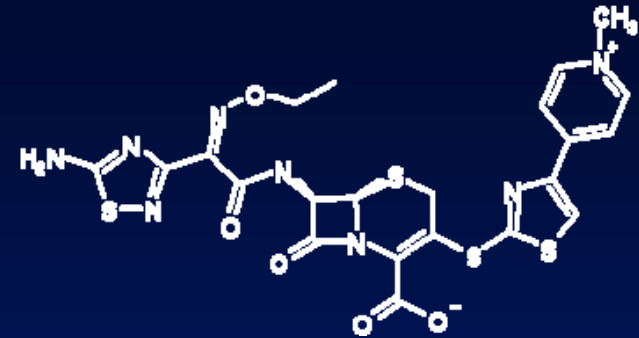
**Dirk Thye, MD**

*President*

*Cerexa, Inc.*

# Ceftaroline Description

- A novel intravenous cephalosporin
- Broad-spectrum activity
  - Gram-positive bacteria (eg, *Streptococcus pneumoniae*, *Staphylococcus aureus*)
  - Gram-negative bacteria (eg, *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*)
- Potent activity vs contemporary resistant pathogens
  - MRSA, MDRSP
- Demonstrated efficacy in CABP and cSSSI
- Well tolerated with safety profile reflective of cephalosporin class



# Proposed Indications

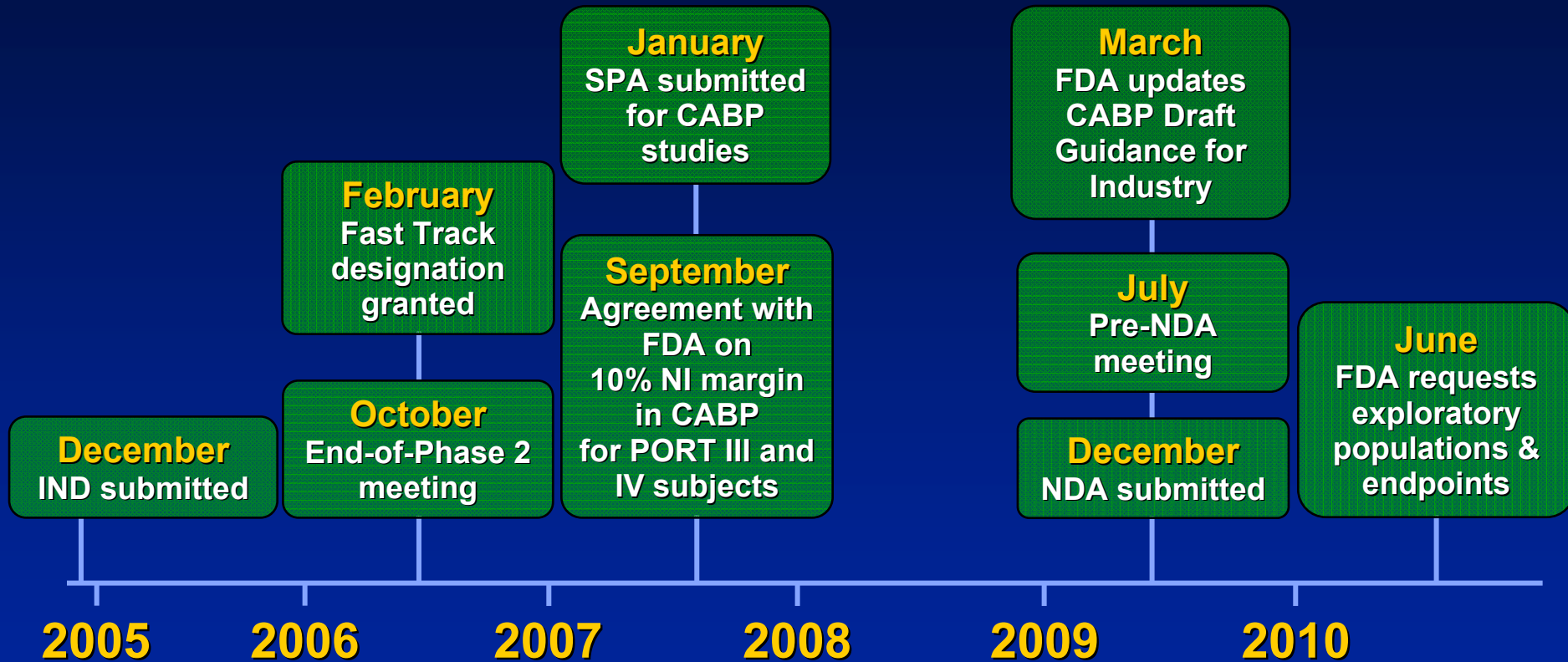
- **Ceftaroline is indicated for patients with CABP caused by susceptible isolates of gram-positive and gram-negative microorganisms:**
  - *S. pneumoniae* (including MDRSP and cases with concurrent bacteremia)
  - *S. aureus* (MSSA)
  - *H. influenzae*
  - *H. parainfluenzae*
  - *K. pneumoniae* (ceftazidime susceptible)
  - *E. coli* (ceftazidime susceptible)
- **Proposed dose**
  - 600 mg q12h IV over 1 hour
  - 400 mg q12h IV over 1 hour for subjects with moderate to severe renal impairment (CrCl < 50 mL/min)

# Program Overview

17 Studies

11 Phase 1 Studies	Two Phase 2 Studies	Four Phase 3 Studies	
<ul style="list-style-type: none"><li>• Healthy adults</li><li>• Mild, moderate, severe renal impairment</li><li>• ESRD receiving hemodialysis</li><li>• Thorough ECG</li><li>• Elderly</li><li>• Adolescents</li><li>• IM administration</li><li>• Fecal microflora</li></ul>	<p>2 cSSSI Studies</p> <p>Intravenous, Intramuscular</p>	<p>2 CABP Studies</p> <p>P903-08, P903-09</p>	<p>2 cSSSI Studies</p> <p>P903-06, P903-07</p>

# Regulatory History



# Agenda

**Introduction**

***Dirk Thye, MD***

*President – Cerexa, Inc.*

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**CABP:  
New Challenges  
in Treatment**

***Donald E. Low, MD, FRCPC***

*Microbiologist-in-Chief  
Mt. Sinai Hospital, Toronto*

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**Microbiology and  
Clinical Pharmacology**

***Ian Critchley, PhD***

*Vice President, Microbiology  
Cerexa, Inc.*

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**Clinical Design and Efficacy**

***Dirk Thye, MD***

**Clinical Safety**

***David Friedland, MD***

*Vice President, Clinical Sciences  
Cerexa, Inc.*

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**CABP:  
Therapeutic Perspective**

***Donald E. Low, MD, FRCPC***

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# Experts Available to Advisory Committee

## **Paul G. Ambrose, PharmD, FIDSA**

President

Institute for Clinical Pharmacodynamics Inc., Latham, NY

## **Robertson D. Davenport, MD**

Associate Professor and Director of the Blood Bank and  
Transfusion Service, Department of Pathology  
University of Michigan Health System, Ann Arbor, MI

## **Jamie P. Dwyer, MD**

Assistant Professor of Medicine

Department of Medicine, Nephrology and Hypertension Division  
Vanderbilt University, Nashville, TN

## **Gary Koch, PhD**

Professor of Biostatistics, Department of Biostatistics  
University of North Carolina, Chapel Hill, NC



# Financial Disclosure for External Consultants

- All have been paid (directly or through their employer) for their time and travel
- None own stock in Forest Laboratories, Inc.
- Dr. Ambrose is a Cerexa consultant and current SGE serving as temporary member of Anti-infective Advisory Committee, and here today with Agency approval

# Community-Acquired Bacterial Pneumonia: Medical Need

**Donald E. Low, MD, FRCPC**

*Microbiologist-in-Chief,  
Department of Microbiology*

*Mount Sinai Hospital, Toronto, Ontario*

# CABP: Burden of Illness

- **7<sup>th</sup> leading cause of death in US<sup>a</sup>**
- **~ 5.6 million cases occur annually<sup>b</sup>**
  - ~ 1.1 million require hospitalization
  - Over 75% treated as outpatients
- **Costs exceed US \$8.4 – \$10 billion/year<sup>a</sup>**
  - Inpatient-care costs are ~ 25-times higher than outpatient-care costs

<sup>a</sup> Mandell LA, et al. *Clin Infect Dis* 2007

<sup>b</sup> *Am J Respir Crit Care Med* 2001

# CABP: Pathogens & Antimicrobial Resistance

- **Pathogens in moderate-to-severe CABP**
  - *Streptococcus pneumoniae*
  - *Staphylococcus aureus*
  - *Haemophilus influenzae*
  - Enteric gram-negative bacilli
- **Antibacterial resistance is common**
  - Penicillin-nonsusceptible and multidrug-resistant *S. pneumoniae* (PRSP, PISP, MDRSP)
  - Nonvaccine *S. pneumoniae* serotypes (eg, 19A)
- **Emerging threat**
  - Community-acquired MRSA

# The Problem with *S. pneumoniae* Serotype 19A

*Now Most Common Invasive Serotype in US and Canada*

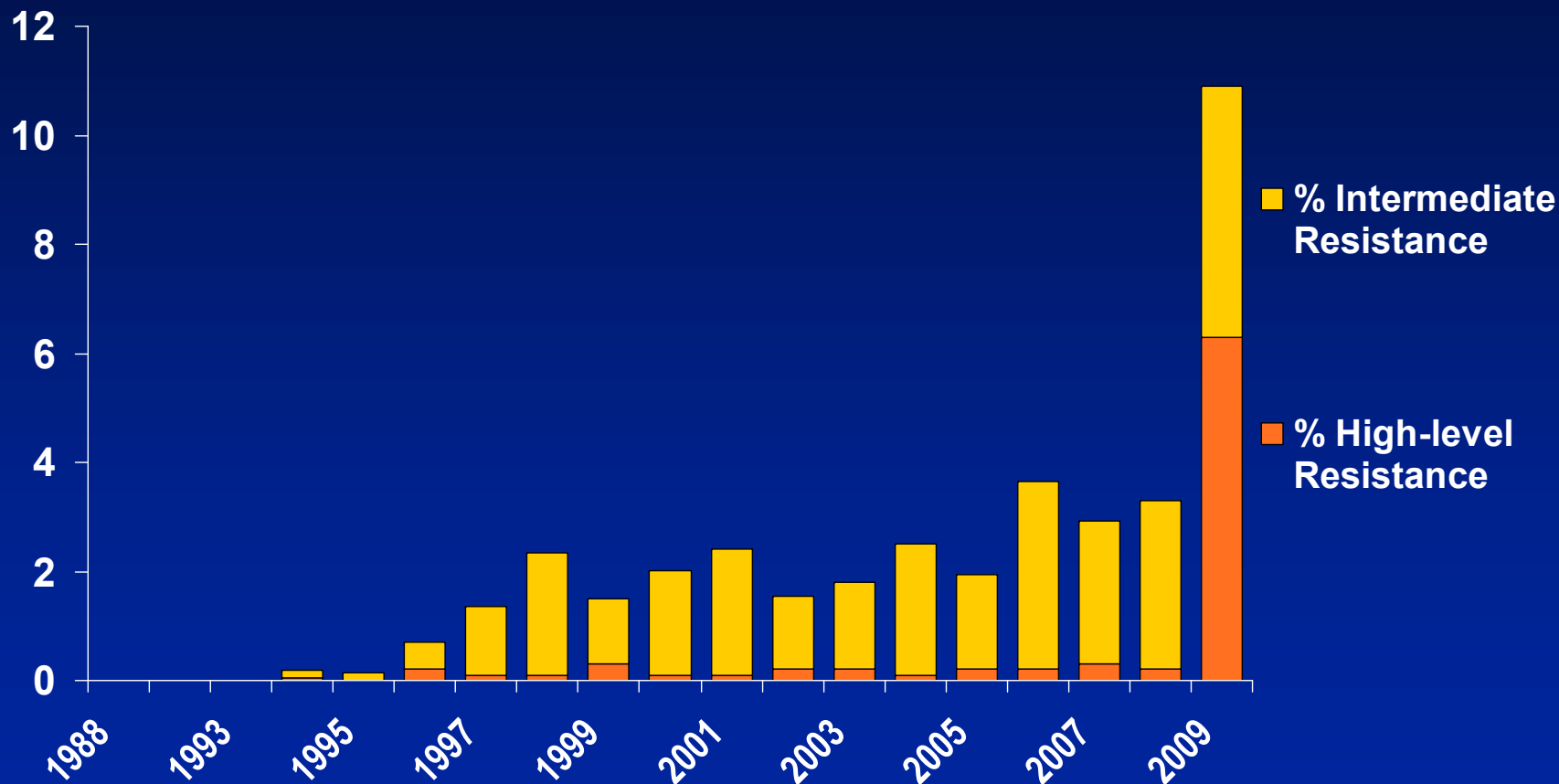
<b>Antimicrobial</b>	<b>MIC<sub>90</sub></b>	<b>% Susceptible</b>
<b>Penicillin</b>	<b>4</b>	<b>46.6%</b>
<b>Ceftriaxone</b>	<b>2</b>	<b>65.6%</b>
<b>Cefuroxime</b>	<b>&gt;8</b>	<b>36.1%</b>
<b>Erythromycin</b>	<b>&gt;2</b>	<b>26.5%</b>
<b>Clindamycin</b>	<b>&gt;2</b>	<b>43.4%</b>
<b>Ceftaroline</b>	<b>0.25</b>	<b>—</b>

189 of 894 isolates (21.1%) were 19A

JMI United States Surveillance Data 2008 (on file)

# Sudden Emergence of Ceftriaxone-resistant Pneumococci:

*Canadian Bacterial Surveillance Network, 1988-2009*



\*Non-meningitis breakpoints used

Canadian Bacterial Surveillance Network, March 2010

## **CABP – Summary**

- **CABP is one of most common infectious diseases, with heavy burden of illness**
- **Significant morbidity and mortality despite advances in medical care**
- **Emerging antimicrobial resistance threatens the utility of our first-line agents**
  - **MDRSP**
  - **CA-MRSA**
- **New safe and effective antibiotics are urgently needed for CABP**

# **Microbiology and Clinical Pharmacology**

**Ian Critchley, PhD**

*Vice President, Microbiology  
Cerexa, Inc.*



# Key Microbiology Attributes

- **Broad-spectrum bactericidal activity**
  - Resistant gram-positive bacteria and common gram-negative pathogens
  - Typical respiratory pathogens including *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*
- **Higher affinity for penicillin-binding proteins (PBPs) than other  $\beta$ -lactams**
- **Low potential for resistance induction in vitro**
- **Excellent bactericidal activity against PRSP or MRSA / VISA in animal efficacy models**

