

# **Solithromycin for the Treatment of Community-Acquired Bacterial Pneumonia (CABP)**

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**November 4, 2016**

Cempra Pharmaceuticals, Inc.

Antimicrobial Drugs Advisory Committee

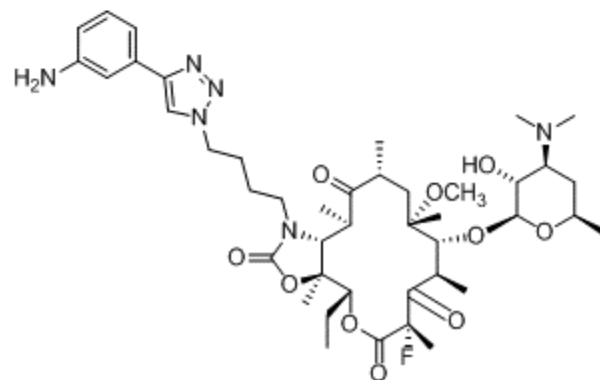
# Introduction

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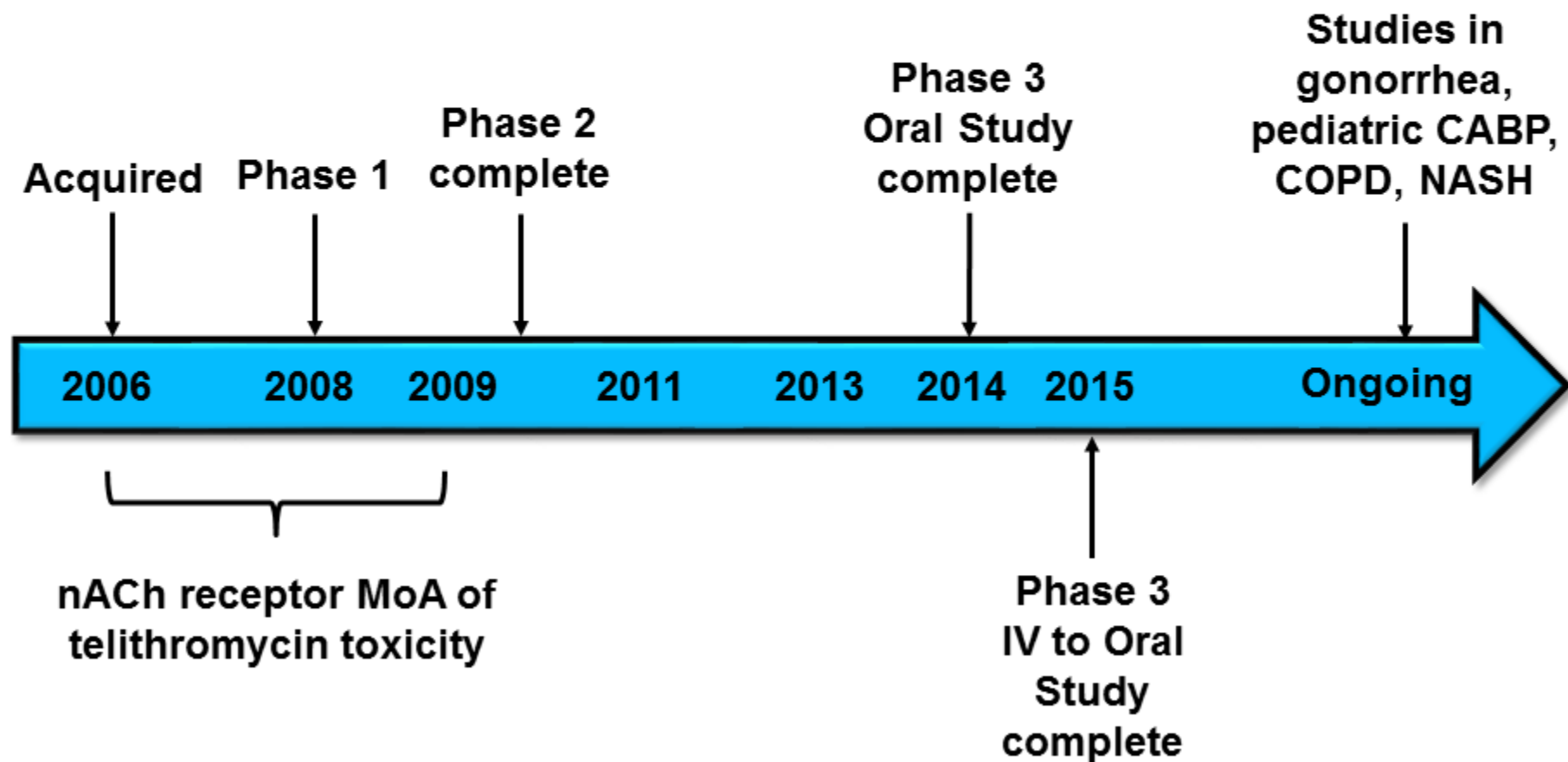
**Prabhavathi Fernandes, PhD**

President and CEO

Cempra Pharmaceuticals, Inc.



# Solithromycin Development History



# Solithromycin Proposed Indication (Oral and IV Formulations)

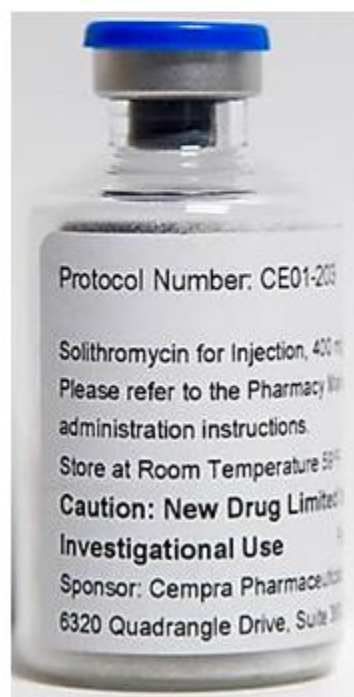
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- For the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative bacteria:  
***Streptococcus pneumoniae*** (including penicillin-resistant isolates, macrolide-resistant isolates, multi-drug-resistant isolates, and cases with concurrent bacteremia),  
***Haemophilus influenzae*** (including beta-lactamase producing isolates), ***Moraxella catarrhalis***,  
***Staphylococcus aureus*** (methicillin-susceptible [MSSA]), and the atypical bacterial pathogens ***Legionella pneumophila*** and ***Mycoplasma pneumoniae***

# Solithromycin Formulations

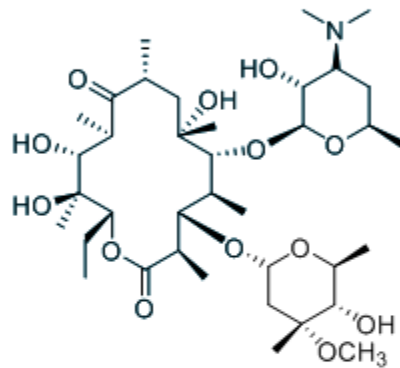
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- Administered both orally and parenterally
  - Switch from IV to Oral possible
- Allows for inpatient and outpatient treatment



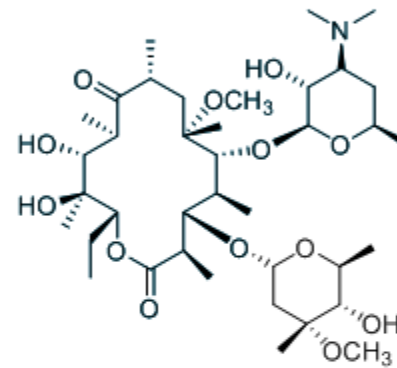
# Solithromycin: 4<sup>th</sup> Generation Macrolide, 1<sup>st</sup> Member of Fluoroketolide Subclass

## 1<sup>st</sup> Generation Macrolide

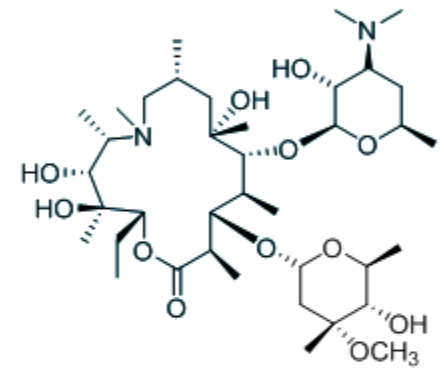


Erythromycin

## 2<sup>nd</sup> Generation Macrolide

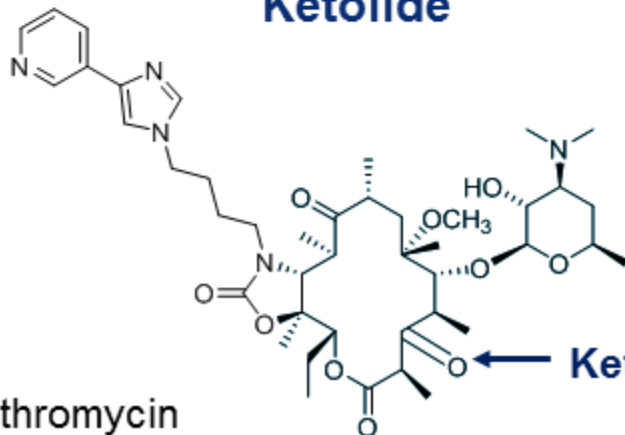


Clarithromycin



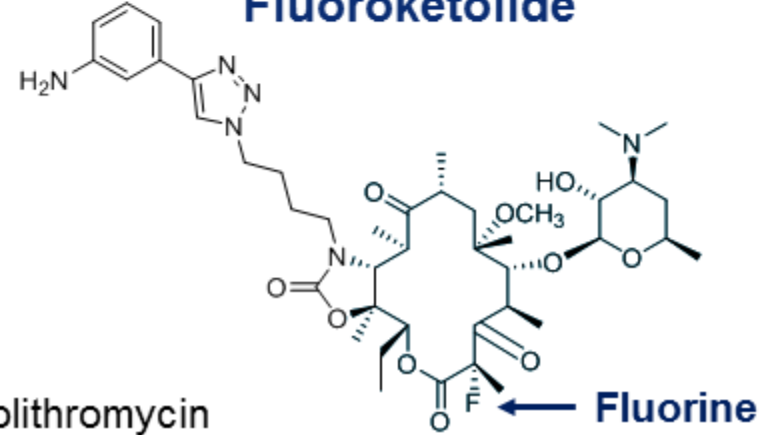
Azithromycin

## 3<sup>rd</sup> Generation Macrolide, Ketolide



Telithromycin

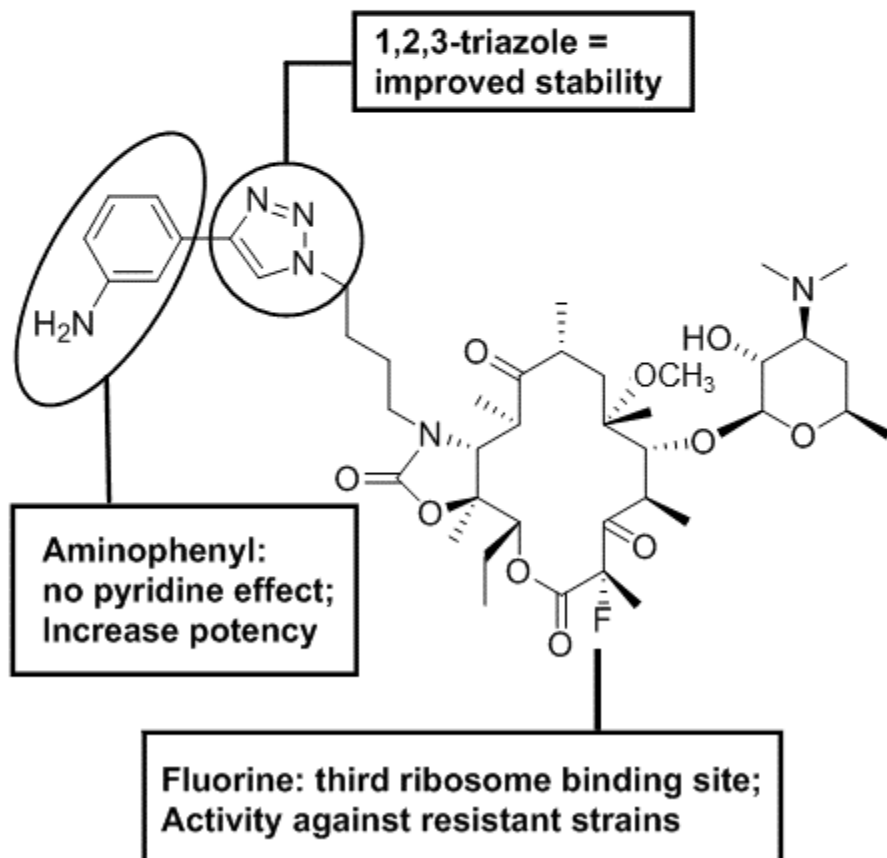
## 4<sup>th</sup> Generation Macrolide, Fluoroketolide