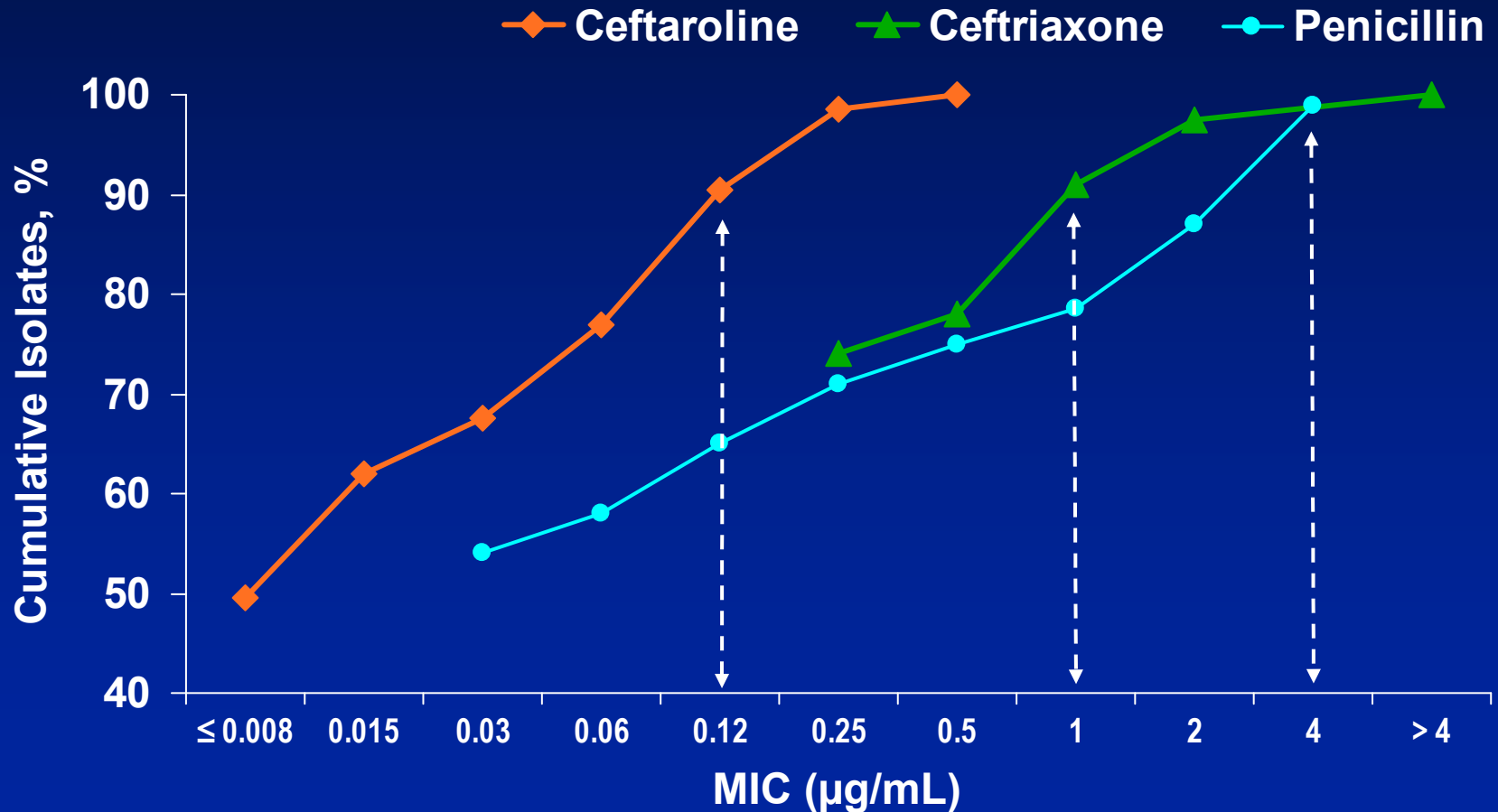
# Clinically Important Pathogens

Organism	Ceftaroline MIC ( $\mu\text{g}/\text{mL}$ )		
	No. tested	MIC Range	90%
<i>S. pneumoniae</i> (All)	894	$\leq 0.008 - 0.5$	0.12
<i>S. pneumoniae</i> (MDR)	125	0.06 – 0.5	0.25
<i>S. aureus</i> (MSSA)	1711	$\leq 0.008 - 0.5$	0.25
<i>S. aureus</i> (MRSA)	2254	0.12 – 2	1
<i>H. influenzae</i> ( $\beta$ -lactamase-negative)	275	$\leq 0.008 - 0.06$	0.015
<i>H. influenzae</i> ( $\beta$ -lactamase-positive)	106	$\leq 0.008 - 0.12$	0.03
<i>E. coli</i> (ceftazidime-susceptible)	1036	0.015 – $> 16$	0.5
<i>K. pneumoniae</i> (ceftazidime-susceptible)	517	$\leq 0.008 - > 16$	0.25

# Lower MICs than Comparators Against *S. pneumoniae*

## US Surveillance Isolates from 2008

891 isolates



Arrows indicate MIC<sub>90</sub> values for each agent

Jacobs RM et al. *Antimicrob Agents Chemother* 2010 54(6):2716-9.

# High Affinity for Modified PBPs in PRSP and MRSA

Higher affinity for modified PBPs results in lower MICs

Antibiotic	PRSP <i>S. pneumoniae</i> 2039		Antibiotic	MRSA Strain 67-0	
	MIC ( $\mu\text{g/mL}$ )	PBP2x $\text{IC}_{50}$ ( $\mu\text{g/mL}$ )		MIC ( $\mu\text{g/mL}$ )	PBP2a $\text{IC}_{50}$ ( $\mu\text{g/mL}$ )
Ceftaroline	0.12	0.17	Ceftaroline	0.5 – 1	0.16
Ceftriaxone	1 – 2	0.64	Ceftriaxone	> 128	677
Penicillin	1 – 2	0.79	Oxacillin	128	408

# Low Potential for Resistance Development In Vitro

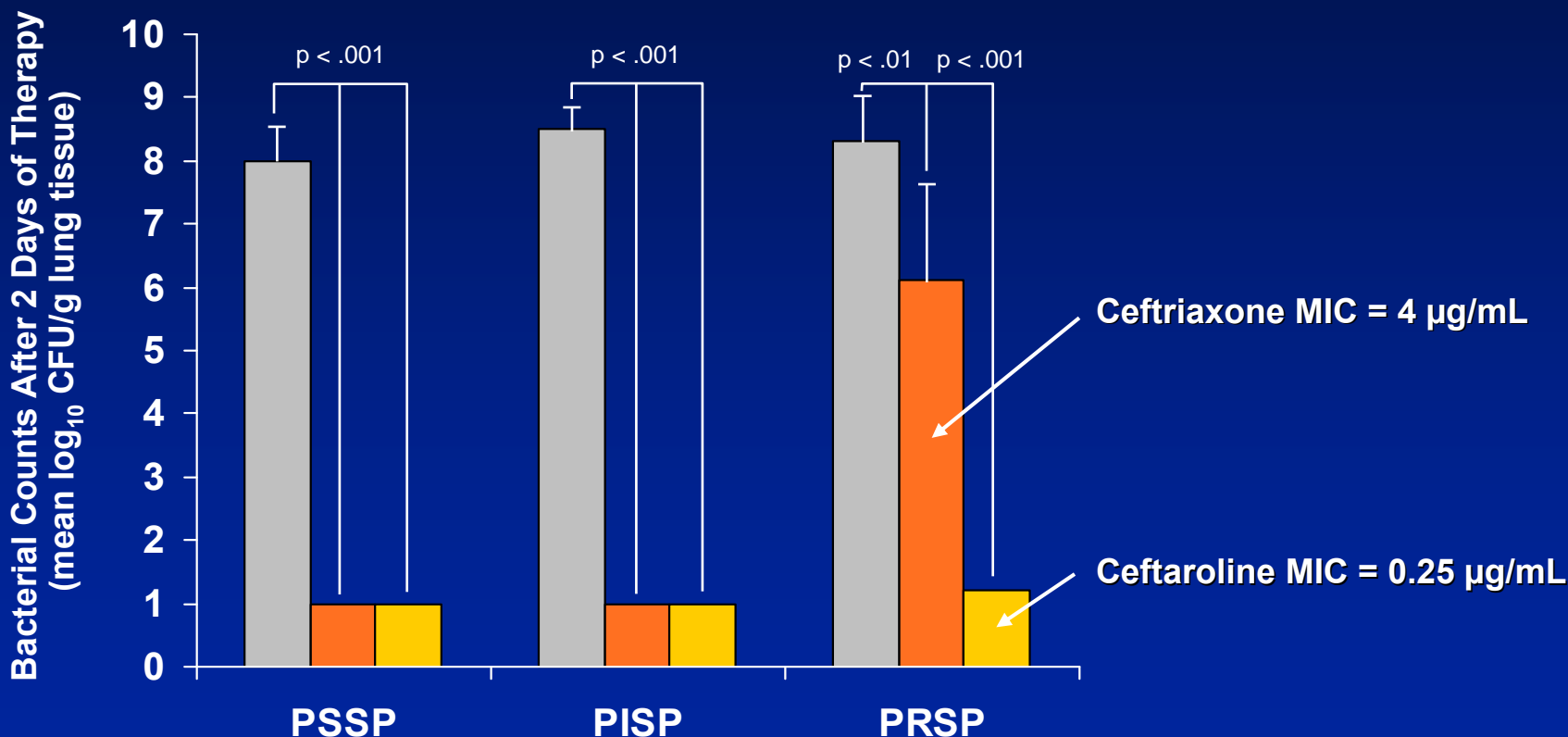
- No MIC shifts > 2 dilutions following serial passage (10 – 50 passages)
- Low spontaneous mutation frequencies

Organism	Phenotype	Spontaneous Mutation Frequency	Serial Passage Resistance Development	
		4 x MIC	Initial MIC (µg/mL)	Final MIC After 10 Passages (µg/mL)
<i>S. aureus</i> 2202	CA-MRSA	< 1.10 x 10 <sup>-10</sup>	1	1
<i>S. pneumoniae</i> 0869	PSSP	< 6.80 x 10 <sup>-9</sup>	0.008	0.015
<i>S. pneumoniae</i> 0884	PRSP	< 7.14 x 10 <sup>-9</sup>	0.12	0.25
<i>H. influenzae</i> 1224		< 4.98 x 10 <sup>-9</sup>	0.06	0.12
<i>H. influenzae</i> 2797	BLNAR	< 1.43 x 10 <sup>-9</sup>	0.06	0.12

- Insignificant induction of AmpC β-lactamases at ≤ 1 x MIC among gram-negative bacilli

# In Vivo Efficacy of Ceftaroline and Ceftriaxone Against *S. pneumoniae* in Rabbit Pneumonia Model

■ Control ■ Ceftriaxone 1g/24h IV\* ■ Ceftaroline 600mg/12h IV\*



\* Simulated human dose regimen

MICs ( $\mu\text{g/mL}$ ) for PSSP (0.015 vs. 0.06), PISP (0.125 vs. 1), and PRSP (0.25 vs. 4) for ceftaroline and ceftriaxone, respectively (Croisier-Bertin D et al. 19th ECCMID, Helsinki 2009 Abstract O382).

# Pharmacokinetics

- **Rapid prodrug conversion to ceftaroline in plasma**
- **Approximately linear PK for doses of 50 – 1000 mg**
- **Half-life of 2.5 hours**
  - No drug accumulation on repeated doses
- **Low protein binding ~ 20%**
- **Low potential for drug-drug interactions**
  - No CYP450-dependent metabolism
  - No inhibition or induction of CYP450 enzymes
- **Elimination mainly through renal excretion**
  - Dose adjustment for moderate and severe renal impairment

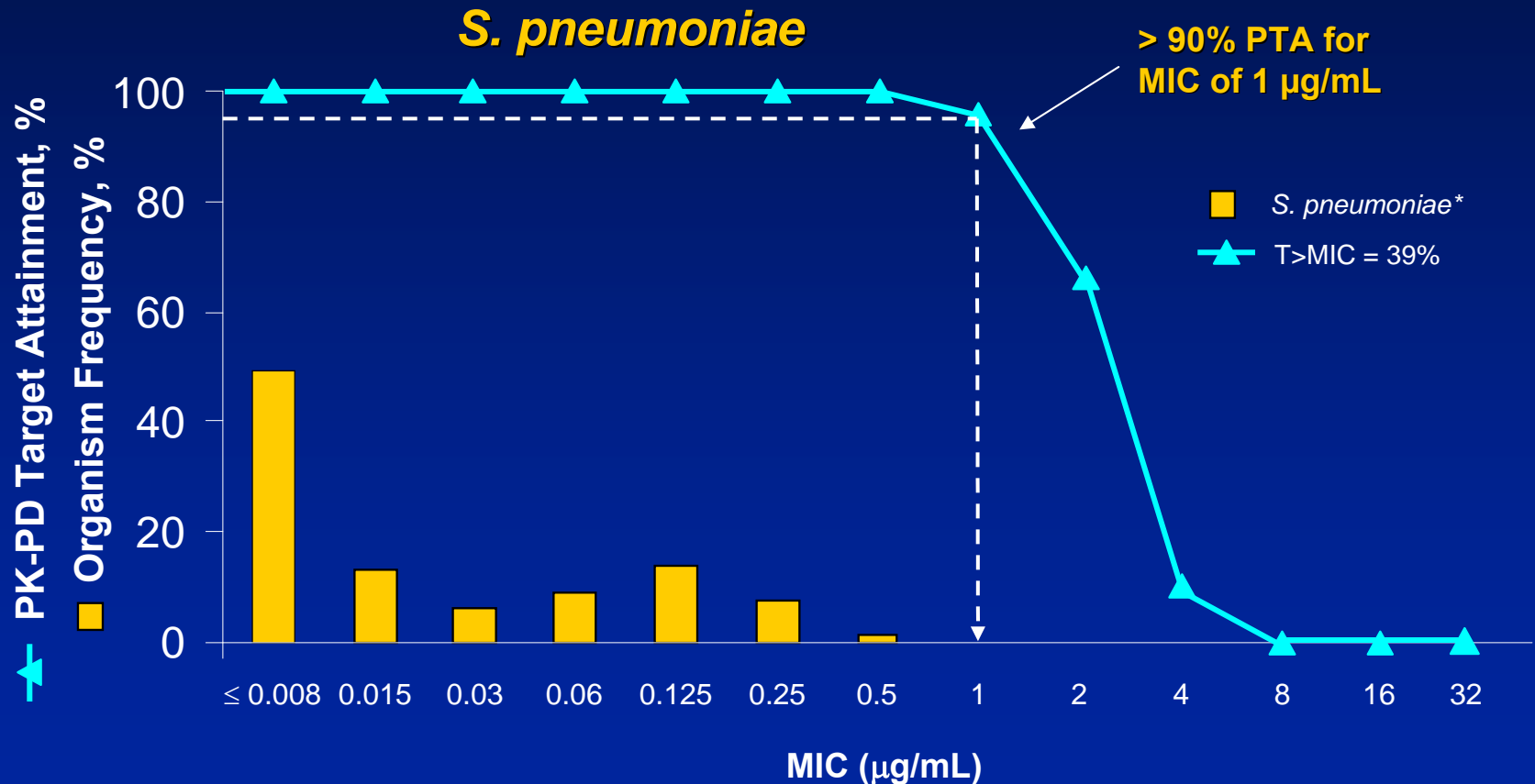
## ***S. pneumoniae* PK/PD**

- **%T>MIC is PK/PD parameter that best predicts efficacy for cephalosporins**
- **Murine neutropenic thigh/ bacteremia infection model standard for determining magnitude of %T>MIC**
- **%T>MIC predicts efficacy for ceftaroline**
- **$\geq 39\%$  T>MIC required for efficacy for *S. pneumoniae***