Solithromycin

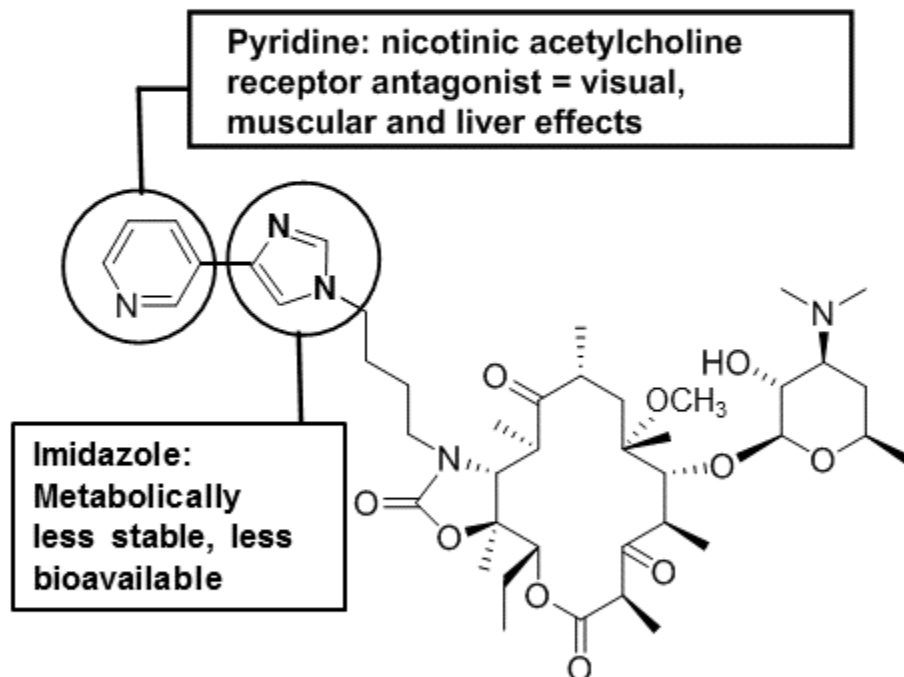
# Chemical Differentiation of Solithromycin from Telithromycin

## Solithromycin



vs

## Telithromycin



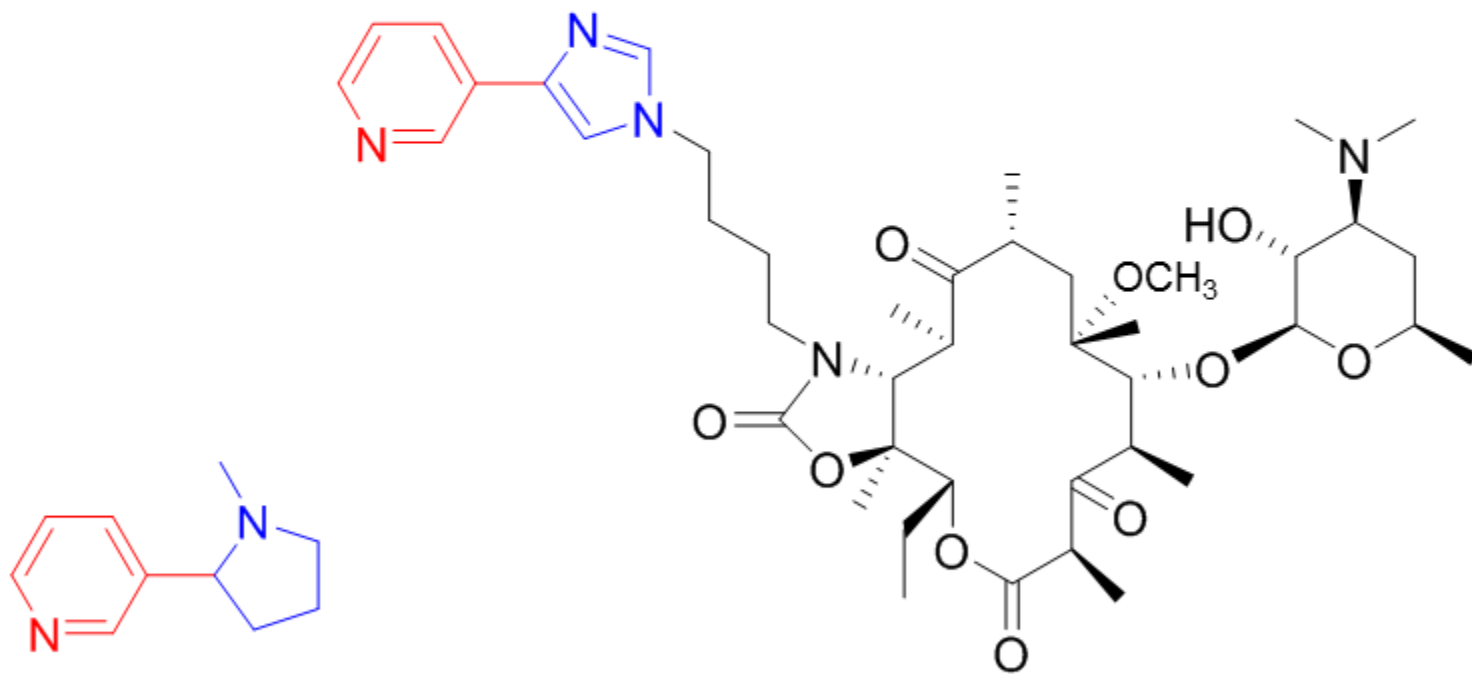
## Side Effects of Telithromycin

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- Visual disturbances
- Myasthenia gravis exacerbations
- Syncope or loss of consciousness
- Liver toxicity

# Similar Telithromycin Side Chain and Nicotinic Acid Structures

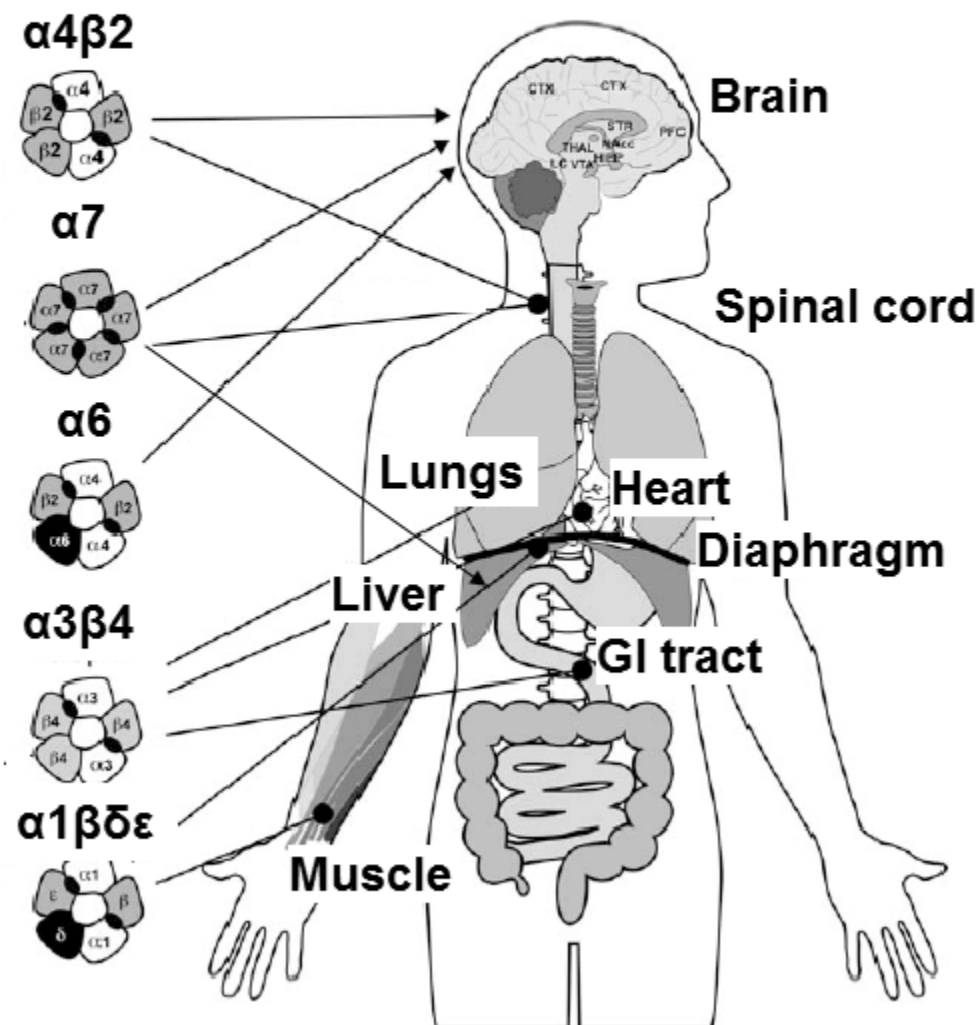
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**Nicotinic acid**

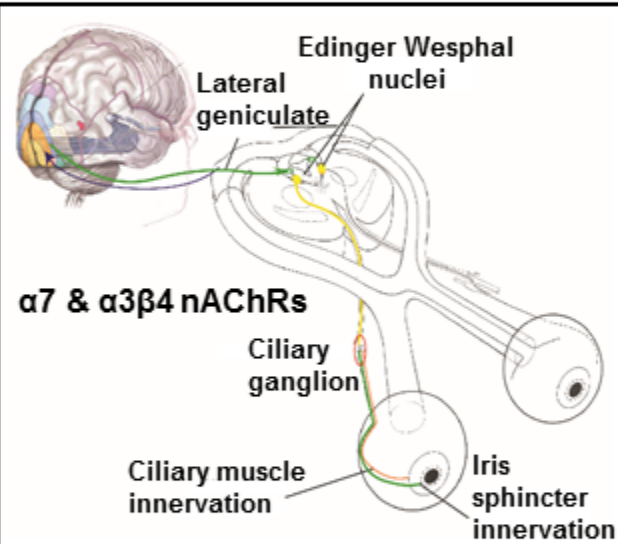
**Telithromycin**

# Broad Distribution of nACh Receptors Throughout Body

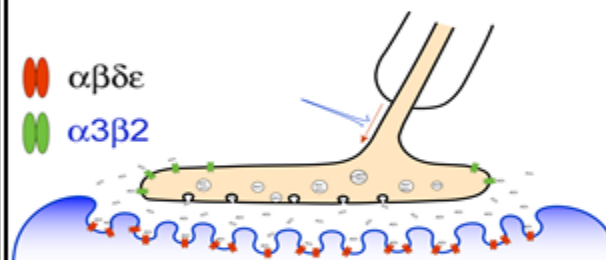


# Mechanistic Off-Target Effects of Telithromycin

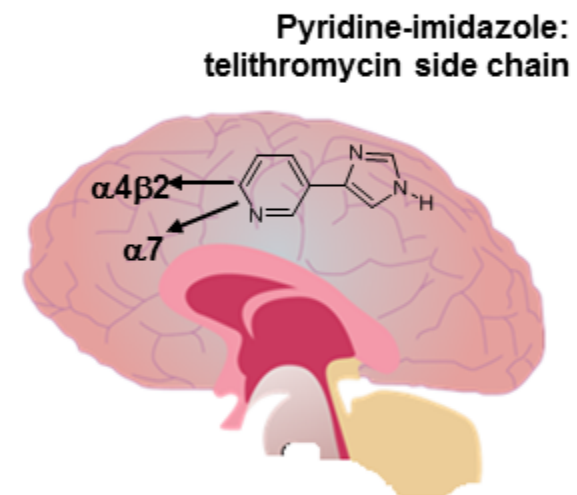
## Visual Disturbances



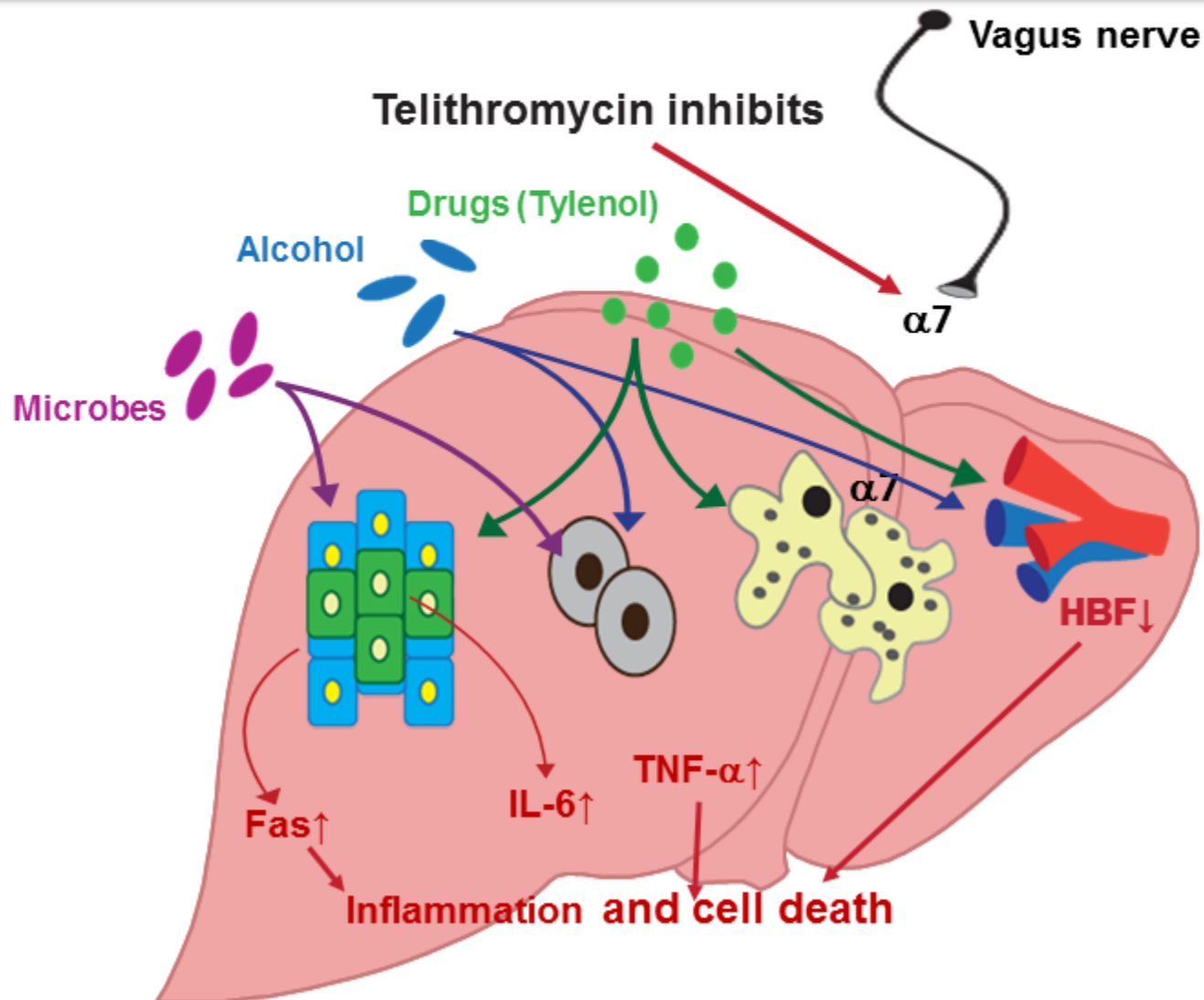
## Myasthenia Gravis



## Syncope



# Mechanistic Off-Target Effects of Telithromycin: Liver Toxicity



# Toxicological Safety Profile of Solithromycin

	<b>Solithromycin</b>	<b>Telithromycin<sup>2</sup></b>	<b>Clarithromycin<sup>3</sup></b>
<b>4-week toxicology in rat (Liver NOAEL)</b>	<b>100 mg/kg/day</b>	<b>100 mg/kg/day</b>	<b>100 mg/kg/day</b>
<b>13-week daily dosing toxicology in rat<sup>1</sup> (Liver NOAEL)</b>	<b>125 mg/kg/day</b>	<b>50 mg/kg/day</b>	<b>15 mg/kg/day</b>
<b>4-week IV toxicology in dog and monkey</b>	<b>Max doses of 15 mg/kg/day, 25 mg/kg/day well-tolerated</b>	<b>No IV QT positive</b>	<b>No IV in US QT positive</b>
<b>Developmental toxicology Segment I, II and III</b>	<b>Non-teratogenic</b>	<b>Non-teratogenic</b>	<b>Teratogenic</b>
<b>Newborn rat</b>	<b>Exposed</b>	<b>NA</b>	<b>NA</b>

NA = Not Available. 1. 13-week study from Bridge 1715-08278. 2. Pharmacology and Toxicology Review, NDA 21-144.

3. FDA Briefing Package, Anti-Infective Advisory Committee, April 2001.

## Phase 3 Data Show Positive Benefit-Risk Profile in CABP

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- IV and oral solithromycin demonstrated
  - Efficacy comparable to approved fluoroquinolone
  - Acceptable safety profile in adults

# Agenda

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**Unmet Need****Julio Ramirez, MD, FACP**

Professor of Medicine  
Chief, Division of Infectious Diseases  
University of Louisville

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**Microbiology / PK / PD****Prabha Fernandes, PhD****Phase 3 Study Design****David Oldach, MD, FIDSA**

Chief Medical Officer  
Cempra Pharmaceuticals, Inc.

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**Efficacy****Anita Das, PhD**

Lead Biostatistician

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**Safety****David Oldach, MD, FIDSA****Paul Watkins, MD**

Hepatologist, University of North Carolina

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**Primary Care Perspective****Steve Vacalis, DO**

Family Medicine Physician  
CaroMont Family Medicine

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# Additional Experts

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**Pharmacologist**

Institute for Clinical Pharmacodynamics, Inc.

**Sujata Bhavnani, PharmD**

**Pharmacologist**

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**Michael Cohen-Wolkowicz, MD, PhD**

**Pediatric Infectious Disease Specialist**

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**J. Carl Craft, MD**

**Infectious Diseases Specialist**

**Pierre Gholam, MD**

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Case Western Reserve University

**Dwight Hardy, PhD**

**Microbiologist**

University of Rochester

**Christopher M. Rubino, PharmD**

**Pharmacologist**

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**Philip Sager, MD**

**Cardiologist**

Stanford University School of Medicine

**Gary Wolfe, PhD**

**Toxicologist**

Gary Wolfe Toxicology, LLC

# Treatment of CAP

## Unmet Need

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**Julio A. Ramirez, MD, FACP**

Professor of Medicine

Chief, Infectious Diseases

University of Louisville

# Treatment of CAP: Unmet Need

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**1. Epidemiology**

**2. National Guidelines**

**3. Current Options**

# Causes of Death U.S. Population

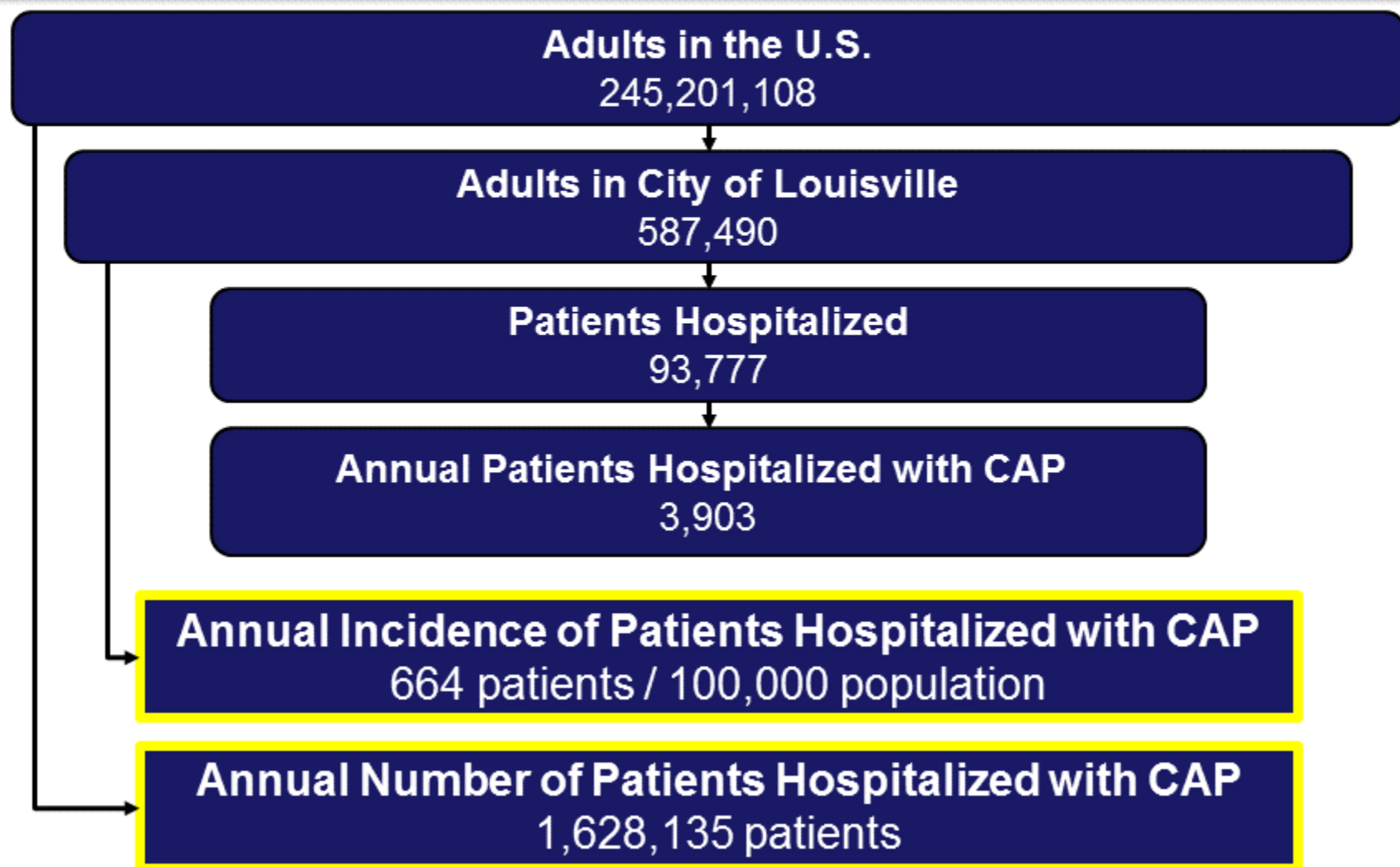
Rank	Cause of Death
1	Heart Disease
2	Cancer
3	Chronic Pulmonary Disease
4	Accidents
5	Stroke
6	Alzheimer's Disease
7	Diabetes
8	Pneumonia

Data based on “underlying cause of death” reported on death certificates

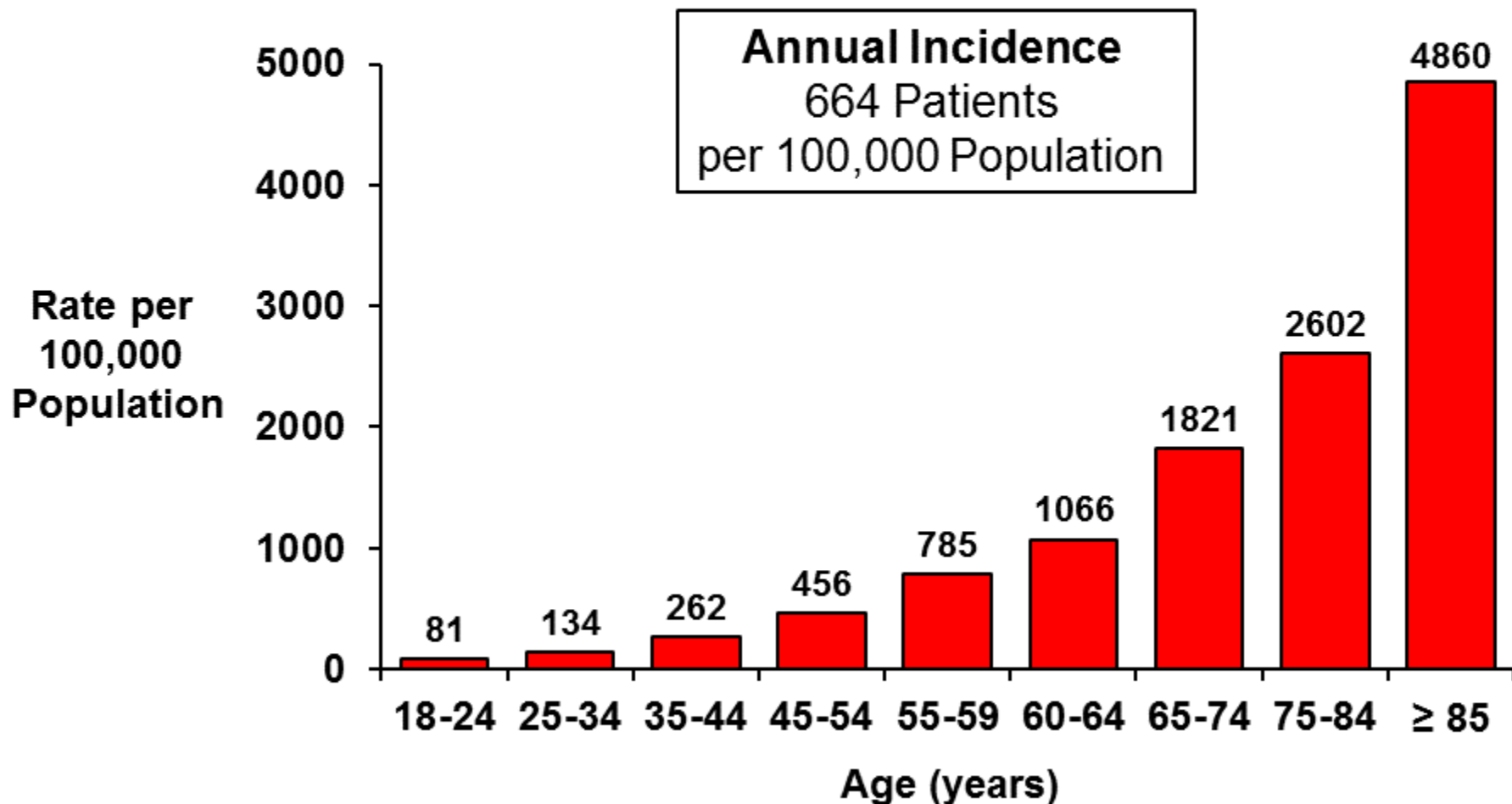
Adapted from CDC National Vital Statistics Report, 2016.

Fauchi et al., JAMA, 2016.