# PK/PD Target Attainment

Monte Carlo simulation-predicted probability (%) of target attainment for 600 mg q12h dose as function of MIC



\* Bars represent percentage of isolates from US surveillance 2008

# Summary

- **Ceftaroline exhibits broad-spectrum antibacterial activity against important respiratory pathogens**
- **Activity against resistant gram-positive bacteria mediated by high-affinity binding to modified PBPs**
- **Low potential for resistance development in vitro**
- **Approximately linear PK profile**
- **Low potential for drug-drug interactions**
- **Dosing regimen of 600 mg q12h provides adequate free-drug %T>MIC to cover key respiratory pathogens**
  - *S. pneumoniae* with MICs  $\leq 0.5 \mu\text{g/mL}$

# Interpretive Criteria Proposed by Sponsor and Agency for CABP

Pathogen	Sponsor-proposed Interpretive Criteria			FDA-proposed Interpretive Criteria		
	S	I	R	S	I	R
<i>S. aureus</i> (excluding methicillin-resistant isolates)	≤ 2 <sup>a</sup>	—	—	≤ 0.25	—	—
<i>S. pneumoniae</i>	≤ 0.5	—	—	≤ 0.008	—	—
<i>H. influenzae</i>	≤ 0.25 <sup>b</sup>	—	—	No interpretive criteria		

<sup>a</sup> Sponsor only proposed interpretive criteria for *S. aureus* regardless of indication

<sup>b</sup> Sponsor proposed interpretive criteria for *Haemophilus* spp.

# Interpretive Criteria

- Important in guiding physicians in selecting most appropriate agent
- Susceptible implies a high probability that patient will respond to treatment with appropriate dosage of antimicrobial agent
- Current FDA-proposed breakpoints
  - Breakpoint divides wild-type MIC distribution
  - 51% of US *S. pneumoniae* isolates nonsusceptible despite adequate exposure and good clinical efficacy

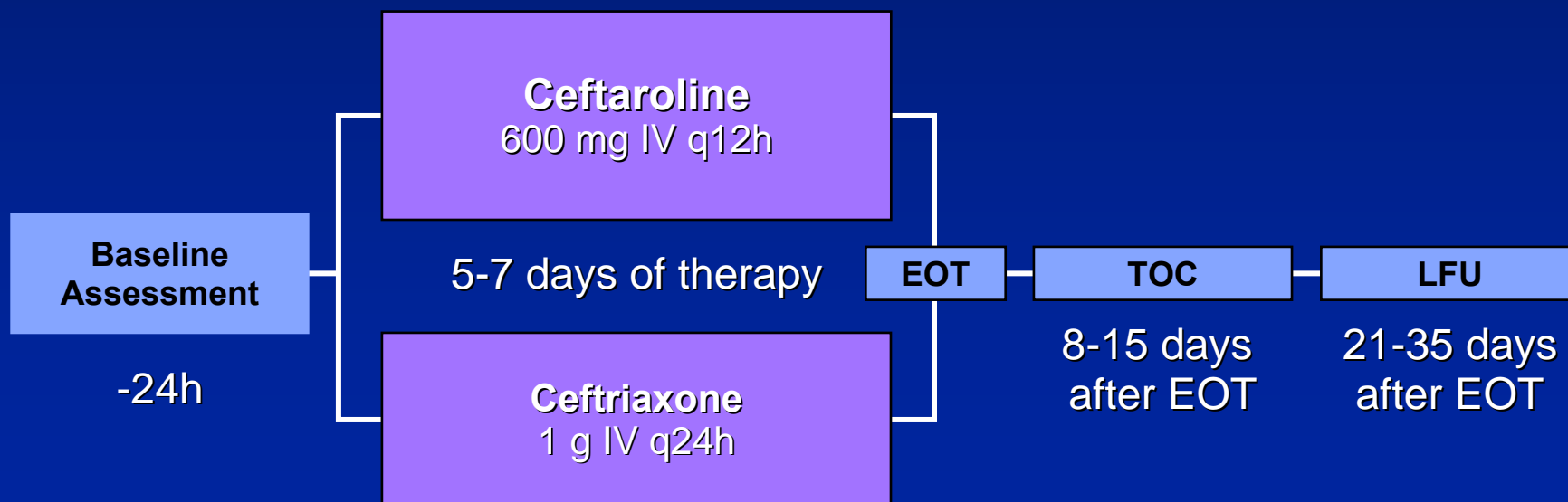
# **Clinical Design and Efficacy**

**Dirk Thye, MD**

# CABP – Study Designs

*P903-08 and P903-09*

- Phase 3, multicenter, randomized, double-blind
- Noninferiority margin (10%) in clinical response at TOC
- All subjects in Study P903-08 in both groups received 2 doses adjunctive clarithromycin (500 mg q12h) on Day 1
- IV therapy only, no oral step-down therapy



# CABP Definition

- **New or progressive infiltrate on chest radiograph**
- **Acute illness ( $\leq 7$  days) with  $\geq 3$  signs or symptoms**
  - **Fever  $> 38^{\circ}\text{C}$  oral or hypothermia  $< 35^{\circ}\text{C}$**
  - **WBC count  $> 10,000$  cells/ $\text{mm}^3$  or  $< 4,500$  cells/ $\text{mm}^3$**
  - **$> 15\%$  bands**
  - **New or increased cough**
  - **Purulent sputum or change in sputum character**
  - **Auscultatory findings consistent with pneumonia**
  - **Dyspnea, tachypnea, or hypoxemia**

# Main Inclusion Criteria

- Adults aged 18 years or older
- Infection requiring treatment with IV antibiotics
- Need for hospitalization
- Only PORT Risk Class III or IV included
  - PORT I / II Low mortality, outpatient
  - **PORT III / IV Moderate mortality, hospitalization**
  - PORT V High mortality, ICU



## **Main Exclusion Criteria**

- **More than 1 dose of short-acting prior antibiotic**
- **Known or suspected ceftriaxone-resistant (eg, MRSA) or atypical pathogen**
- **Admission to ICU**
- **Healthcare- or hospital-acquired pneumonia**
- **Immediate life-threatening disease or evidence of significant hepatic, hematologic, or immunologic disease**

# Efficacy Endpoints

- **Primary Efficacy Endpoint**
  - Clinical cure rate at TOC
- **Secondary Efficacy Endpoints**
  - Clinical cure rate at EOT
  - Microbiological success rate at TOC
  - Clinical & microbiological response by pathogen at TOC
  - Relapse at LFU
  - Reinfection/ recurrence at LFU

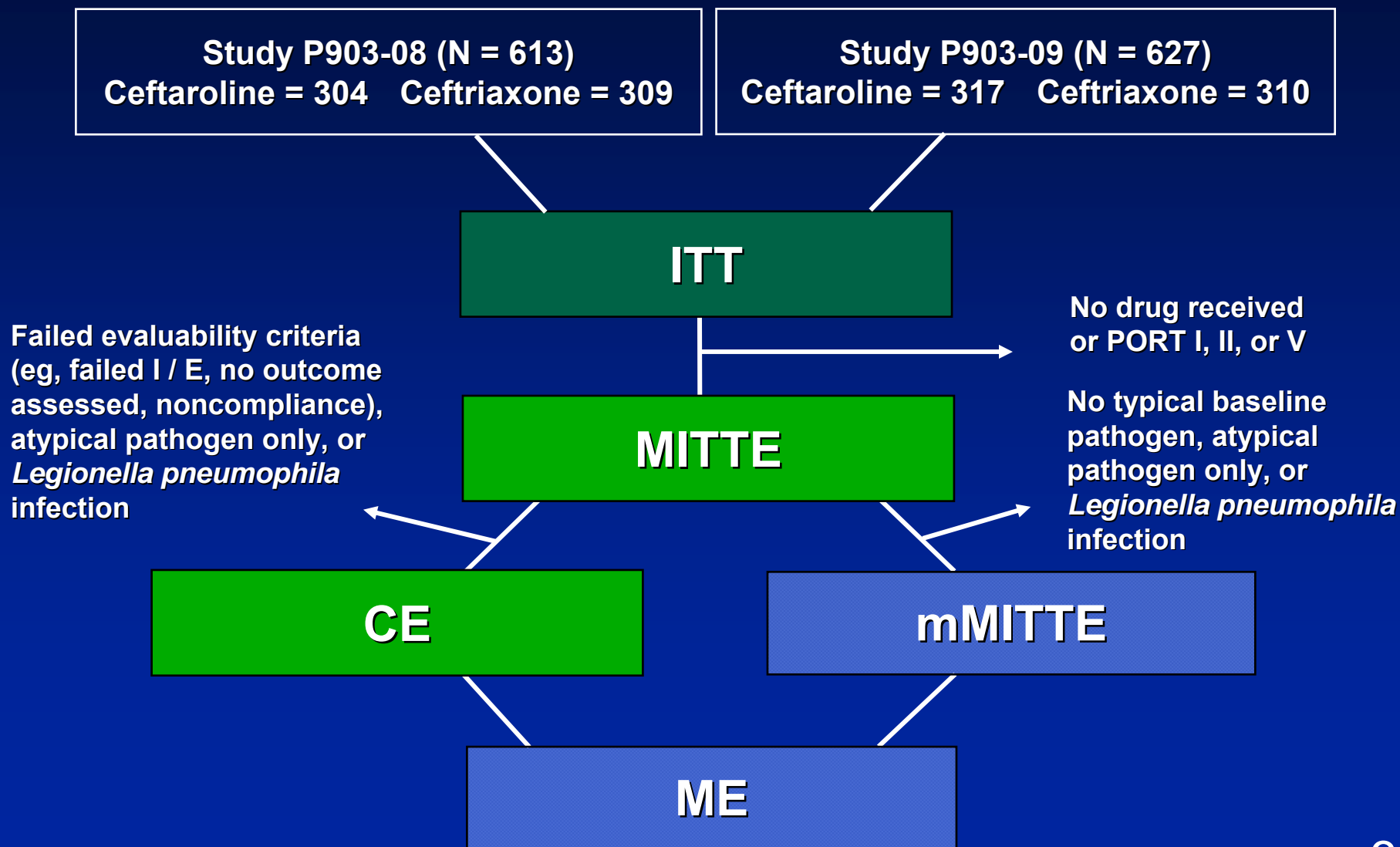
# Primary Endpoint Definitions

*Determined at TOC*

- **Clinical cure**
  - Total resolution of all signs and symptoms of pneumonia or improvement to extent that further antimicrobial therapy not necessary
- **Clinical failure (any of following):**
  - Persistence, incomplete clinical resolution, or worsening in signs and symptoms of CABP that required alternative antimicrobial therapy
  - AE leading to discontinuation of study drug when subject required alternative antimicrobial therapy
  - All-cause mortality
- **Indeterminate**

# Analysis Populations

## Phase 3 CABP Studies Combined



# Demographics and Baseline Characteristics

## *CABP Studies Combined*

<b>Characteristic</b>	<b>MITTE Population</b>	
	<b>Ceftaroline N = 580</b>	<b>Ceftriaxone N = 573</b>
<b>Age</b>		
<b>Mean years <math>\pm</math> SD</b>	<b>60.8 <math>\pm</math> 16.4</b>	<b>61.6 <math>\pm</math> 15.6</b>
<b><math>\geq</math> 65 years, %</b>	<b>47.1</b>	<b>49.0</b>
<b>&gt; 50 years, %</b>	<b>75.5</b>	<b>77.7</b>
<b>Male, %</b>	<b>62.4</b>	<b>63.9</b>
<b>PORT Risk Class, %</b>		
<b>III</b>	<b>62.1</b>	<b>61.6</b>
<b>IV</b>	<b>37.9</b>	<b>38.4</b>
<b>Met modified ATS severe CAP criteria, %</b>	<b>31.2</b>	<b>29.5</b>
<b>Met SIRS criteria, %</b>	<b>74.8</b>	<b>74.2</b>
<b>Bacteremia, %</b>	<b>4.0</b>	<b>3.5</b>
<b>Prior antibiotics*, %</b>	<b>40.9</b>	<b>45.4</b>

\* Single dose of a short-acting antibiotic

# Baseline Pathogens

*Phase 3 CABP Studies Combined*

<b>Organism</b>	<b>MITTE Population, n (%)</b>	
	<b>Ceftaroline N = 580</b>	<b>Ceftriaxone N = 573</b>
<b>Any pathogen</b>	<b>240 (41.4)</b>	<b>235 (41.0)</b>
<b>Typical</b>	<b>170 (29.3)</b>	<b>175 (30.5)</b>
<b>Atypical only</b>	<b>70 (12.1)</b>	<b>60 (10.5)</b>