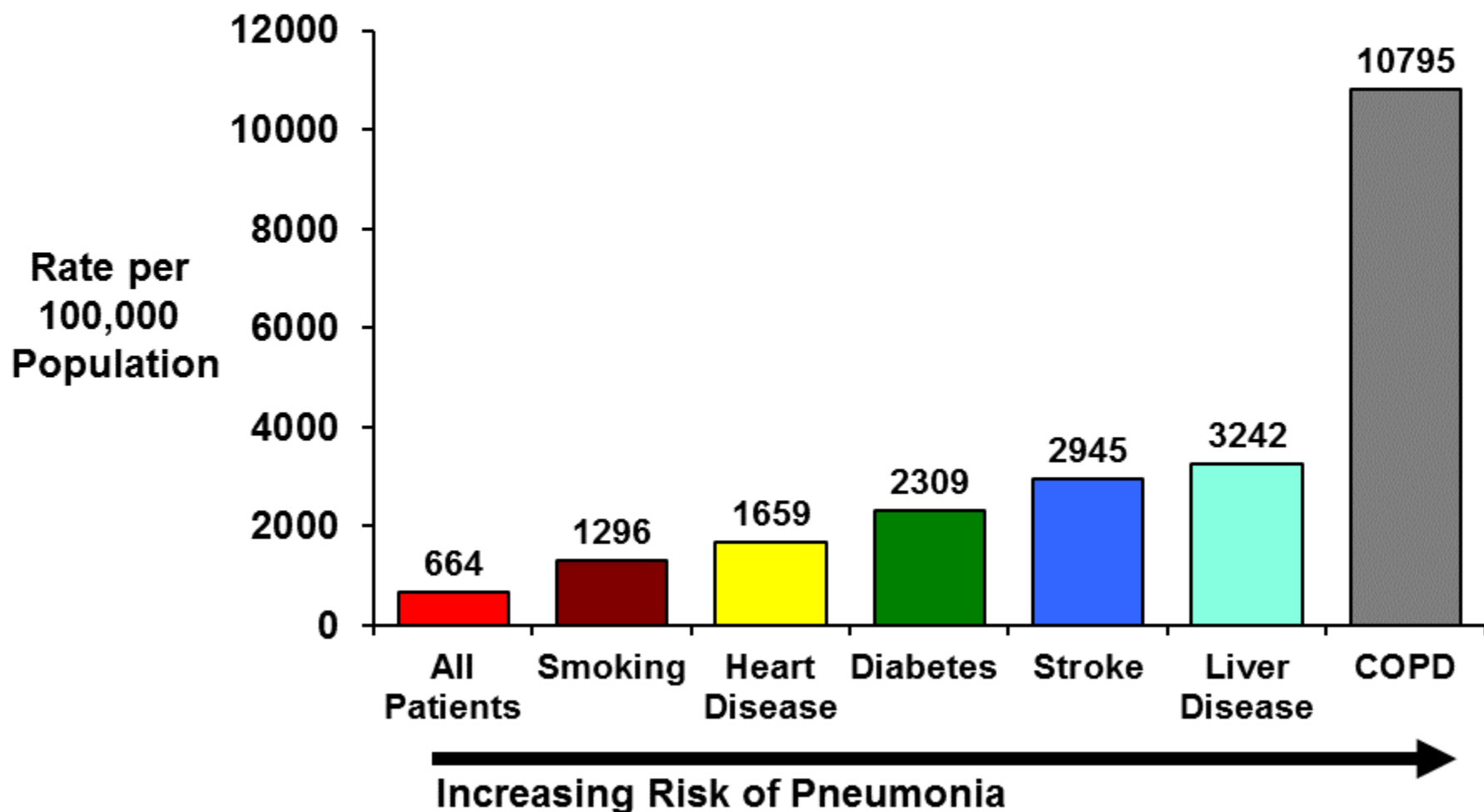
# UofL CAP Study: Incidence



# UofL CAP Study: Age



# UofL CAP Study: Comorbidities



# Treatment of CAP: Unmet Need

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**1. Epidemiology**

**2. National Guidelines**

**3. Current Options**

# Treatment: National Guidelines

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## American Thoracic Society

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### **Guidelines for the Management of Adults with Community-acquired Pneumonia**

#### **Diagnosis, Assessment of Severity, Antimicrobial Therapy, and Prevention**

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS  
MARCH 9, 2001

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VICTOR L. YU, M.D.

# Treatment of Typical and Atypical Pathogens According to National Guidelines

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## Typical pathogens

- *S. pneumoniae*
- *H. influenzae*
- *M. catarrhalis*

## Atypical pathogens

- *L. pneumophila*
- *M. pneumoniae*
- *C. pneumoniae*

# Treatment: 2001 ATS National Guidelines

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**Group I: Outpatients  
Modifying Factors (-)**

**Macrolide**

**Group II: Outpatients  
Modifying Factors (+)**

**Quinolone**

**Group III: Inpatients  
Not ICU / IV Therapy**

**$\beta$ -lactam plus Macrolide**

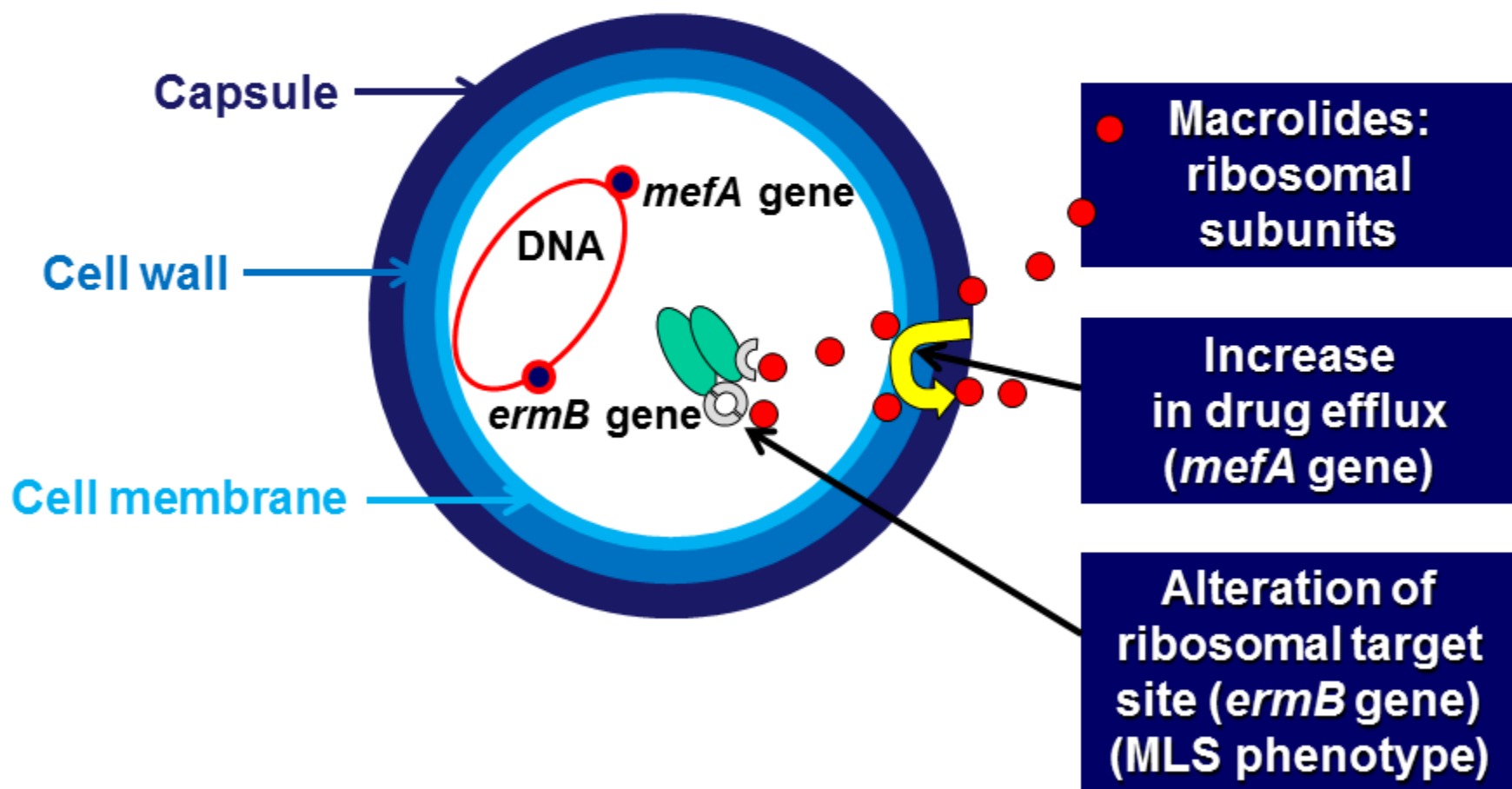
**Quinolone**

**Group III: Inpatients  
Not ICU / Switch Therapy**

**Macrolide**

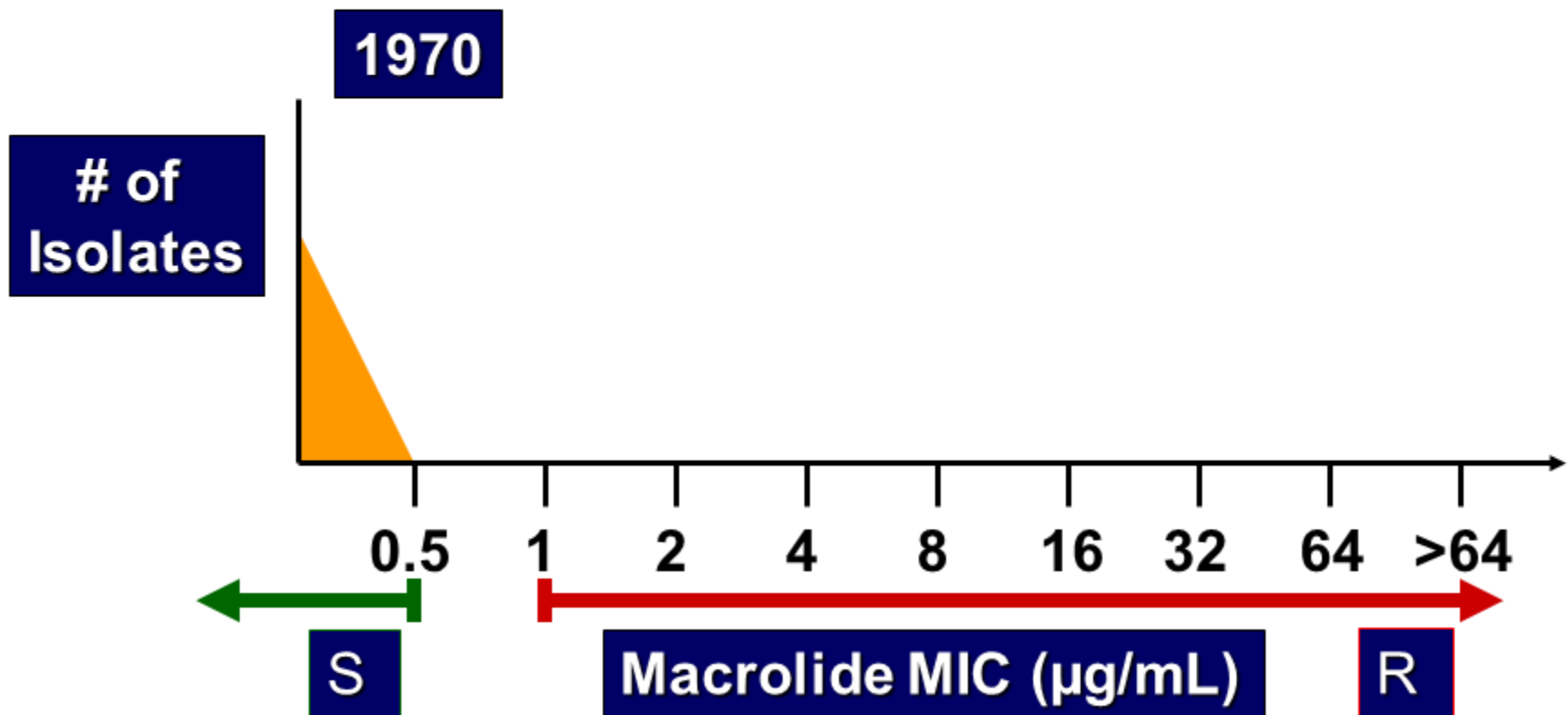
**Quinolone**

# Resistance Guided Recommendations



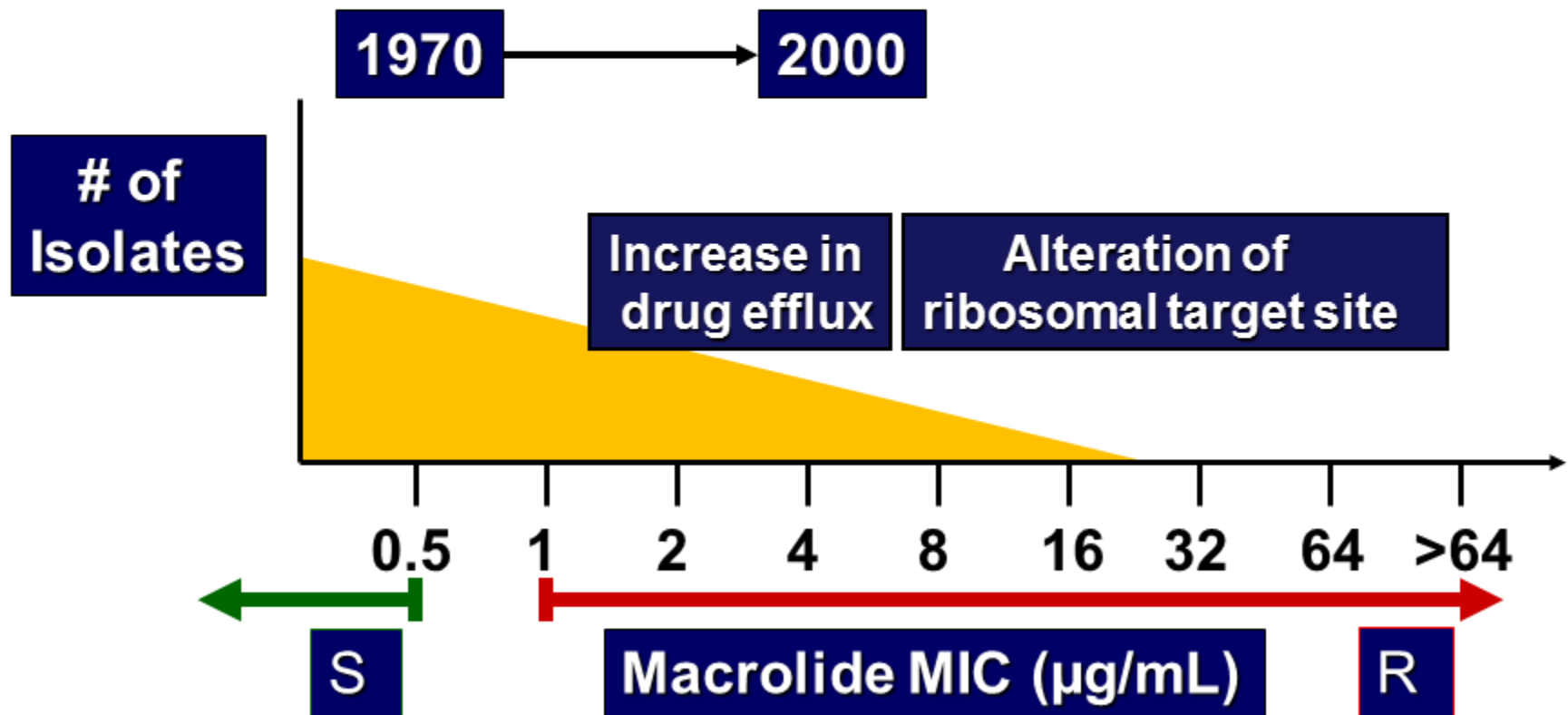
# History of Resistance

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# Resistance Grew to 10% by 2000

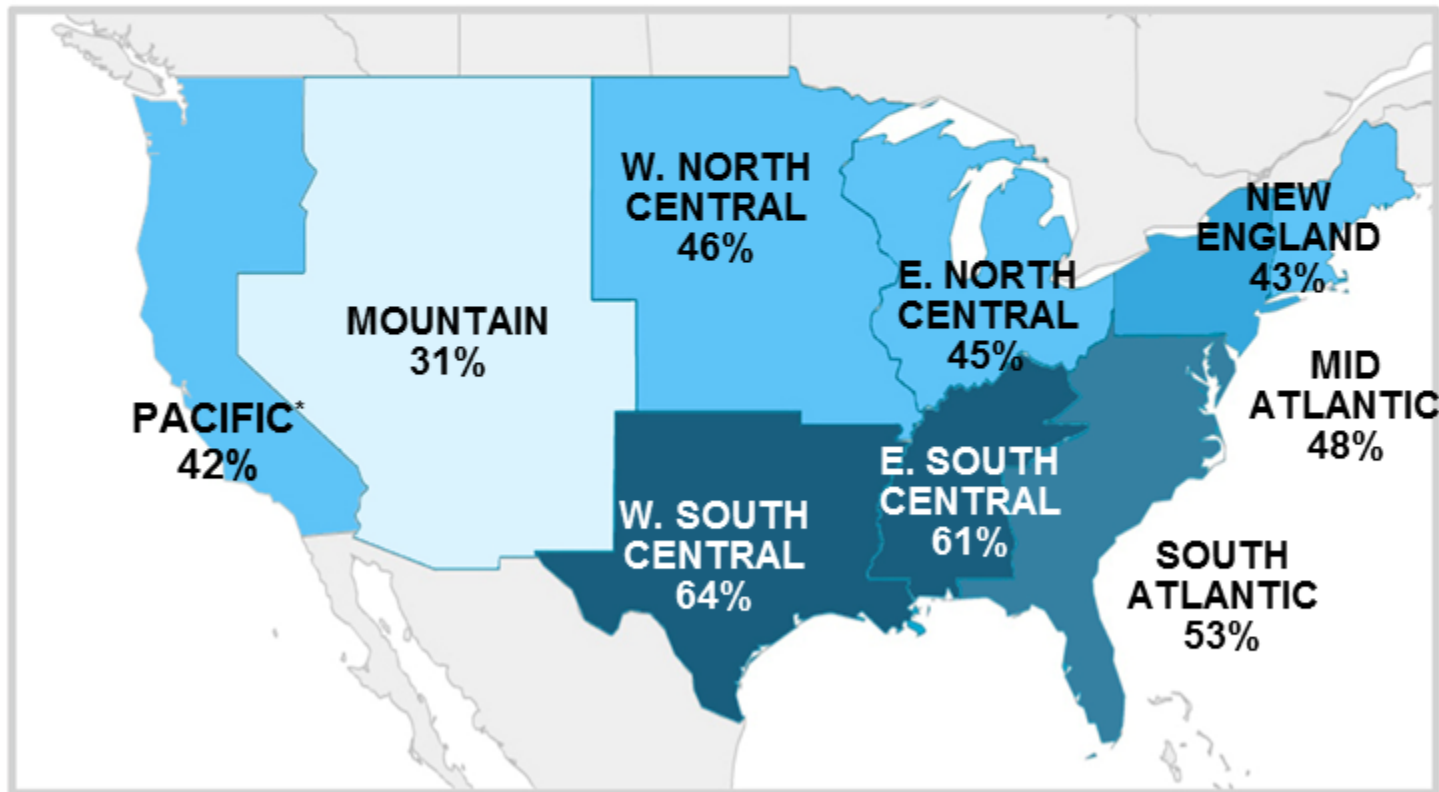
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# Growing Problem of Macrolide Resistance

2006: resistance ~35%<sup>1</sup>

2014: resistance ~50%<sup>2</sup> (high level ~33%)

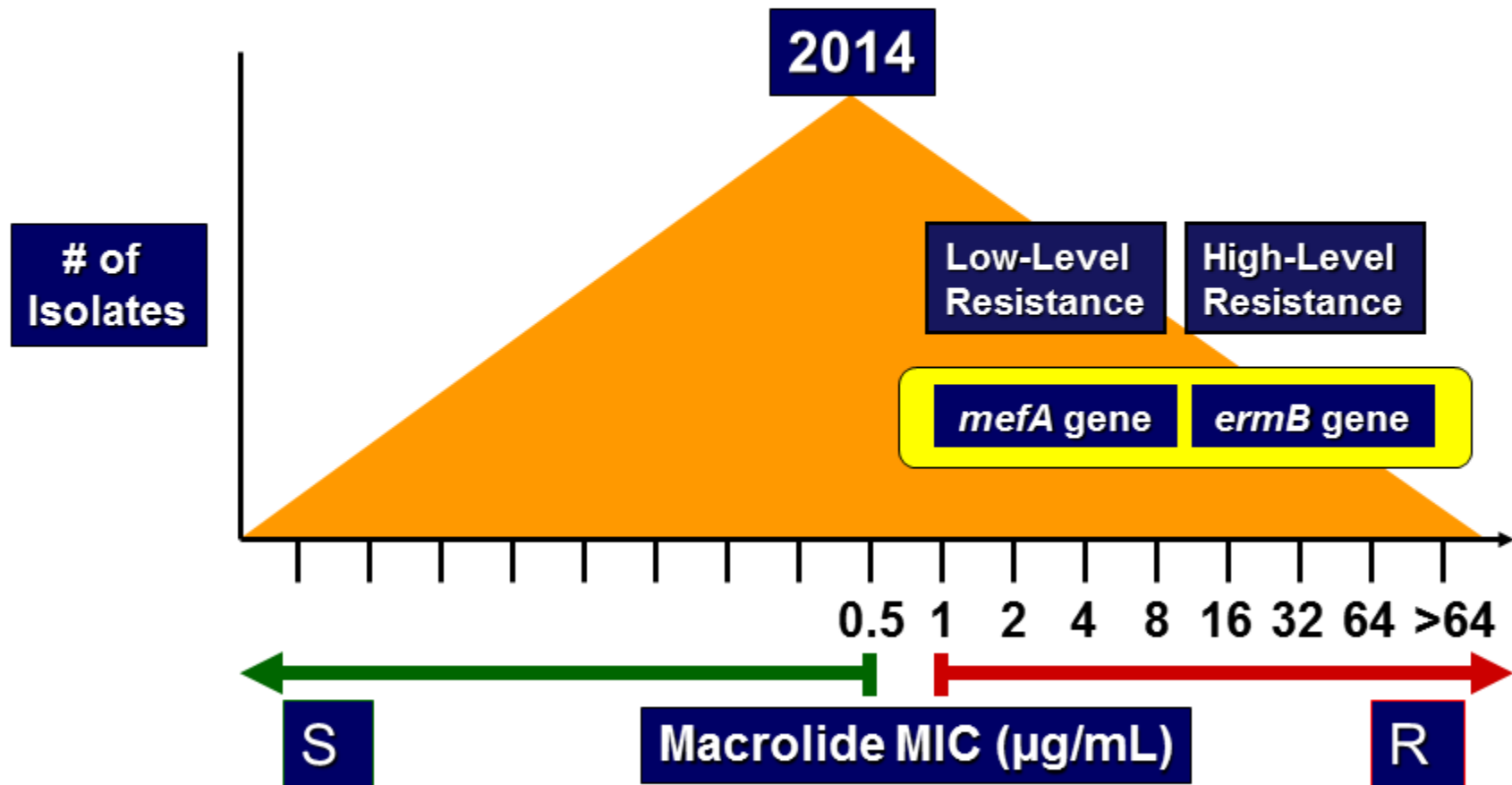


\*Includes Alaska and Hawaii

1. Jenkins, S. and Farrell, D. Emerging Infectious Diseases, vol 15, page 1264, 2009.

2. Keedy K., et al. MAD-ID-19 Poster abstract #81. Orlando, 2016.

# Resistance to Macrolide Antibiotics

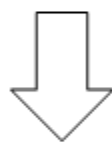


At what level of antibiotic resistance should a particular antibiotic not be recommended for empiric therapy?

## 2007 Guidelines: Alternative Agent Recommended When >25% Have High-Level Resistance

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Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults



**Alternative Agents to Macrolides**  
“in regions with a high rate (>25%) of infection with high-level (MIC  $\geq$  16  $\mu$ g/mL) macrolide-resistant *S. pneumoniae*”