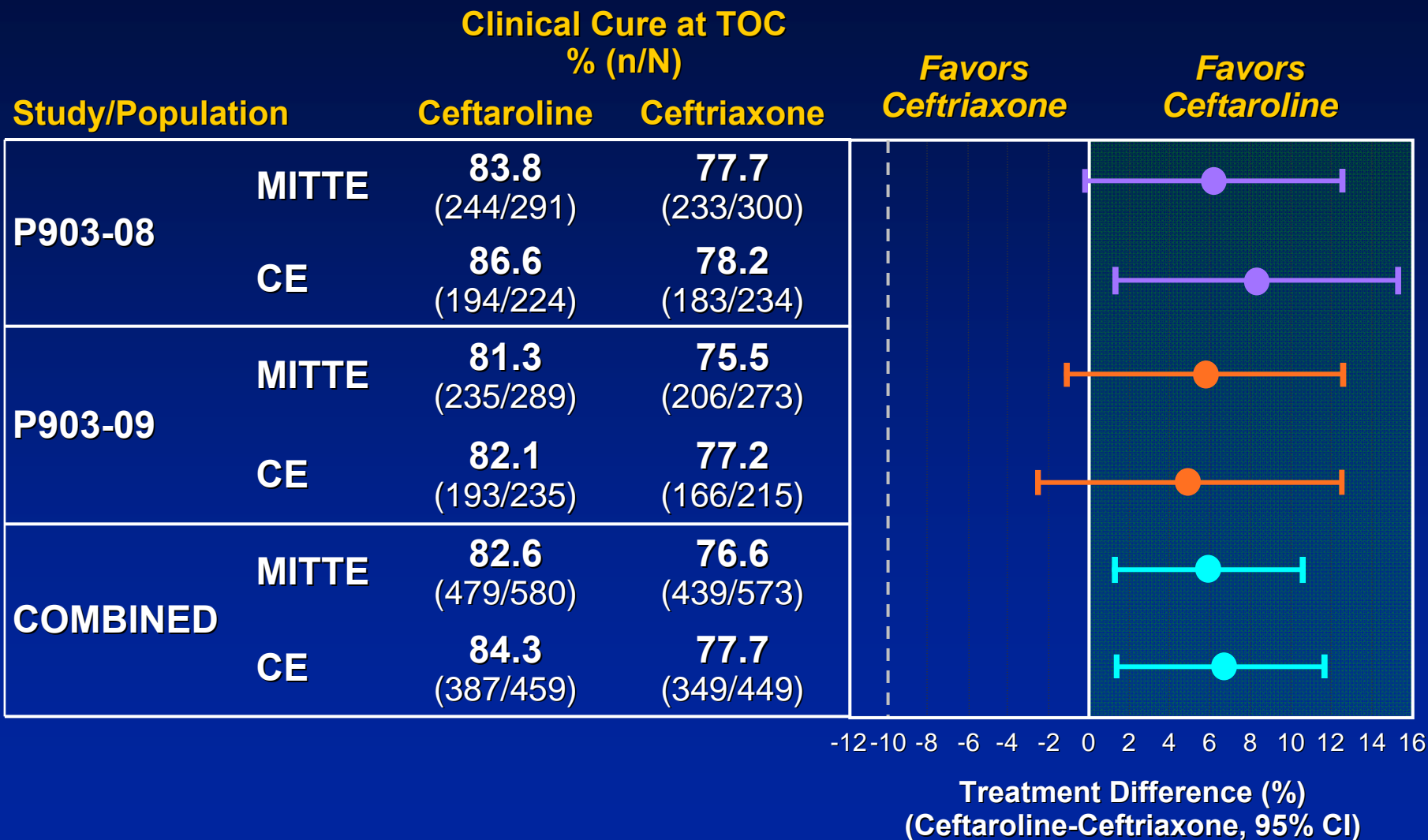
# Key Baseline Pathogens

Phase 3 CABP Studies Combined

Organism	mMITTE Population, n (%)	
	Ceftaroline N = 165	Ceftriaxone N = 168
<i>S. pneumoniae</i>	69 (41.8)	70 (41.7)
<i>S. aureus</i>	25 (15.2)	30 (17.9)
<i>H. influenzae</i>	20 (12.1)	24 (14.3)
<i>H. parainfluenzae</i>	17 (10.3)	18 (10.7)
<i>K. pneumoniae</i>	15 (9.1)	13 (7.7)
<i>E. coli</i>	12 (7.3)	13 (7.7)

# Primary Endpoint

*Clinical Cure at TOC*





# Clinical Cure by Pathogen

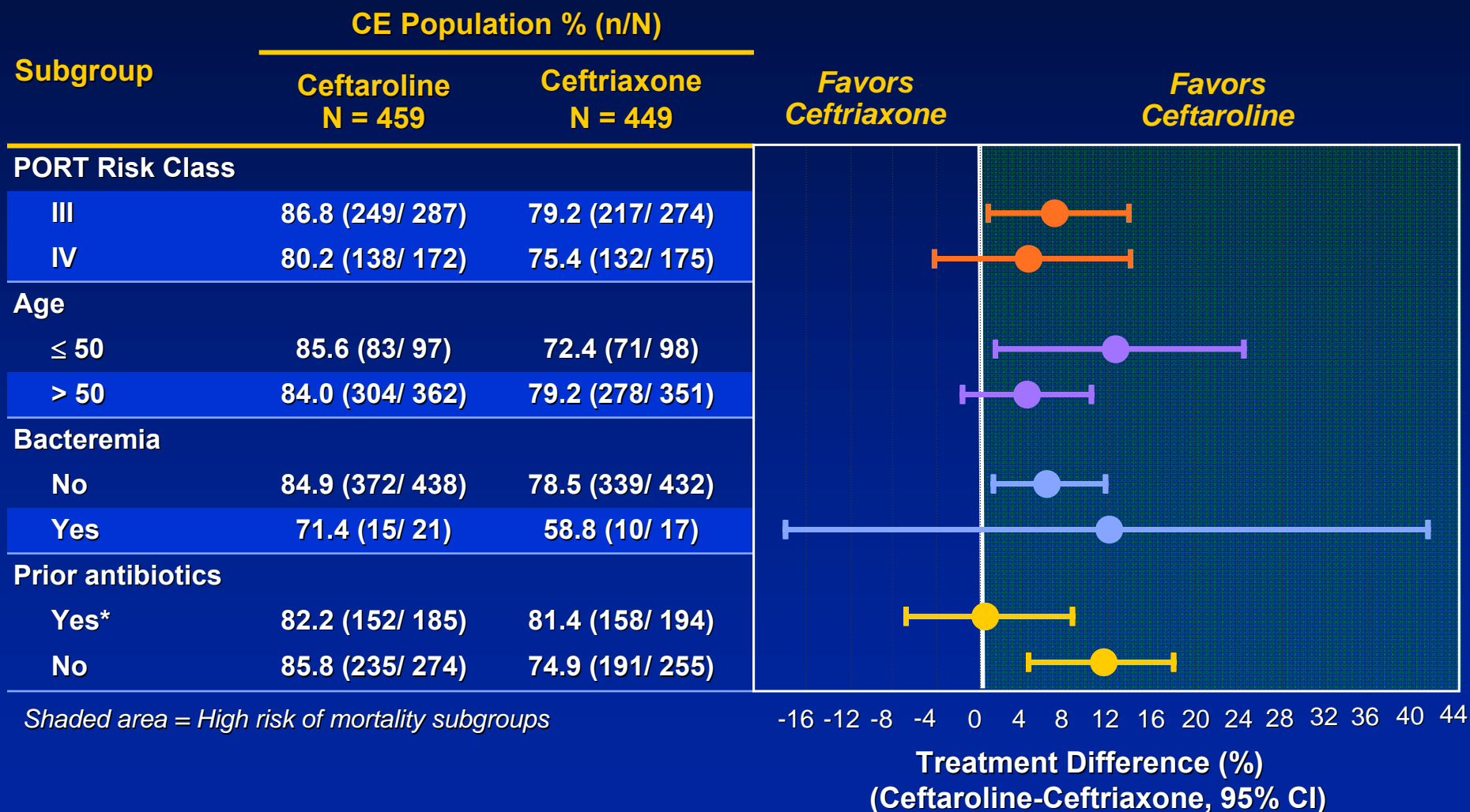
Phase 3 CABP Studies Combined

Organism	mMITTE Population, n/N (%)		Difference (95% CI)
	Ceftaroline N = 165	Ceftriaxone N = 168	
<i>S. pneumoniae</i>	59/69 (85.5)	48/70 (68.6)	17.0 (2.9, 30.7)
MDRSP*	4/4 (100)	2/9 (22.2)	
<i>S. aureus</i>	18/25 (72.0)	18/30 (60.0)	12.7 (-13.1, 36.3)
<i>H. influenzae</i>	17/20 (85.0)	20/24 (83.3)	1.7
<i>H. parainfluenzae</i>	16/17 (94.1)	15/18 (83.3)	10.8
<i>K. pneumoniae</i>	14/15 (93.3)	10/13 (76.9)	16.4
<i>E. coli</i>	10/12 (83.3)	9/13 (69.2)	14.1

\* MDRSP = multidrug resistant *S. pneumoniae*, resistant to  $\geq 2$  classes of antibiotics

# Clinical Cure by Subgroup

## Phase 3 CABP Studies Combined



\* No more than 1 dose of short-acting antibiotic

# FDA-defined Exploratory Primary Analysis

## *FDA-mITT Population*

- **Subjects with  $\geq 1$  acceptable pathogen**
  - Isolated from blood, pleural fluid, BAL
  - Isolated from adequate sputum specimen ( $\leq 10$  squamous epithelial cells/LPF and  $> 10$  WBC/LPF)
  - Positive urinary antigen test for *S. pneumoniae*
  - Specific gram-negative rods and only if  $\geq$  PORT III and isolate from appropriate sample
- **Subjects with *H. parainfluenzae* excluded**
- **Subjects with sole atypical pathogens (*L. pneumophila*, *M. pneumoniae*, or *C. pneumoniae*) excluded**

# FDA-defined Exploratory Primary Analysis

## *Clinical Responder at Study Day 4*

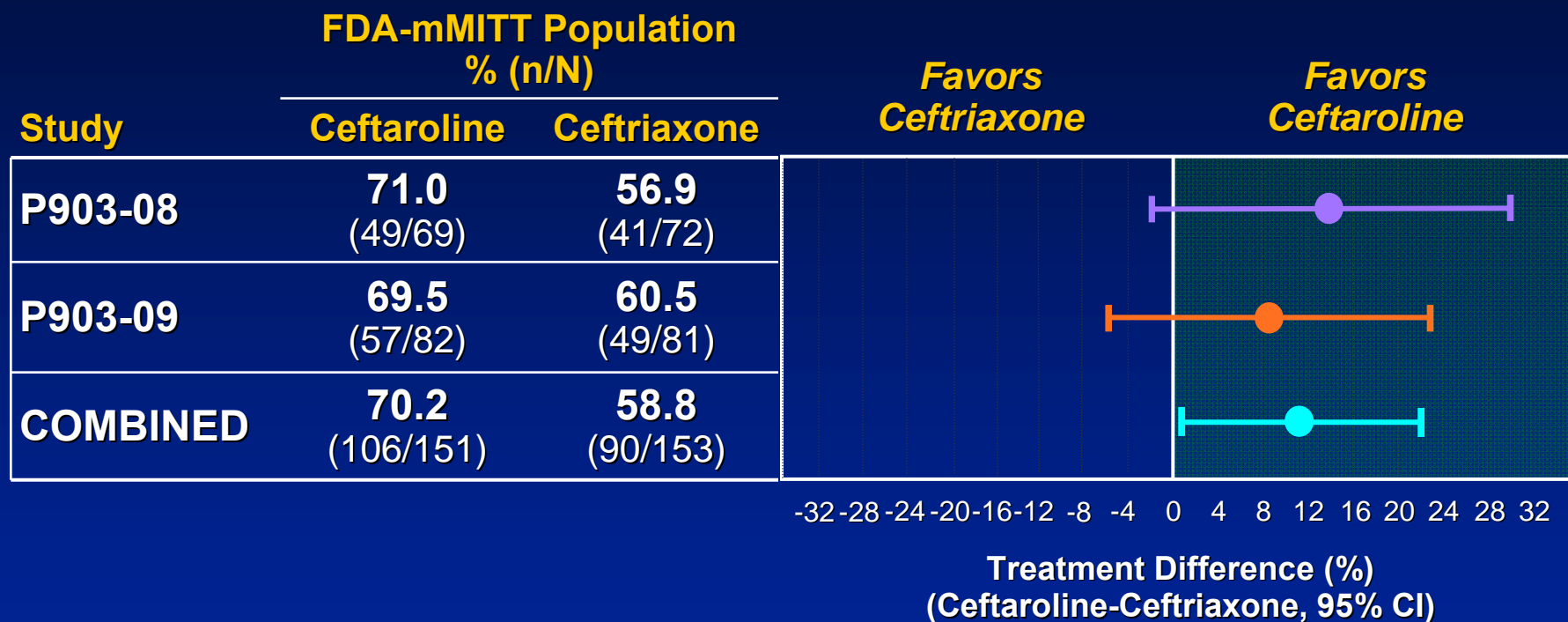
- **Clinically stable**
  - Temperature  $\leq 37.8^{\circ}\text{C}$
  - Heart rate  $\leq 100$  bpm
  - Respiratory rate  $\leq 24$  breaths per min
  - SBP  $\geq 90$  mmHg
  - Oxygen saturation  $\geq 90\%$
  - Confusion/ disorientation absent

**AND**

- **Symptoms criteria success (compared to baseline)**
  - None of 4 symptoms (cough, dyspnea, chest pain, sputum production) worsening
  - $\geq 1$  symptom improving

# FDA-defined Exploratory Primary Analysis

## *Clinical Responders at Study Day 4*



# CABP Efficacy Conclusions

- **Ceftaroline efficacious for treatment of CABP**
  - Pre-specified, traditional primary endpoint (TOC)
  - Exploratory, FDA-defined early time point (Day 4)
  - Secondary and subgroup analyses provide robust support
- **Efficacy demonstrated against important pathogens**
  - *S. pneumoniae*
  - *S. aureus*
  - *H. influenzae*
- **Totality of data demonstrates trends favoring ceftaroline over ceftriaxone for treatment of CABP**