# Treatment of CAP: Unmet Need

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**1. Epidemiology**

**2. National Guidelines**

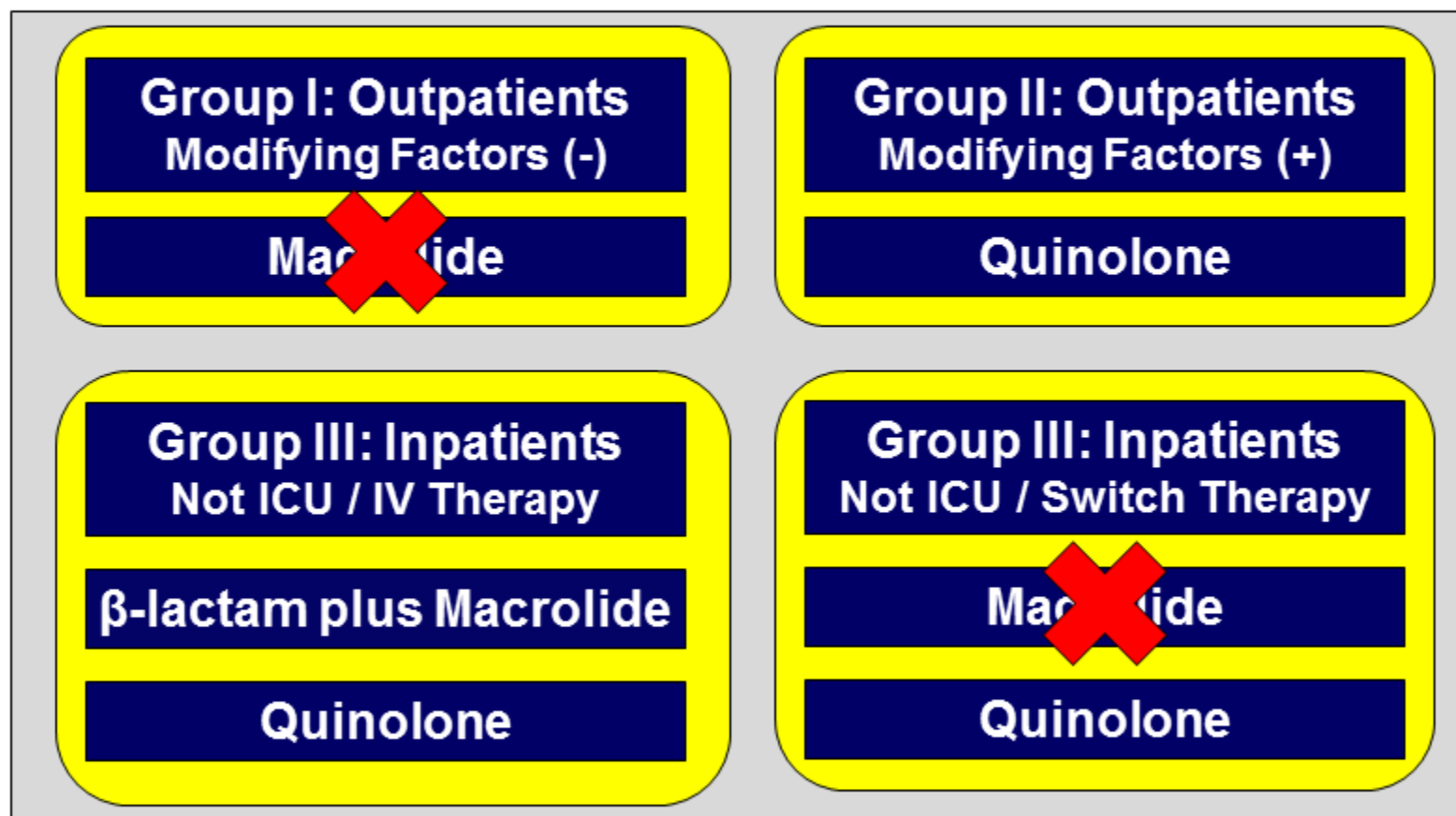
**3. Current Options**

# Current CAP Treatment Based on 2007 Guidelines

<b>Group I: Outpatients Modifying Factors (-)</b> <b>Macrolide</b>	<b>Group II: Outpatients Modifying Factors (+)</b> <b>Quinolone</b>
<b>Group III: Inpatients Not ICU / IV Therapy</b> <b><math>\beta</math>-lactam plus Macrolide</b> <b>Quinolone</b>	<b>Group III: Inpatients Not ICU / Switch Therapy</b> <b>Macrolide</b> <b>Quinolone</b>

Alternative agents to macrolides: in regions with a high rate (>25%) of infection with high-level (MIC  $\geq 16$   $\mu\text{g/mL}$ ) macrolide-resistant *S. pneumoniae*

# Reality in 2016



Alternative agents to macrolides: in regions with a high rate (>25%) of infection with high-level (MIC  $\geq 16$   $\mu\text{g/mL}$ ) macrolide-resistant *S. pneumoniae*

# Treatment of CAP: First-Line Options

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	Typical Pathogens	Atypical Pathogens
Macrolides	+	+
$\beta$ -lactams	+	-
Quinolones	+	+

# Quinolones Associated with Collateral Damage (*C. difficile* Associated Diarrhea)

	Typical Pathogens	Atypical Pathogens	Enteric Gram (-)
Macrolides	+	+	+
$\beta$ -lactams	+	-	++
Quinolones	+	+	+++
			Collateral Damage

# Quinolones Associated with Potential Permanent Side Effects

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- FDA safety announcement
  - Fluoroquinolones when used systemically may be associated with disabling and potentially permanent serious side effects
  - “These side effects can involve the tendons, muscles, joints, nerves, and central nervous system.”

# Stewardship Needs in Field of CAP

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- IDSA and SHEA guidelines to improve antibiotic stewardship
  - Interventions to reduce use of antibiotics with high *C. difficile* risk
  - Interventions to reduce antibiotic therapy to shortest effective duration
  - Promotion of IV to Oral switch options

# Need for Macrolide Options to Treat CAP Patients

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- Benefit of macrolides for first-line monotherapy
  - Well-understood benefits
  - Well-characterized safety profile
  - Targeted spectrum of activity

# Microbiology and Pharmacokinetics

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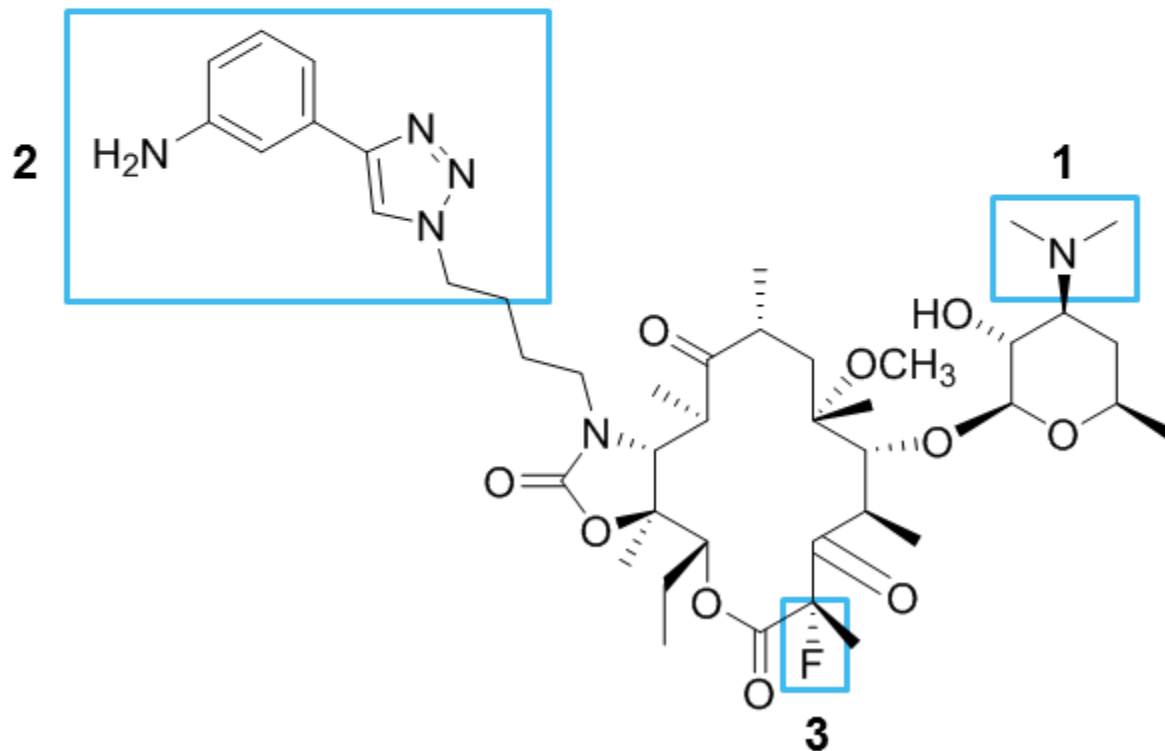
**Prabha Fernandes, PhD**

President and CEO

Cempra Pharmaceuticals, Inc.

# Solithromycin MOA Improved Compared to Other Macrolides

- Inhibits protein synthesis
- Binds in peptide tunnel of bacterial ribosome



Solithromycin

# Solithromycin MOA: Three Interaction Sites

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- Tight binding results in mostly bactericidal activity
- Additional interactions
  - Low resistance rates
  - Improved activity against macrolide resistant strains

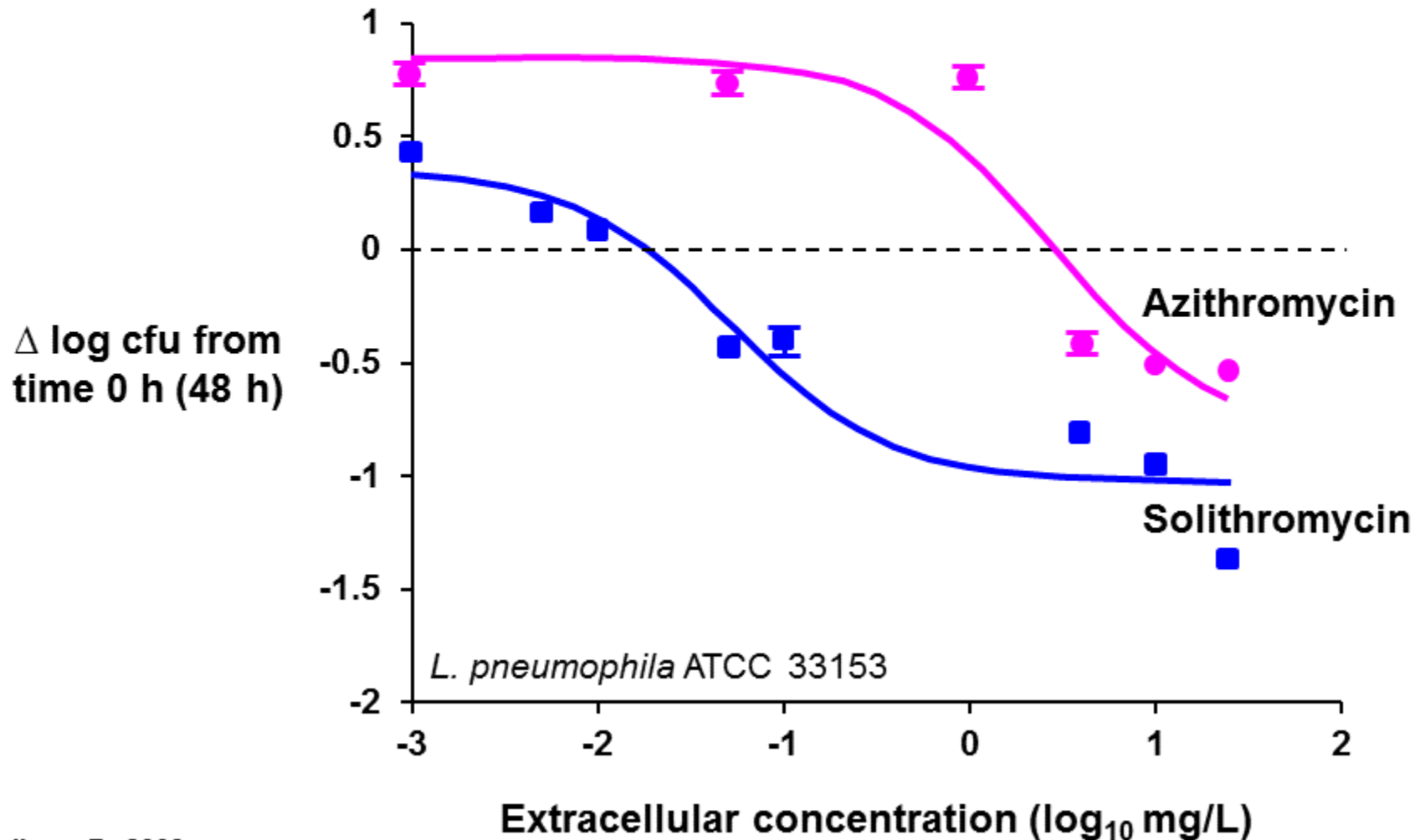
# Solithromycin has Potent Activity Against Typical Bacterial Pathogens

Organism group (# tested)	Drug	MIC (µg/mL)	
		MIC <sub>90</sub>	Range
<i>Streptococcus pneumoniae</i> (1713)	Solithromycin	0.12	0.002 - 1
	Azithromycin	>32	0.015 - >32
<i>Streptococcus pyogenes</i> (689)	Solithromycin	0.015	0.008 - 0.25
	Azithromycin	2	0.03 - >32
<i>Methicillin-Susceptible Staphylococcus aureus</i> (667)	Solithromycin	0.06	0.03 - >32
	Azithromycin	>32	0.008 - >32
<i>Methicillin-Resistant Staphylococcus aureus</i> (357)	Solithromycin	>32	0.008 - >32
	Azithromycin	>32	0.25 - >32
<i>Haemophilus influenzae</i> (1308)	Solithromycin	2	≤ 0.06 - >8
	Azithromycin	1	≤ 0.03 - >4
<i>Moraxella catarrhalis</i> (577)	Solithromycin	0.12	0.002 - 2
	Azithromycin	0.06	0.002 - 0.5

# Solithromycin has Potent Activity Against Atypical Bacterial Pathogens

Organism group (# tested)	Drug	MIC ( $\mu\text{g/mL}$ )	
		MIC <sub>90</sub>	Range
<i>Mycoplasma pneumoniae</i> (36)	Solithromycin	0.000125	$\leq 0.000000063 - 0.5$
	Azithromycin	0.0005	$\leq 0.000016 - \geq 32$
<i>Legionella pneumophila</i> (300)	Solithromycin	0.016	$\leq 0.004 - 0.06$
	Azithromycin	0.25	0.008 - 1
<i>Chlamydophila pneumoniae</i> (10)	Solithromycin	0.25	0.25 - 1
	Azithromycin	0.125	0.015 - 0.125