# Clinical Safety

**David Friedland, MD**

*Vice President, Clinical Sciences  
Cerexa, Inc.*

# Safety Population

## All Clinical Studies

<b>Study Grouping</b>	<b>Ceftaroline</b>	<b>Comparator</b>	<b>Total</b>
<b>Clinical Pharmacology</b>	<b>275</b>	<b>84</b>	<b>305*</b>
<b>Combined Phase 2 Studies</b>	<b>165</b>	<b>77</b>	<b>242</b>
<b>Total Phase 3 CABP and cSSSI Studies</b>	<b>1305</b>	<b>1301</b>	<b>2606</b>
<b>Combined Phase 3 CABP Studies</b>	<b>613</b>	<b>615</b>	<b>1228</b>
<b>Combined Phase 3 cSSSI Studies</b>	<b>692</b>	<b>686</b>	<b>1378</b>
<b>Total All Studies</b>	<b>1745</b>	<b>1462</b>	<b>3153</b>

\* 54 subjects in the TQT crossover study are counted only once in the total column



# Adverse Event Overview

## Phase 3 CABP Studies

Safety Event	Safety Population, %	
	Ceftaroline N = 613	Ceftriaxone N = 615
Any TEAE	47.0	45.7
Any SAE	11.3	11.7
Discontinuations due to TEAE	4.4	4.1
Death	2.4	2.0

# Adverse Events $\geq$ 2% in Ceftaroline Group

*Phase 3 CABP Studies*

Safety Event	Safety Population, %	
	Ceftaroline N = 613	Ceftriaxone N = 615
Diarrhea	4.2	2.6
Headache	3.4	1.5
Insomnia	3.1	2.3
Phlebitis	2.8	2.1
Hypertension	2.3	2.6
Hypokalemia	2.3	2.4
Nausea	2.3	2.3

# Serious Adverse Events

*Phase 3 CABP Studies*

<b>Safety Event</b>	<b>Safety Population, %</b>	
	<b>Ceftaroline N = 613</b>	<b>Ceftriaxone N = 615</b>
<b>Pneumonia</b>	<b>1.5</b>	<b>1.5</b>
<b>Pleural effusion</b>	<b>0.8</b>	<b>1.0</b>
<b>Pulmonary embolism</b>	<b>0.8</b>	<b>0.7</b>
<b>COPD</b>	<b>0.7</b>	<b>1.0</b>
<b>Respiratory failure</b>	<b>0.7</b>	<b>0.2</b>
<b>Pyothorax</b>	<b>0.7</b>	<b>0</b>
<b>Lung abscess</b>	<b>0.3</b>	<b>0.7</b>

# Adverse Events Leading to Discontinuation of Study Drug or Study

## *Phase 3 CABP Studies*

- **Low and similar incidences**
  - 4.4% ceftaroline vs 4.1% ceftriaxone
- **Few assessed as study drug related**
  - 0.8% ceftaroline vs 1.0% ceftriaxone
- **No individual AE leading to discontinuation in > 2 ceftaroline subjects**

# Summary of Deaths

## *Phase 3 CABP Studies*

- **Number of deaths low and similar between groups**
  - 15 subjects (ceftaroline) vs 12 subjects (ceftriaxone)
  - Potentially drug-related equal (1 subject each group)
  - Primary infection-related similar (2 vs 3 subjects)
- **Additional 5 deaths after LFU (1 vs 4 subjects)**
- **No predominant cause of death identified**
- **Timing of deaths**
  - Few deaths while on therapy (2 vs 4 subjects)
  - Day 14 mortality similar (6 vs 7 subjects)
  - Day 30 mortality equal (12 subjects each group)

# Organ Systems or Events of Interest Relevant to Cephalosporin Class

*Combined CABP and cSSSI Phase 3 Safety Data*

*Comparator Agents: ceftriaxone (CABP)*

*vancomycin + aztreonam (cSSSI)*

# Summary of Organ Systems

## *Pooled Phase 3 CABP and cSSSI Studies*

- **Similar renal safety**
  - TEAEs of potential renal impairment (1.5% vs 0.8%)
  - PCS Cr increase (1.4% vs 1.9%)
  - PCS CrCl decrease (0.7% vs 1.3%)
- **Similar hematological safety**
  - Increased Coombs seroconversion (10.7% vs 4.4%)
  - TEAEs of potential drug-induced anemia (1.2% vs 1.3%)
  - No hemolytic anemia or other hematological signals
- **No evidence of cardiac toxicity**
  - No cardiac signal (TEAEs and ECGs) in Phase 3 studies
  - No QT prolongation (supratherapeutic dose)
- **Similar hepatic safety**
  - TEAEs of potential hepatic toxicity (2.5% vs 3.6%)
  - No ceftaroline-treated subject met Hy's Law

# Events of Interest Relevant to Cephalosporin Class

## *Pooled Phase 3 CABP and cSSSI Studies*

- **Seizures were uncommon (2 vs 1 subjects)**
  - None related to study drug
- **Lower incidence of potential allergic reactions**
  - TEAEs of potential allergic reactions (5.4% vs 8.5%)
  - Serious/ severe TEAEs (3 vs 6 subjects)
- **Similar incidence of antibiotic-associated diarrhea**
  - TEAEs of potential antibiotic-associated diarrhea (4.5% vs 3.2%)
  - *C. difficile*-associated diarrhea uncommon (2 vs 1 subjects)



# Safety Conclusions

- **Safety results similar between ceftaroline and ceftriaxone including:**
  - TEAEs
  - SAEs
  - Discontinuations due to AE
  - Deaths
- **No safety signal identified by Organ System or safety events of interest review**
- **Ceftaroline well tolerated and safety profile reflective of cephalosporin class**

# **Ceftaroline in CABP Therapeutic Perspective**

**Donald E. Low, MD, FRCPC**

# Ceftaroline Meets Urgent Medical Needs

- Broad spectrum of activity against gram-positives and gram-negatives
- Potent activity and proven effectiveness for treatment of CABP
- Treatment advantage over ceftriaxone for CABP including *S. pneumoniae* and *S. aureus*
- Good safety profile consistent with cephalosporin class
- Ceftaroline represents significant advancement in antibiotic treatment of CABP

## Where Would I Use Ceftazidime

- **First-line empiric therapy for patients with moderate to severe CABP requiring hospitalization**
- **Alternative therapy for patients having failed on other antibiotics**

**Anti-infective Drugs  
Advisory Committee  
(cSSSI)**

**Ceftaroline fosamil**

*Cerexa, Inc.*

*A subsidiary of Forest Laboratories, Inc.*

*07 September 2010*

# Proposed Indications

- **Ceftaroline is indicated for patients with cSSSI caused by susceptible isolates of gram-positive and gram-negative microorganisms**
  - *S. aureus* (including MSSA and MRSA)
  - *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, *S. anginosus* group
  - *E. coli* (ceftazidime-susceptible)
  - *K. pneumoniae*, *K. oxytoca* (ceftazidime-susceptible)
  - *M. morgani* (ceftazidime-susceptible)
- **Proposed dose**
  - 600 mg q12h IV over 1 hour
  - 400 mg q12h IV over 1 hour for subjects with moderate to severe renal impairment (CrCl < 50mL/min)

# Agenda

**Introduction**

***Dirk Thye, MD***

President – Cerexa, Inc.

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**ABSSSI: New Challenges  
in Treatment**

***G. Ralph Corey, MD***

Professor of Medicine  
Duke Clinical Research Institute

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**Microbiology**

***Ian Critchley, PhD***

Vice President, Microbiology  
Cerexa, Inc.

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**Clinical Design and Efficacy**

***Dirk Thye, MD***

**Clinical Safety**

***David Friedland, MD***

Vice President, Clinical Sciences  
Cerexa, Inc.

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**ABSSSI  
Therapeutic Perspective**

***G. Ralph Corey, MD***

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# Financial Disclosure for External Consultants

- All have been paid (directly or through their employer) for their time and travel
- None own stock in Forest Laboratories, Inc.
- Dr. Corey is a Cerexa consultant for ceftaroline clinical trials
- Dr. Ambrose is a Cerexa consultant and current SGE serving as temporary member of Anti-infective Advisory Committee, and here today with Agency approval



# **ABSSSI (cSSSI)**

## **New Challenges in Treatment**

**G. Ralph Corey, MD**

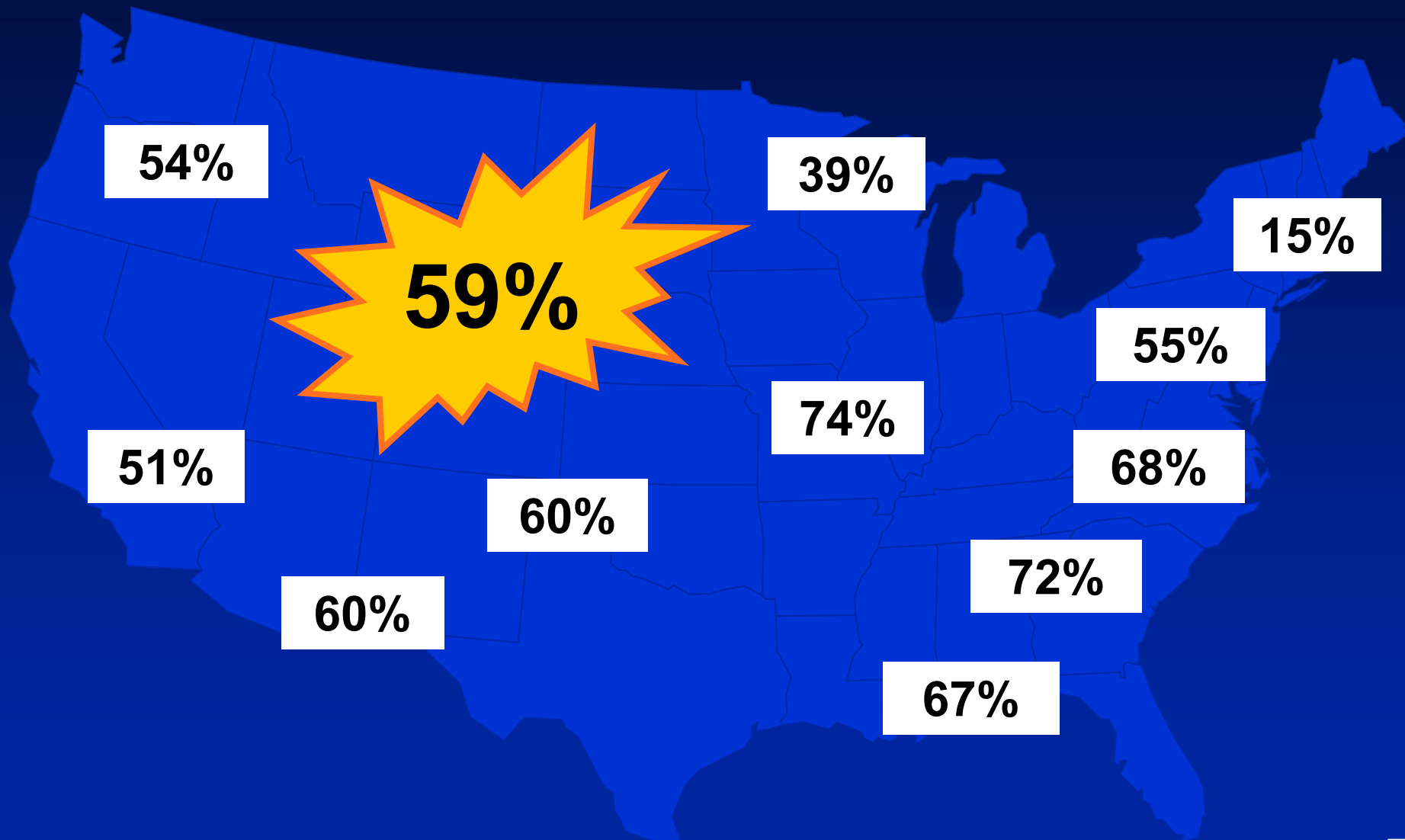
*Professor of Medicine*  
*Duke Clinical Research Institute*

# The Ongoing Epidemic of MRSA-induced ABSSSI

- **14 million medical visits annually**
  - 600,000 hospitalizations each year
- **Most caused by *S. aureus* USA300**
  - Reproduces every 30 mins (1 to 1 trillion in 20 hrs)
  - Genetically promiscuous and acquisitive
    - Resulting increase in virulence/ resistance

# MRSA among 422 ED Patients with ABSSSI

August 2004



# ABSSSI Includes Primarily Moderate Infections



# However, Occasionally Moderate Infections Develop Severe, Life-threatening Complications



# Vancomycin: The Gold Standard for Rx of MRSA

- A large hydrophilic molecule
  - Slowly bactericidal
  - Poor tissue penetration
- Increasing resistance with worsening outcomes
  - VISA (1996), hVISA (1997), VRSA (2002), ↑MICs
- Increasing nephrotoxicity with high serum levels
  - 22% with levels > 20 µg/L

**Clearly new antibiotics are needed to  
treat infections caused by a  
resistant, evolving  
*Staphylococcus aureus***

# **Microbiology**

**Ian Critchley, PhD**

*Vice President, Microbiology  
Cerexa, Inc.*

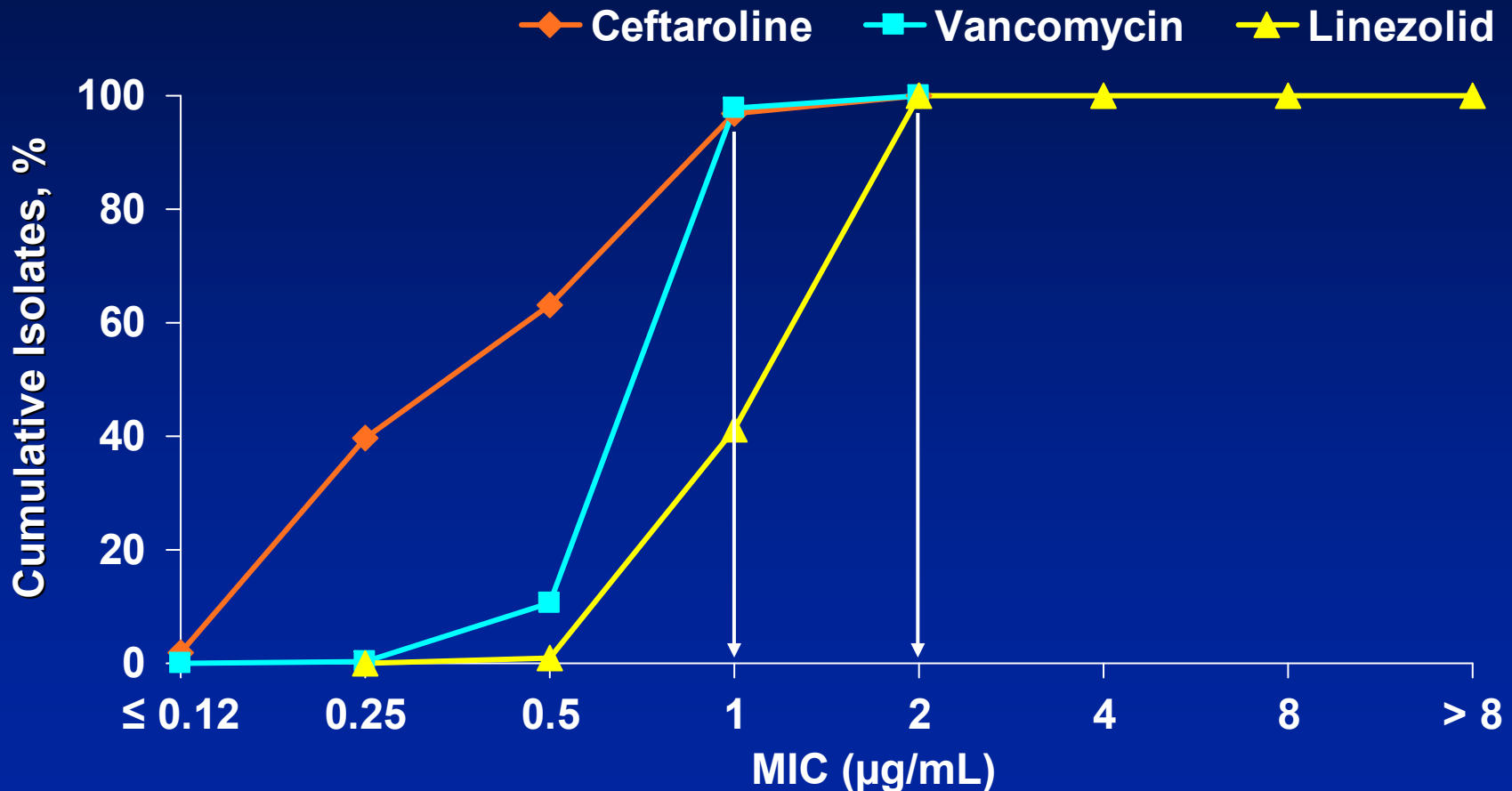


# Broad Spectrum Activity vs Clinically Important Gram-positive Cocci and Gram-negative Pathogens

Organism	Ceftaroline MIC ( $\mu\text{g/mL}$ )		
	No. tested	MIC Range	90%
<i>S. aureus</i> (MSSA)	1711	$\leq 0.008 - 0.5$	0.25
<i>S. aureus</i> (MRSA)	2254	0.12 – 2	1
<i>S. pyogenes</i>	132	$\leq 0.008 - 0.015$	$\leq 0.008$
<i>S. agalactiae</i>	157	$\leq 0.008 - 0.03$	0.015
<i>S. dysgalactiae</i>	12	$\leq 0.008 - 0.03$	0.015
Viridans group streptococci	110	$\leq 0.008 - 1$	0.12
<i>E. coli</i> (ceftazidime-susceptible)	1036	0.015 – $> 16$	0.5
<i>K. pneumoniae</i> (ceftazidime-susceptible)	517	$\leq 0.008 - > 16$	0.25

# Activities of Ceftaroline, Vancomycin and Linezolid Against 2008 US Surveillance Isolates of *S. aureus*

3965 isolates



Arrows indicate MIC<sub>90</sub> values for each agent  
Data from 2008 US Surveillance, JMI Laboratories

# Active Against Contemporary Resistant Phenotypes of *S. aureus*

Antimicrobial Agent	CA-MRSA (n = 92)	VISA (n = 23)	VRSA (n = 10)	DAP-NS (n = 7)
	MIC <sub>90</sub>	MIC <sub>90</sub>	MIC Range	MIC Range
Ceftaroline	1	1	0.12 – 1	0.25 – 1
Vancomycin	1	8	32 – > 64	1 – 2
Daptomycin	1	4	0.5 – 1	4
Linezolid	2	2	1 – 4	1 – 2

# High Affinity for Modified PBP2a in MRSA

## MRSA Strain 67-0

<b>Antibiotic</b>	<b>MIC (<math>\mu\text{g}/\text{mL}</math>)</b>	<b>PBP2a IC<sub>50</sub> (<math>\mu\text{g}/\text{mL}</math>)</b>
<b>Ceftaroline</b>	<b>0.5 – 1</b>	<b>0.16</b>
<b>Ceftriaxone</b>	<b>&gt; 128</b>	<b>677</b>
<b>Oxacillin</b>	<b>128</b>	<b>408</b>

# Ceftaroline Resistance Development for cSSSI Pathogens During Serial Passage

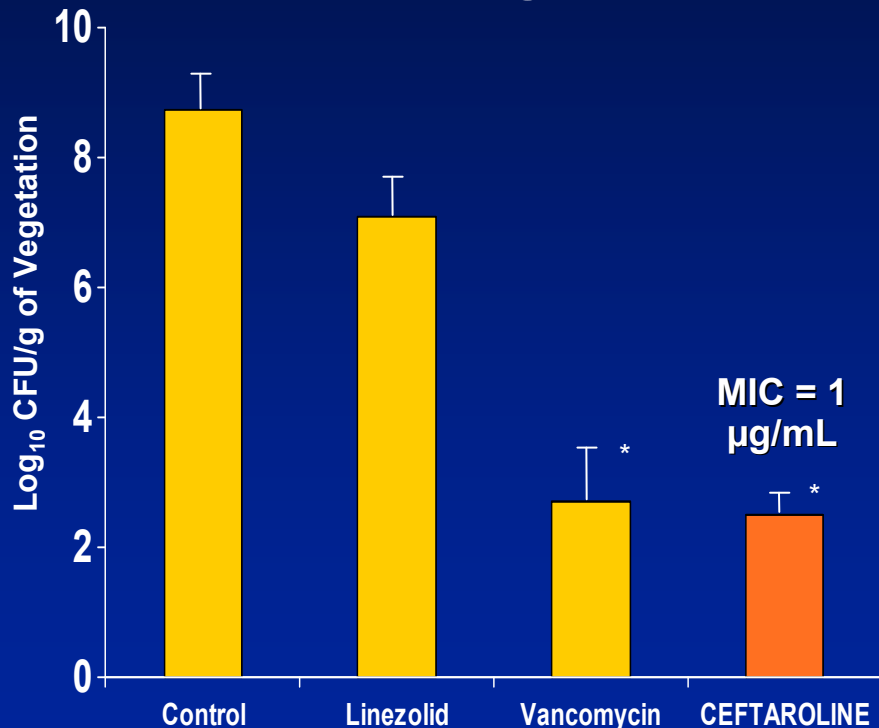
- No MIC shifts > 2 dilutions following 50 serial passages

Organism	Phenotype	Ceftaroline MIC ( $\mu\text{g/mL}$ )	
		Initial MIC	MIC After 50 passages
<i>S. aureus</i> 1449	CA-MRSA	0.5	0.5
<i>S. aureus</i> 873	hVISA	1	2
<i>S. aureus</i> 555	VISA (DAP-NS)	0.5	0.5
<i>S. aureus</i> 543	MSSA	0.25	1
<i>S. pyogenes</i> 2132	Macrolide-S	0.004	0.004
<i>S. pyogenes</i> 2368	Macrolide-R	0.004	0.004
<i>S. pyogenes</i> 1077	Macrolide-R	0.004	0.004

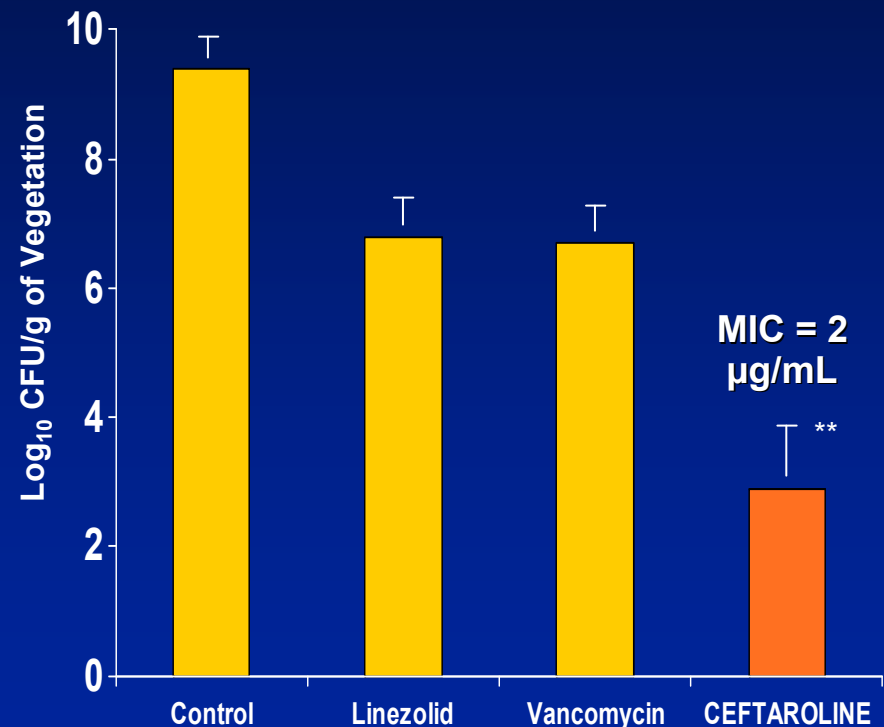
# Efficacy of Ceftaroline and Comparators Against *S. aureus* in Rabbit Endocarditis Model

## Simulated Human Dosing

### MRSA



### hVISA



\*  $p \leq 0.001$  versus control and linezolid

\*\*  $p \leq 0.001$  versus control, linezolid, and vancomycin

## ***S. aureus* PK/PD**

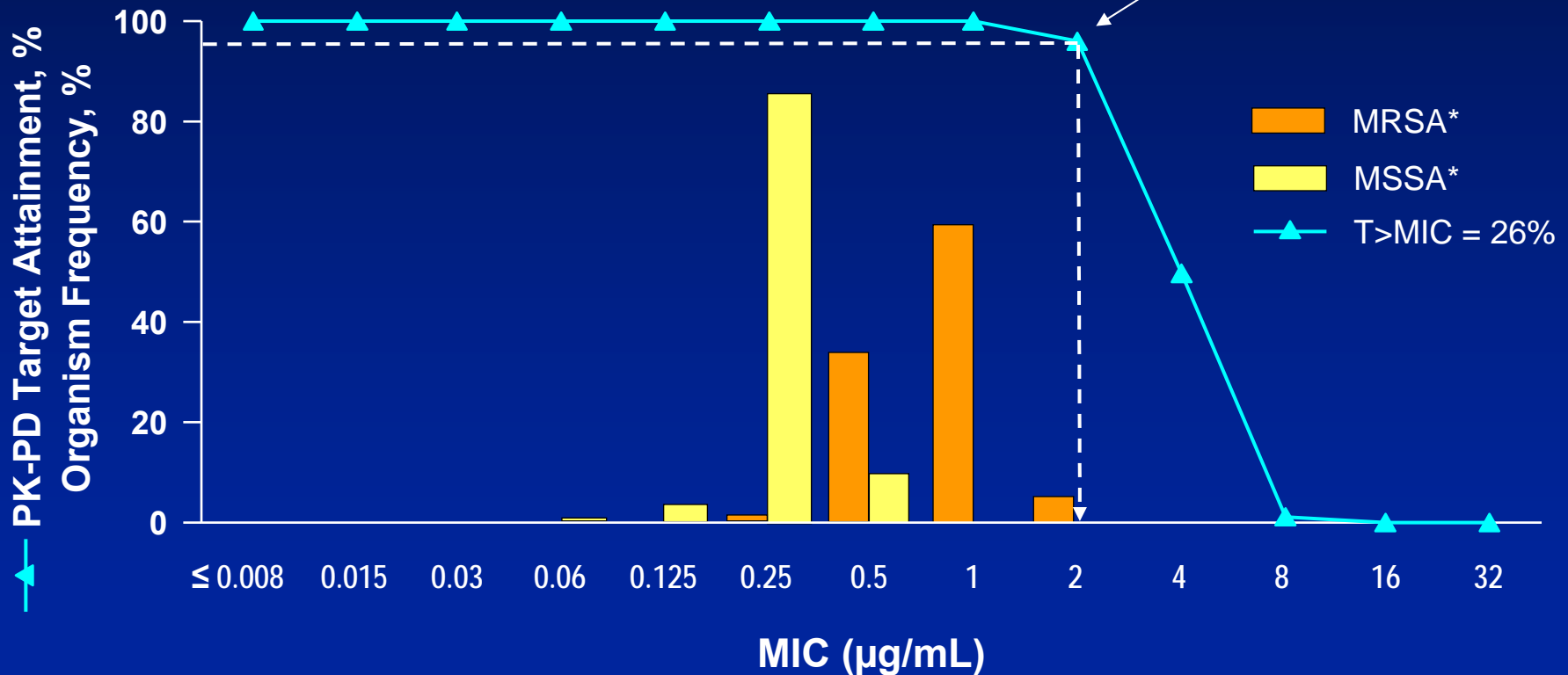
- **%T>MIC is PK/PD parameter that best predicts efficacy for cephalosporins**
- **Murine neutropenic thigh/ bacteremia infection model standard for determining magnitude of %T>MIC**
- **%T>MIC predicts efficacy for ceftaroline**
- **$\geq 26\%$  T>MIC required for efficacy for *S. aureus***

# PK/PD Target Attainment

Monte Carlo simulation-predicted probability (%) of target attainment for the 600 mg q12h dose as a function of MIC

*S. aureus*

> 90% PTA for MIC of 2 µg/mL



\* Bars represent percentage of isolates from US surveillance 2008



# Interpretive Criteria Proposed by Sponsor and Agency for *S. aureus*

Pathogen	Sponsor-proposed Interpretive Criteria			FDA-proposed Interpretive Criteria		
	S	I	R	S	I	R
<i>S. aureus</i> (includes methicillin-resistant isolates)	≤ 2	—	—	≤ 0.5	—	—