# Solithromycin Potently Inhibits Intracellular Legionella



# Solithromycin has Activity Against Azithromycin and Fluoroquinolone Resistant Pneumococcus

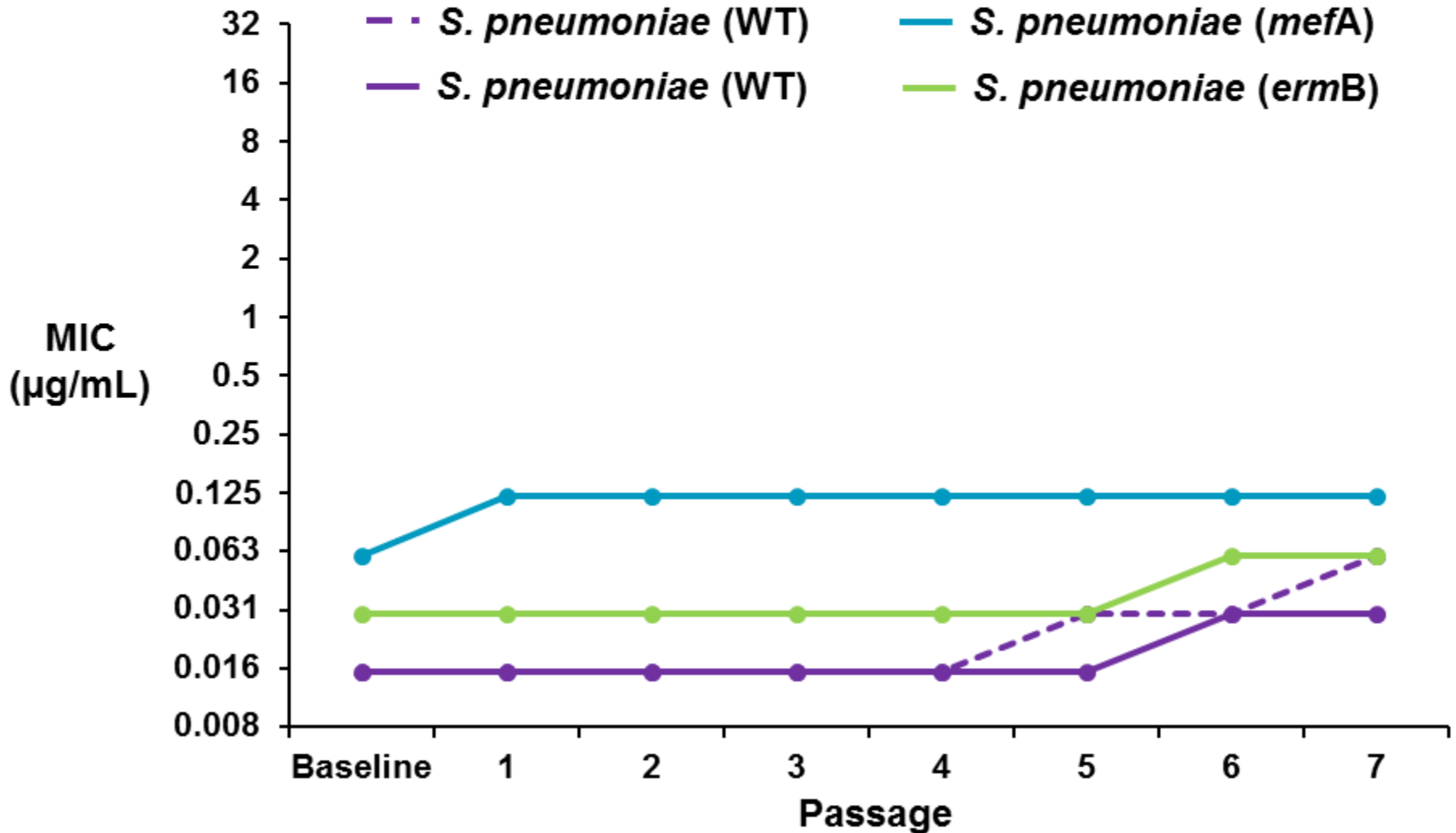
Pneumococcal isolates	Solithromycin (µg/mL)		Azithromycin (µg/mL)	
	MIC <sub>90</sub>	Range	MIC <sub>90</sub>	Range
Total (221)	0.25	0.002 - 1	>64	0.06 - >64
Penicillin S (53)	0.125	0.002 - 0.25	>64	0.06 - >64
Penicillin I (63)	0.25	0.002 - 0.25	>64	0.06 - >64
Penicillin R (105)	0.25	0.004 - 1	>64	0.06 - >64
Macrolide S (50)	0.015	0.002 - 0.015	0.0125	0.06 - 0.25
<i>ermB</i> (54)	0.5	0.004 - 1	>64	>64 - >64
<i>mefA</i> (51)	0.125	0.008 - 0.25	8	1 - >64
<i>ermA</i> (4)	-	0.008 - 0.015	-	2 - 8
<i>ermB mefA</i> (31)	0.25	0.015 - 1	>64	2 - >64
L4 mutations (27)	0.125	0.03 - 0.125	>64	2 - >64
23S rRNA mutations (4)	-	0.002 - 0.03	-	32 - >64
Quinolone S (195)	0.25	0.002 - 1	>64	0.06 - >64
Quinolone R (27)	0.06	0.004 - 0.25	>64	0.06 - >64

# Solithromycin Low Rate of Spontaneous Mutations

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- Low rate in single-step mutational analyses
  - *S. pneumoniae*, *S. pyogenes*, *S. aureus*
  - 2x, 4x, 8x and 16x MIC
  - Frequency  $<10^{-9}$

# Serial Passage Confirms Low Rate of Resistance Development



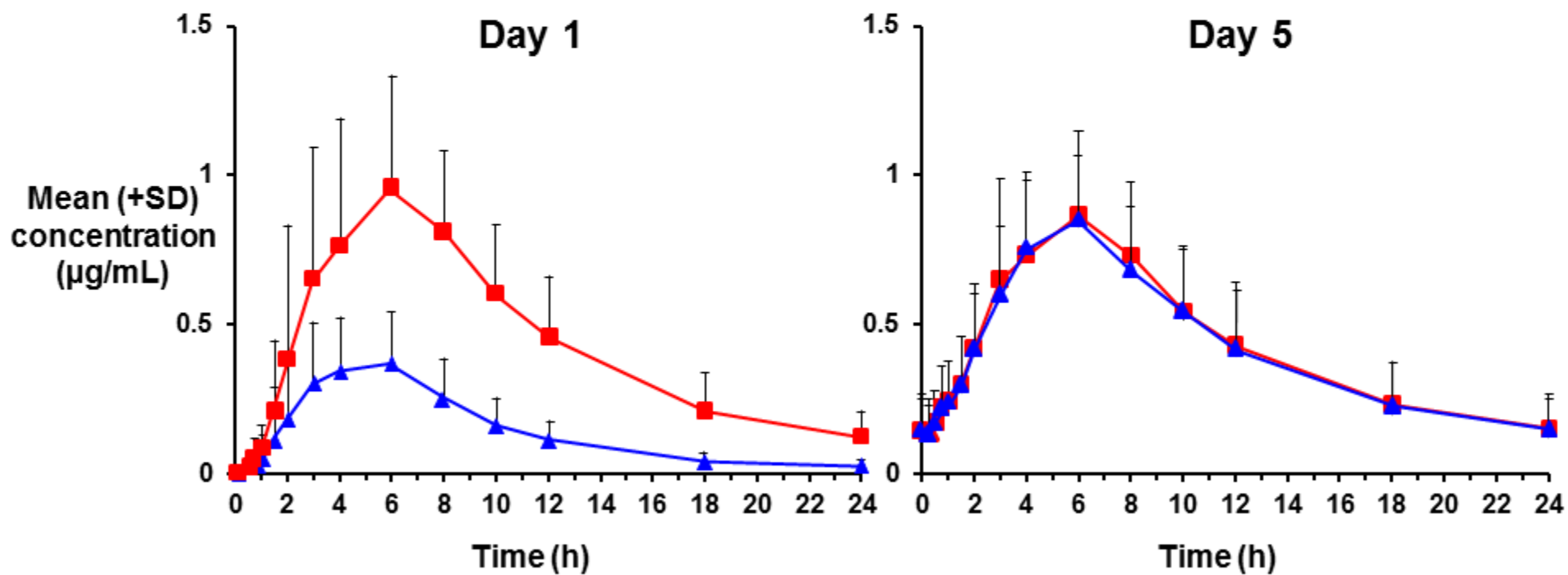
# Solithromycin Low Potential for *C. difficile* Associated Diarrhea

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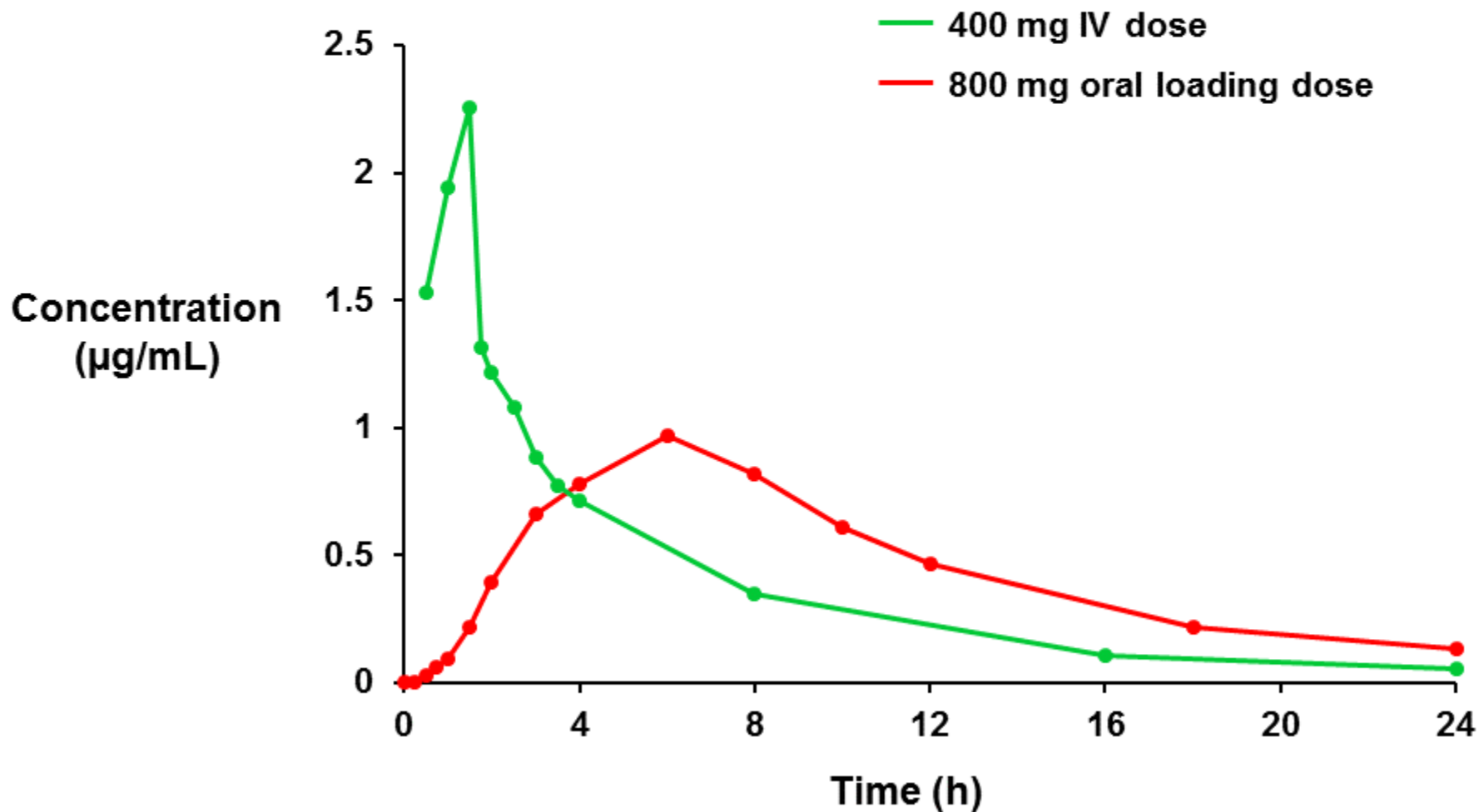
- Phase 1 human microflora study
  - Minimal effect on anaerobic Gram-negative microflora (*Bacteroides*)
- No *C. difficile* strains or toxin identified