# Summary

- **Ceftaroline exhibits broad-spectrum antibacterial activity against important skin pathogens**
- **Activity against resistant gram-positive bacteria mediated by high-affinity binding to modified PBPs**
- **Low potential for resistance development in vitro**
- **Dosing regimen of 600 mg q12h provides adequate free-drug %T>MIC to cover key skin pathogens**
- **Data support breakpoint of  $\leq 2 \mu\text{g/mL}$  for *S. aureus***

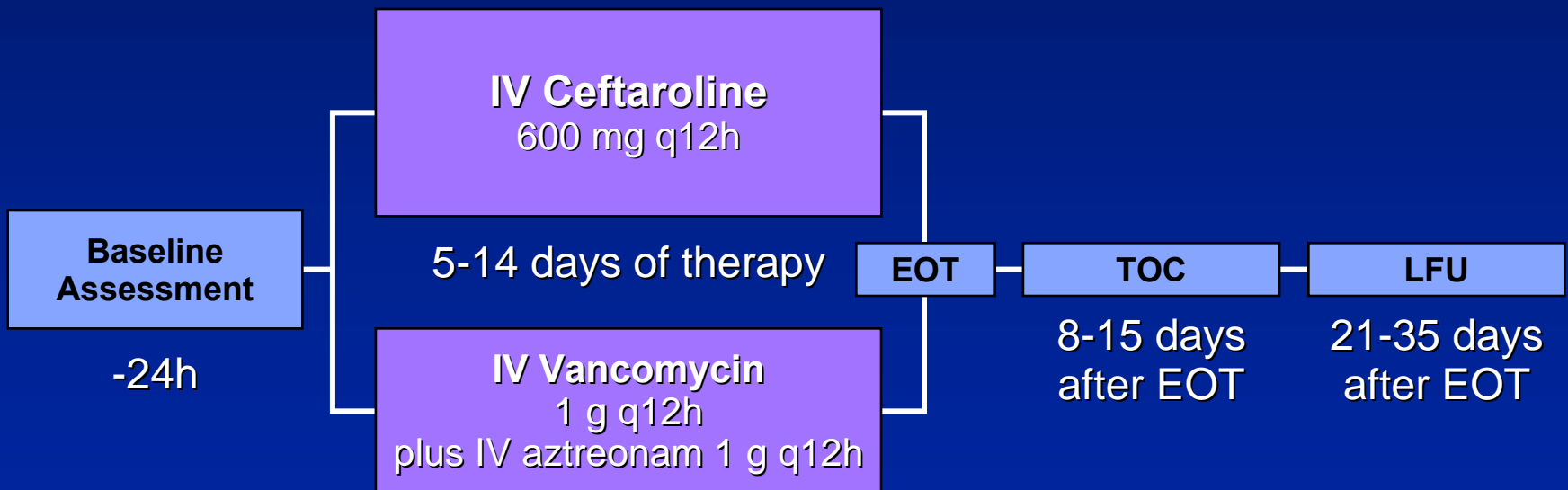
# Clinical Design and Efficacy

**Dirk Thye, MD**

*Cerexa, Inc.*

# cSSSI – Study Design

- Phase 3, multinational, randomized, double-blind
- Noninferiority margin (10%) in clinical response at TOC
- IV therapy only, no oral step-down therapy



# cSSSI Definition

- Involving deep soft tissue or requiring significant surgical intervention
  - Major abscess required  $\geq 2$  cm of cellulitis extending from abscess margin

OR

Involving cellulitis/ abscess of lower extremity in subjects with DM or PVD

- In addition:  $\geq 3$  clinical signs and symptoms
  - Fever  $> 38^{\circ}\text{C}$  oral or hypothermia  $< 35^{\circ}\text{C}$
  - WBC count  $> 10,000/\text{mm}^3$
  - $> 10\%$  bands
  - Purulent or seropurulent drainage
  - Erythema
  - Fluctuance
  - Heat
  - Pain or tenderness to palpation

# Main Inclusion Criteria

- **Adults aged 18 years or older**
- **Need for hospitalization or treatment in emergency room or urgent care setting**
- **Expected to require  $\geq 5$  days of IV antimicrobial therapy**

## **Main Exclusion Criteria**

- **> 24 hours of prior antibiotics for treatment of current cSSSI**
  - **Unless treatment failure with microbiological persistence**
- **Decubitus ulcers and diabetic foot ulcers involving osteomyelitis or requiring surgery**
- **Necrotizing fasciitis or gangrene**
- **Immediate life-threatening disease or evidence of significant hepatic, hematologic, or immunologic disease**

# Efficacy Endpoints

- **Primary Efficacy Endpoint**
  - Clinical cure rate at TOC in MITT and CE Populations
- **Secondary Efficacy Endpoints**
  - Clinical cure rate at EOT
  - Microbiological success rate at TOC
  - Clinical and microbiological response by pathogen at TOC
  - Relapse at LFU
  - Reinfection / recurrence at LFU



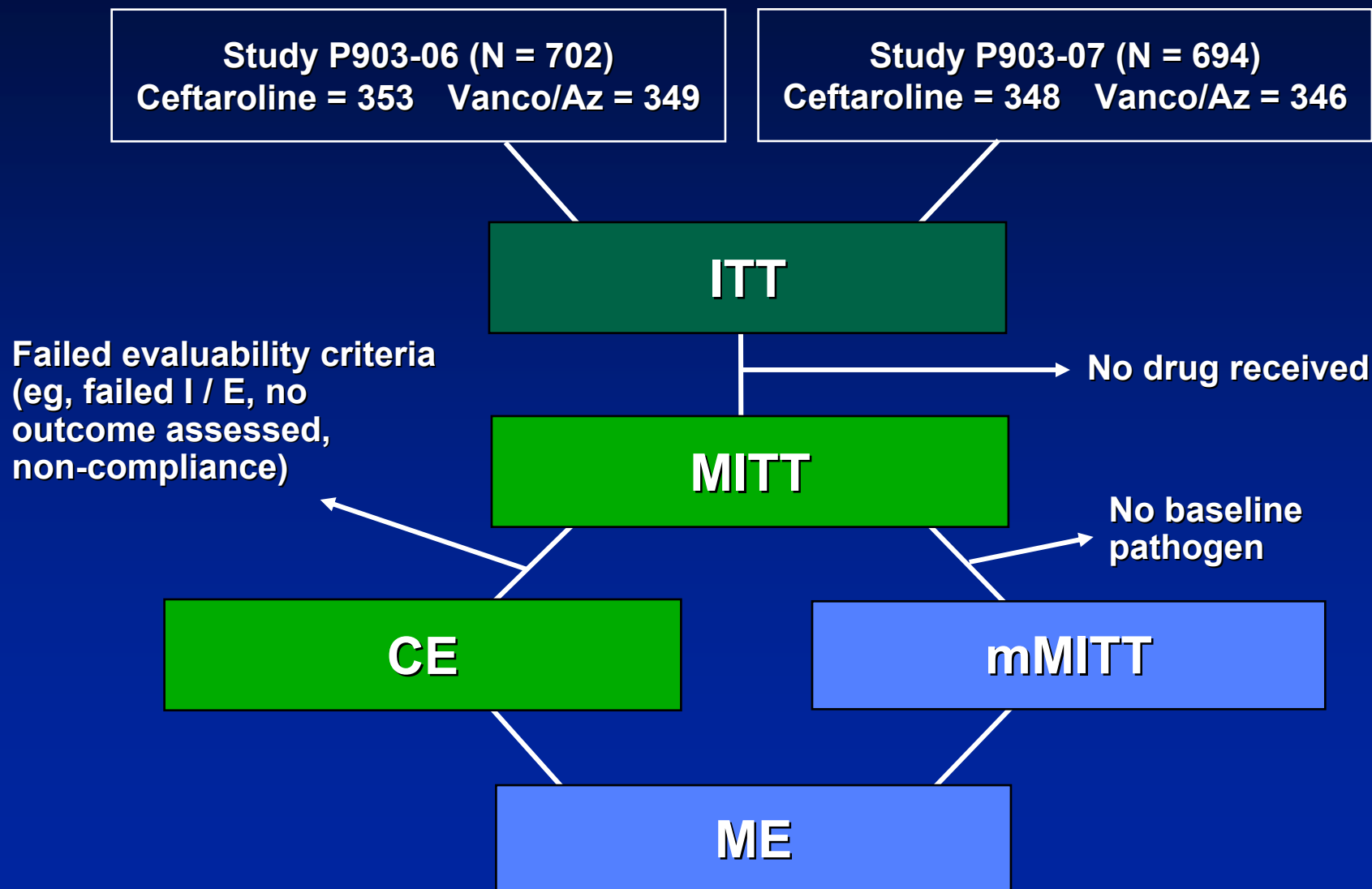
# Primary Endpoint Definitions

*Determined at TOC*

- **Clinical cure**
  - Total resolution of signs and symptoms or improvement to extent that further antibiotics not necessary
- **Clinical failure (any of the following)**
  - Persistence, incomplete resolution, or worsening that requires alternative antibiotics
  - Surgical intervention due to failure of study drug
  - New signs and symptoms at infection site
  - AE leading to study drug discontinuation when subject required alternative antimicrobial therapy
  - Death wherein cSSSI considered causative
- **Indeterminate**

# Analysis Populations

## Phase 3 cSSSI Studies Combined



# Demographics and Baseline Characteristics

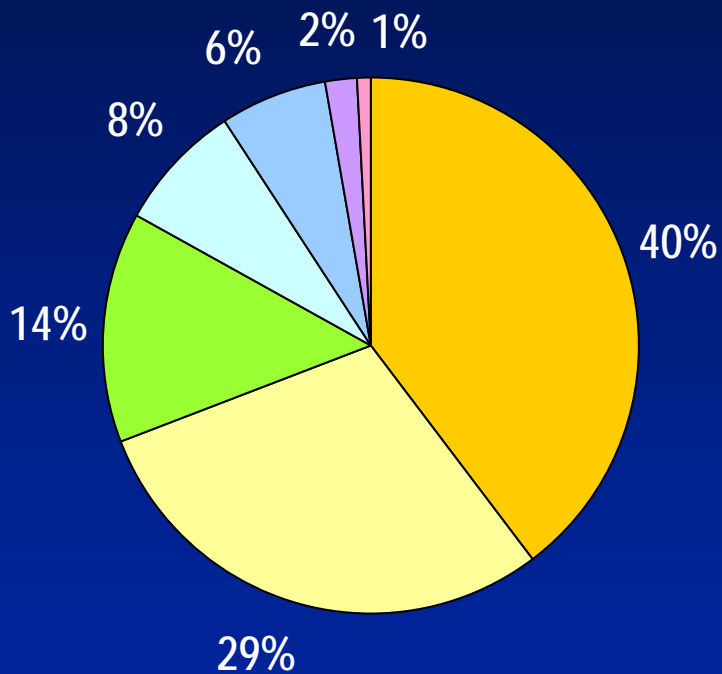
*Phase 3 cSSSI Studies Combined*

<b>Characteristic</b>	<b>MITT Population</b>	
	<b>Ceftaroline N = 693</b>	<b>Vanco/Az N = 685</b>
<b>Age</b>		
<b>mean years <math>\pm</math> SD</b>	<b>47.5 <math>\pm</math> 17.0</b>	<b>48.4 <math>\pm</math> 16.6</b>
<b><math>\geq</math> 65 years, %</b>	<b>17.3</b>	<b>19.0</b>
<b>Male, %</b>	<b>64.1</b>	<b>61.2</b>
<b>BMI, mean kg/m<sup>2</sup> <math>\pm</math> SD</b>	<b>28.4 <math>\pm</math> 7.1</b>	<b>28.7 <math>\pm</math> 7.0</b>
<b>Diabetes, %</b>	<b>17.6</b>	<b>17.5</b>
<b>PVD, %</b>	<b>13.4</b>	<b>13.6</b>
<b>Bacteremia, %</b>	<b>4.2</b>	<b>3.8</b>

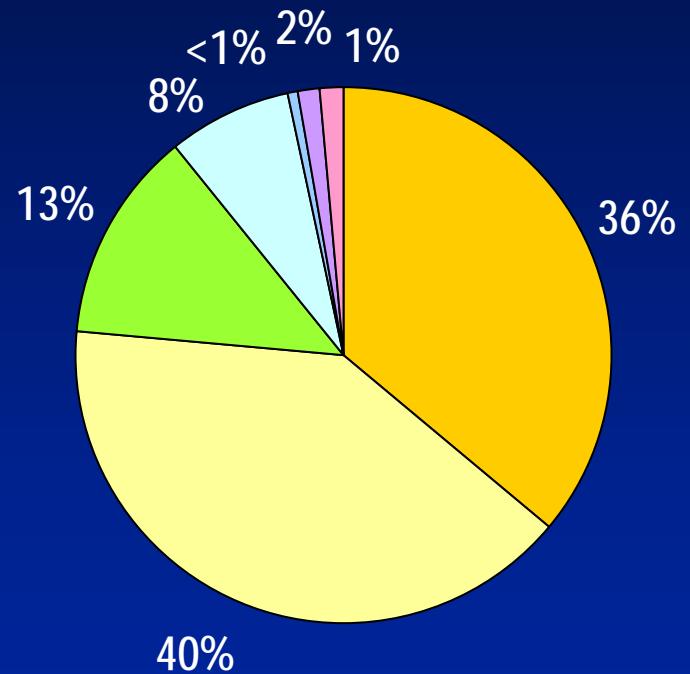
# Baseline Infection Type: Wound, Abscess, Cellulitis

*Individual Phase 3 cSSSI Studies (MITT)*

**Study P903-06**



**Study P903-07**



- Cellulitis
- Abscess
- Infected wound
- Infected ulcer
- Infected burn
- Infected bite
- Other

# Key Baseline Pathogens

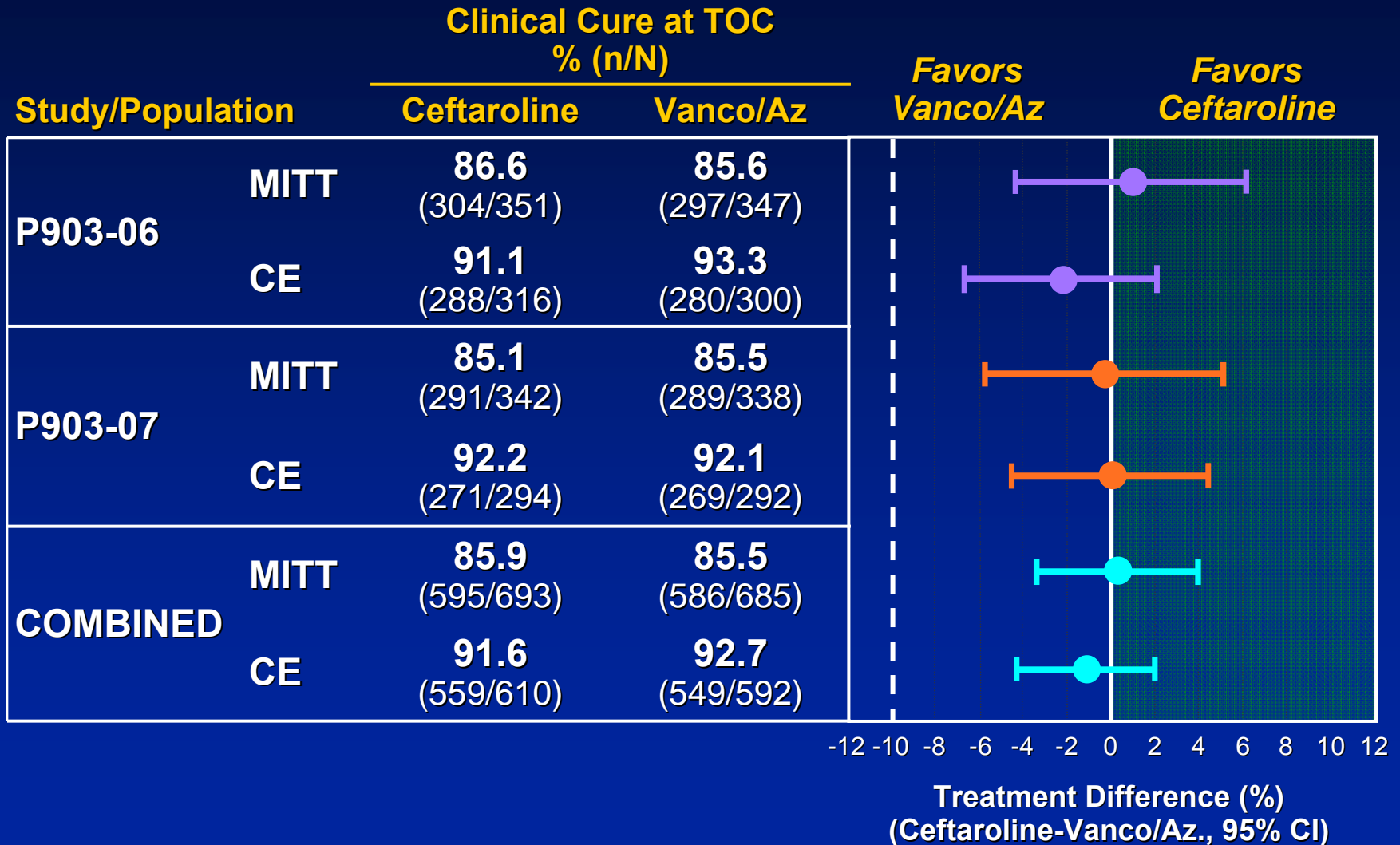
## Phase 3 cSSSI Studies Combined

mMITT Population, n (%)

Organism	Ceftaroline N = 540	Vanco/Az N = 522
<i>S. aureus</i>	425 (78.7)	409 (78.4)
MSSA	245 (45.4)	258 (49.4)
MRSA	179 (33.1)	151 (28.9)
<i>S. pyogenes</i>	63 (11.7)	62 (11.9)
<i>S. agalactiae</i>	27 (5.0)	21 (4.0)
<i>E. coli</i>	23 (4.3)	21 (4.0)
<i>K. pneumoniae</i>	18 (3.3)	19 (3.6)
<i>S. anginosus</i> group	15 (2.8)	18 (3.4)
<i>S. dysgalactiae</i>	14 (2.6)	17 (3.3)
<i>K. oxytoca</i>	12 (2.2)	8 (1.5)
<i>M. morgani</i>	12 (2.2)	7 (1.3)

# Primary Endpoint Analysis

## Clinical Cure at TOC



# Clinical Cure by Pathogen

Phase 3 cSSSI Studies Combined

	mMITT Population, n/N (%)		Difference (95% CI)
	Ceftaroline N = 540	Vanco/Az N = 522	
<i>S. aureus</i>	377/425 (88.7)	356/409 (87.0)	1.6 (-2.8, 6.1)
MSSA	221/245 (90.2)	233/258 (90.3)	-0.1 (-5.5, 5.2)
MRSA	155/179 (86.6)	124/151 (82.1)	4.4 (-3.4, 12.6)
<i>S. pyogenes</i>	56/63 (88.9)	57/62 (91.9)	-1.8 (-13.3, 9.5)

# Clinical Cure by Pathogen (cont'd)

Phase 3 cSSSI Studies Combined

Organism	mMITT Population, n/N (%)	
	Ceftaroline N = 540	Vanco/Az N = 522
<i>S. agalactiae</i>	25/27 (92.6)	19/21 (90.5)
<i>E. coli</i>	21/23 (91.3)	19/21 (90.5)
<i>K. pneumoniae</i>	17/18 (94.4)	14/19 (73.7)
<i>S. anginosus</i> group	12/15 (80.0)	16/18 (88.9)
<i>S. dysgalactiae</i>	14/14 (100.0)	15/17 (88.2)
<i>K. oxytoca</i>	10/12 (83.3)	7/8 (87.5)
<i>M. morgani</i>	11/12 (91.7)	5/7 (71.4)



# FDA-defined Exploratory Primary Analysis

## *Clinical Response at Study Day 3*

- **FDA-MITT Population**

- Lesion size  $\geq 75 \text{ cm}^2$
- Infection type:
  - Infected wound
  - Major abscess (surrounding erythema  $\geq 5 \text{ cm}$ )
  - Deep/ extensive cellulitis
  - Lower extremity SSSI in subjects with DM or PVD

- **Clinical responders**

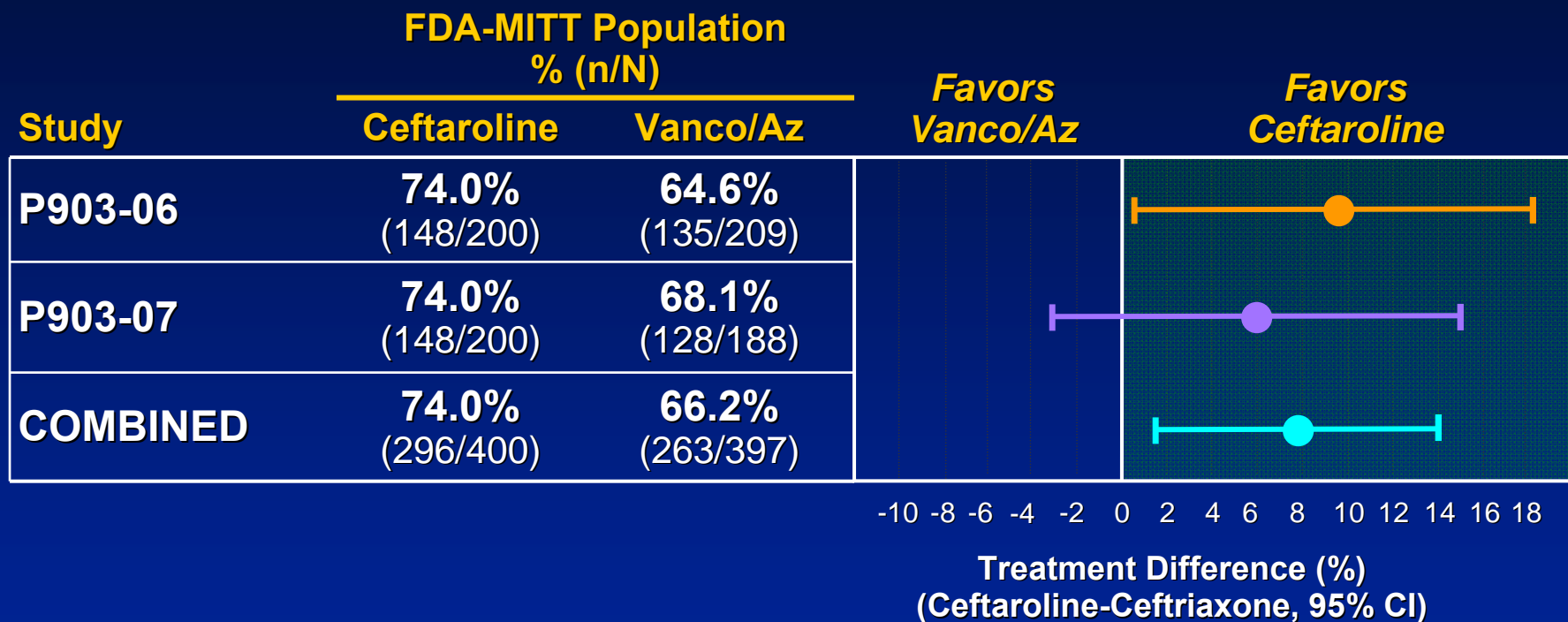
- Cessation of lesion spread at Day 3 (based on both length and width compared to baseline)

AND

- Afebrile at Day 3 ( $\leq 37.6^\circ\text{C}$ )

# FDA-defined Exploratory Primary Analysis

## Clinical Responders at Study Day 3



# cSSSI Efficacy Conclusions

- **Ceftaroline noninferior to vancomycin + aztreonam for treatment of cSSSI**
  - Pre-specified, traditional primary endpoint (TOC)
  - Exploratory, FDA-defined early time point (Day 3)
  - Secondary and subgroup analyses supportive
- **Efficacy demonstrated against important pathogens**
  - *S. aureus*, including MRSA
  - *S. pyogenes* and other *Streptococcus* spp.
  - *Enterobacteriaceae*
- **Totality of data provides robust evidence for the effectiveness of ceftaroline for treatment of cSSSI**

# Clinical Safety

**David Friedland, MD**

*Vice President, Clinical Sciences  
Cerexa, Inc.*

# Safety Population

*All Clinical Studies*

<b>Study Grouping</b>	<b>Ceftaroline</b>	<b>Comparator</b>	<b>Total</b>
<b>Clinical Pharmacology</b>	<b>275</b>	<b>84</b>	<b>305*</b>
<b>Combined Phase 2 Studies</b>	<b>165</b>	<b>77</b>	<b>242</b>
<b>Total Phase 3 CABP and cSSSI Studies</b>	<b>1305</b>	<b>1301</b>	<b>2606</b>
<b>    Combined Phase 3 CABP Studies</b>	<b>613</b>	<b>615</b>	<b>1228</b>
<b>    Combined Phase 3 cSSSI Studies</b>	<b>692</b>	<b>686</b>	<b>1378</b>
<b>Total All Studies</b>	<b>1745</b>	<b>1462</b>	<b>3153</b>

\* 54 subjects in the TQT crossover study are counted only once in the total column

# Adverse Event Overview

*Phase 3 cSSSI Studies*

Safety Event	Safety Population, %	
	Ceftaroline N = 692	Vancomycin + Aztreonam N = 686
Any TEAE	44.7	47.5
Any SAE	4.3	4.1
Discontinuations Due to TEAE	3.0	4.8
Death	0.4	0

# Adverse Events $\geq 2\%$ in Ceftaroline Subjects

## Phase 3 cSSSI Studies

Safety Event	Safety Population, %	
	Ceftaroline N = 692	Vancomycin + Aztreonam N = 686
Nausea	5.9	5.1
Headache	5.2	4.5
Diarrhea	4.9	3.8
Pruritus	3.5	8.2
Rash	3.2	2.5
Vomiting	2.9	2.6
Constipation	2.6	2.6
Insomnia	2.5	2.5
Pruritus generalized	2.2	2.8
Dizziness	2.0	1.2

# Serious Adverse Events

## *Phase 3 cSSSI Studies*

- **Low and similar incidence**
  - 4.3% ceftaroline vs 4.1% vancomycin + aztreonam
- **Few were assessed as study drug related**
  - 0.6% ceftaroline vs 0.4% vancomycin + aztreonam
- **No individual SAE occurred in > 2 ceftaroline subjects**



# **AEs Leading to Discontinuation of Study Drug or Study**

## *Phase 3 cSSSI Studies*

- **Low and similar incidence**
  - 3.0% ceftaroline vs 4.8% vancomycin + aztreonam
- **Skin and Subcutaneous Tissue Disorders was only body system with incidence > 1%**
  - 1.2% ceftaroline vs 2.5% vancomycin + aztreonam
- **Only AE leading to discontinuation in > 2 subjects in ceftaroline group was hypersensitivity**
  - 0.4% ceftaroline vs 0.9% vancomycin + aztreonam

# Summary of Deaths

## *Phase 3 cSSSI Studies*

- **3 deaths prior to LFU visit**
  - 3 ceftaroline vs 0 vancomycin + aztreonam
  - None study drug related
  - Due to underlying disease:
    - Single cases of: respiratory failure; neoplasm progression; cardiopulmonary failure
  - Deaths occurred between 3 and 23 days after EOT
- **Additional 4 deaths after LFU visit**
  - 2 ceftaroline vs 2 vancomycin + aztreonam
  - None study drug related

# Safety Conclusions

## *Phase 3 cSSSI Studies*

- **Safety results similar between ceftaroline and vancomycin + aztreonam including:**
  - TEAEs
  - SAEs
  - Discontinuations due to AE
  - Deaths
- **No safety signal identified by review of Organ System or safety events of interest**
- **Ceftaroline well tolerated and safety profile reflective of cephalosporin class**

# Ceftaroline in ABSSSI Therapeutic Perspective

**G. Ralph Corey, MD**

*Professor of Medicine  
Duke Clinical Research Institute*

# Ceftaroline Characteristics

- **Demonstrated Efficacy**
  - Against wide range of pathogens
  - Across varying infections and populations
  - Protocol-defined endpoints
  - New FDA-defined early endpoints
    - Cessation of spread and resolution of fever
    - Percent reduction in infection area
- **Safe and well tolerated**

# When Would I Use Ceftaroline for ABSSSI?

- **In community-acquired infections**
  - When MRSA suspected
  - When gram-negative bacilli suspected
- **In nosocomial infections when MRSA is suspected**
- **As a replacement for double coverage for patients with suspected/ proven MRSA infections involving SSS**
- **I would use in patients in my practice**

# Infectious Diseases Society of America

**Bad Bugs  
Need Drugs**



Ten new **ANTIBIOTICS** by 2020