# Oral Loading Dose Regimen Achieves Near Steady State at Day 1

- 800 mg oral loading dose, 400 mg oral dose
- 400 mg oral dose



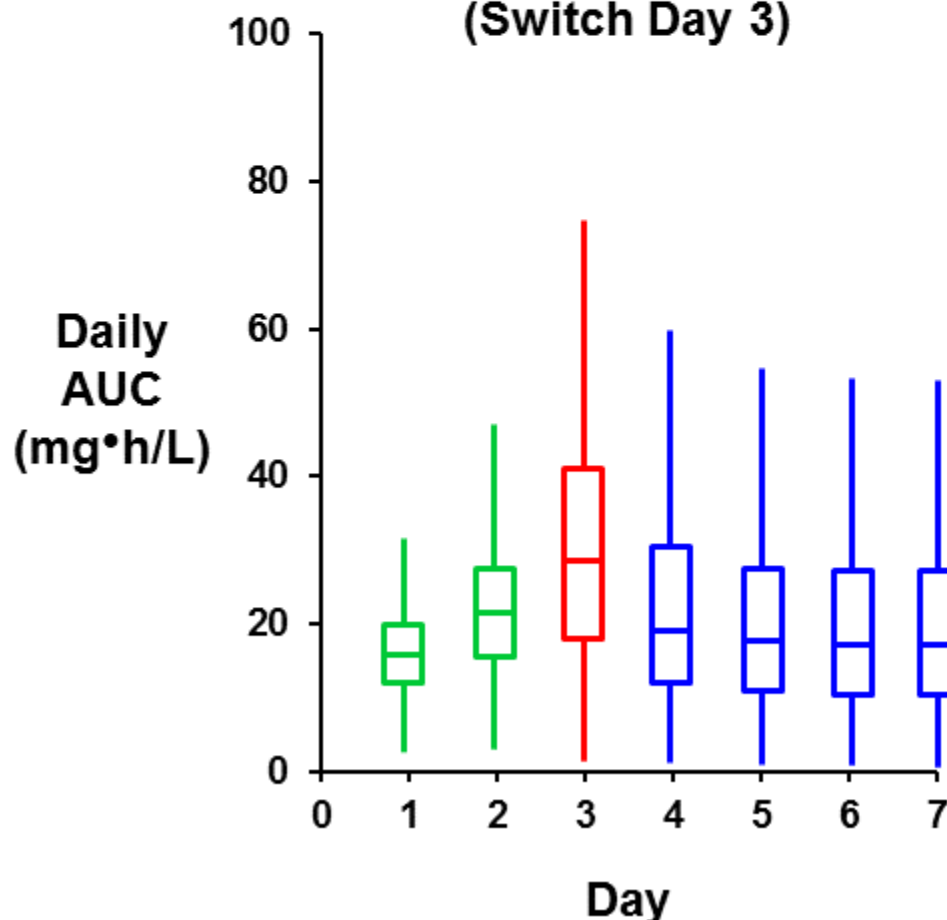
# Concentration Comparison 400 mg IV and 800 mg Oral Solithromycin



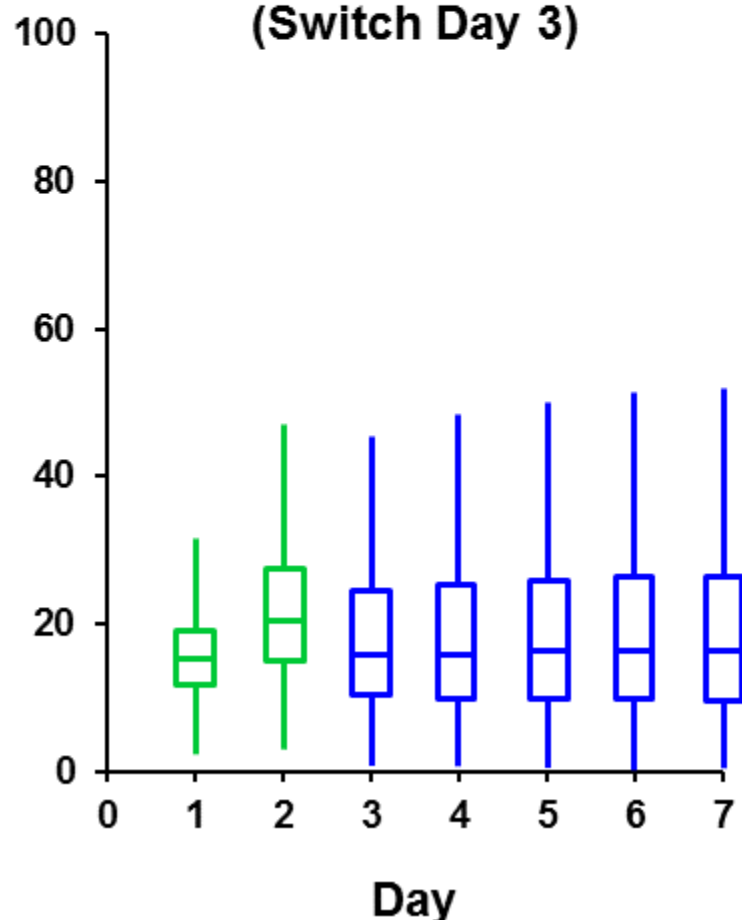
# Simulated Daily Solithromycin Exposure by Dosing Regimen: IV to Oral With or Without Oral Loading Dose (Phase 3 Studies)

400 mg IV    800 mg Oral    400 mg Oral

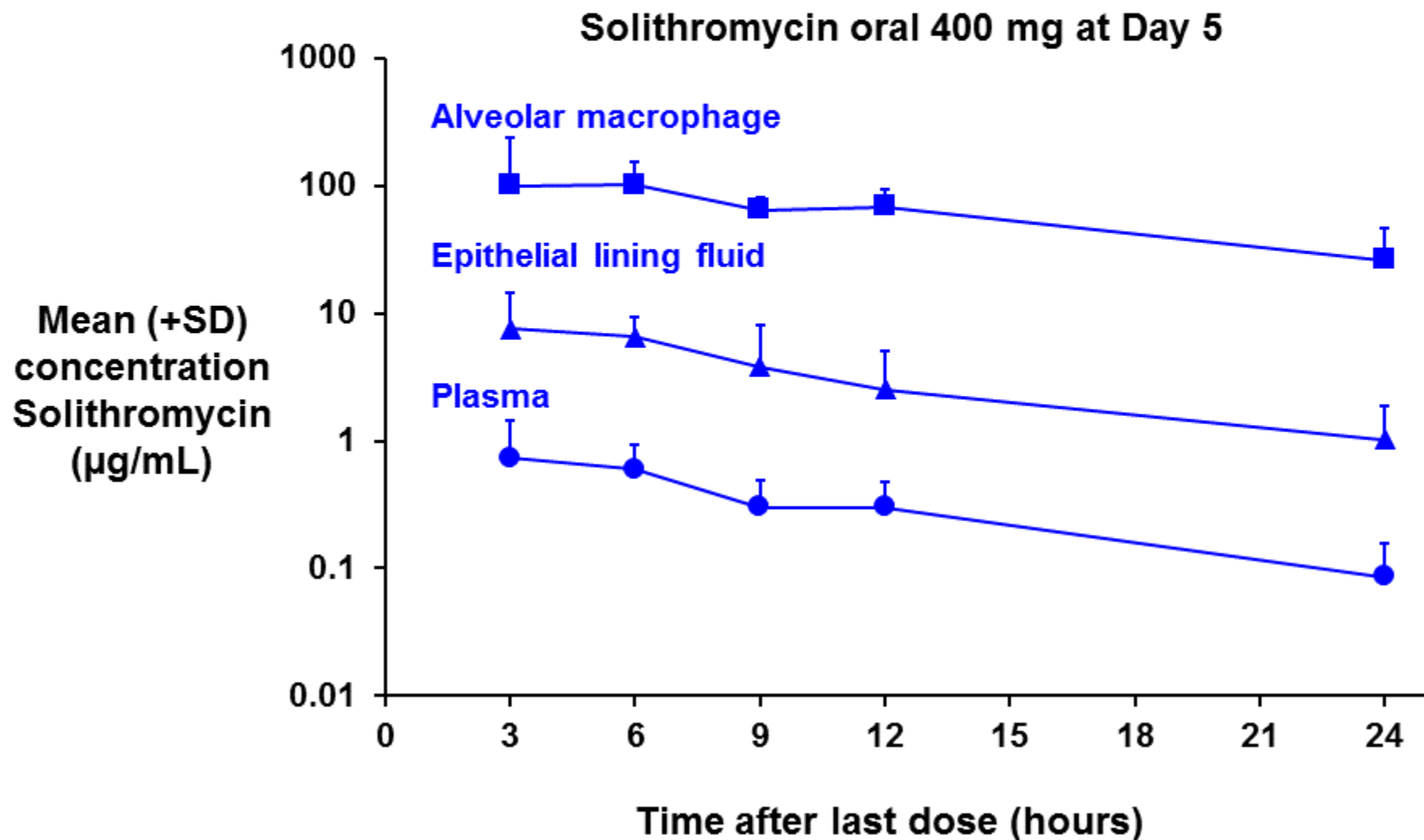
With Oral Loading Dose  
(Switch Day 3)



Without Oral Loading Dose  
(Switch Day 3)

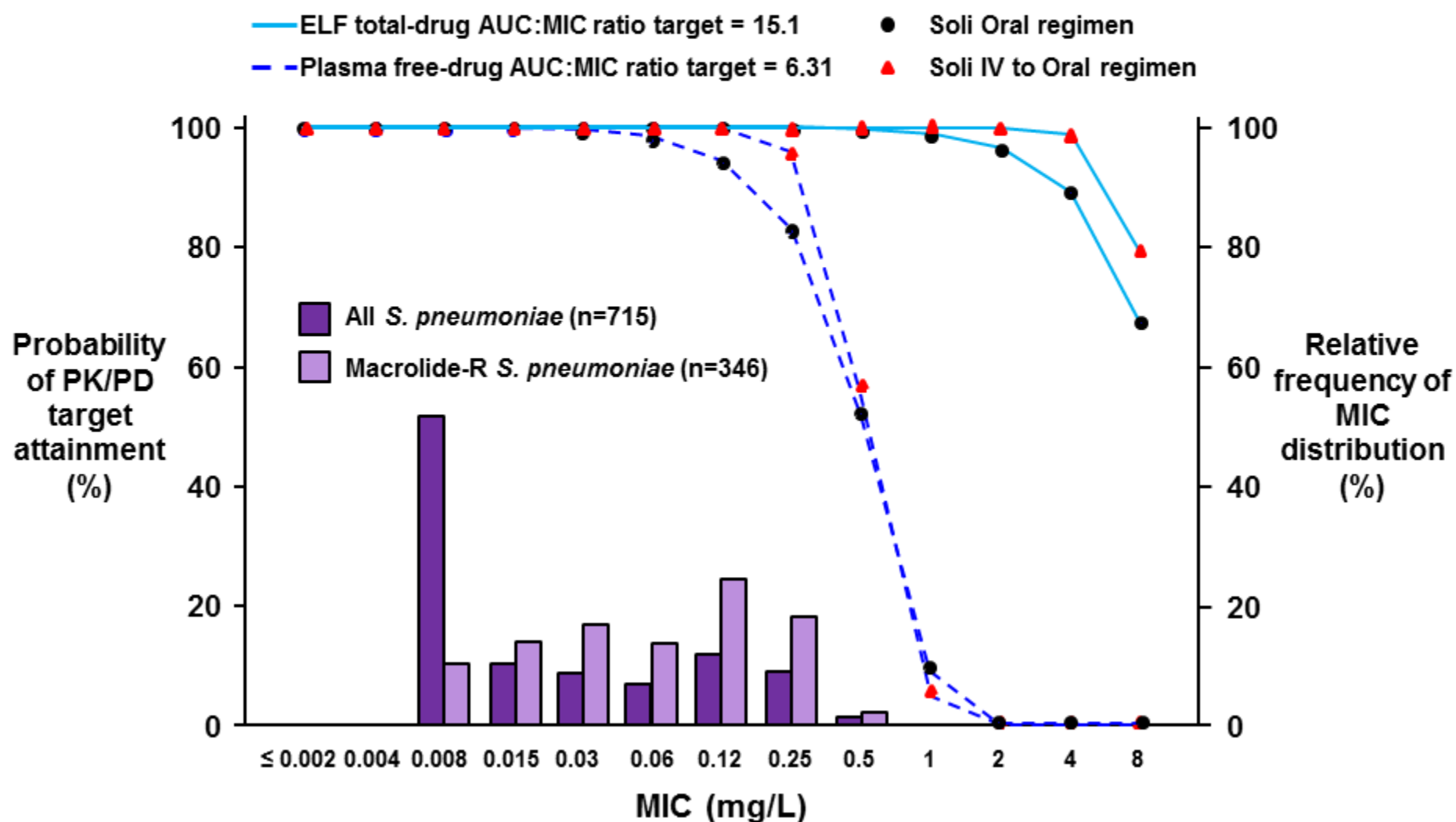


# Pulmonary Levels of Solithromycin



# PK/PD Target Attainment for Solithromycin Based on ELF Total-Drug and Plasma Free-Drug AUC:MIC

CO-55



# Clinical Pharmacokinetics

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- Not influenced by food
- No dose adjustment needed
  - Mild to severe hepatic impairment
  - Mild or moderate renal impairment
- Dose adjustments recommended for severe renal impairment
  - Plasma levels increased 2-fold

# Drug-Drug Interactions

	Mechanism	Concomitant medications	Interaction
Effect on Solithromycin	CYP3A4 / P-gp induction	Rifampin	↓ Solithromycin AUC 99%
	CYP3A4 inhibition	Ketoconazole	↑ Solithromycin AUC 2.5-fold
Effect on concomitant medications	P-gp inhibition	Digoxin	↑ Digoxin AUC 1.4-fold
	CYP3A4 inhibition	Midazolam	↑ Midazolam AUC 9-fold

## Summary of Microbiology and PK

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- Active against typical and atypical CABP pathogens including macrolide resistant strains
- Potent against intracellular pathogens
- Low potential for *C. difficile* associated diarrhea
- Low rate of resistance development
- Target attainment >90%
- IV and oral options available

## Phase 3 Study Design

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**David Oldach, MD, FIDSA**

Chief Medical Officer

Cempra Pharmaceuticals, Inc.

# Similar Study Design for Both Phase 3 Studies

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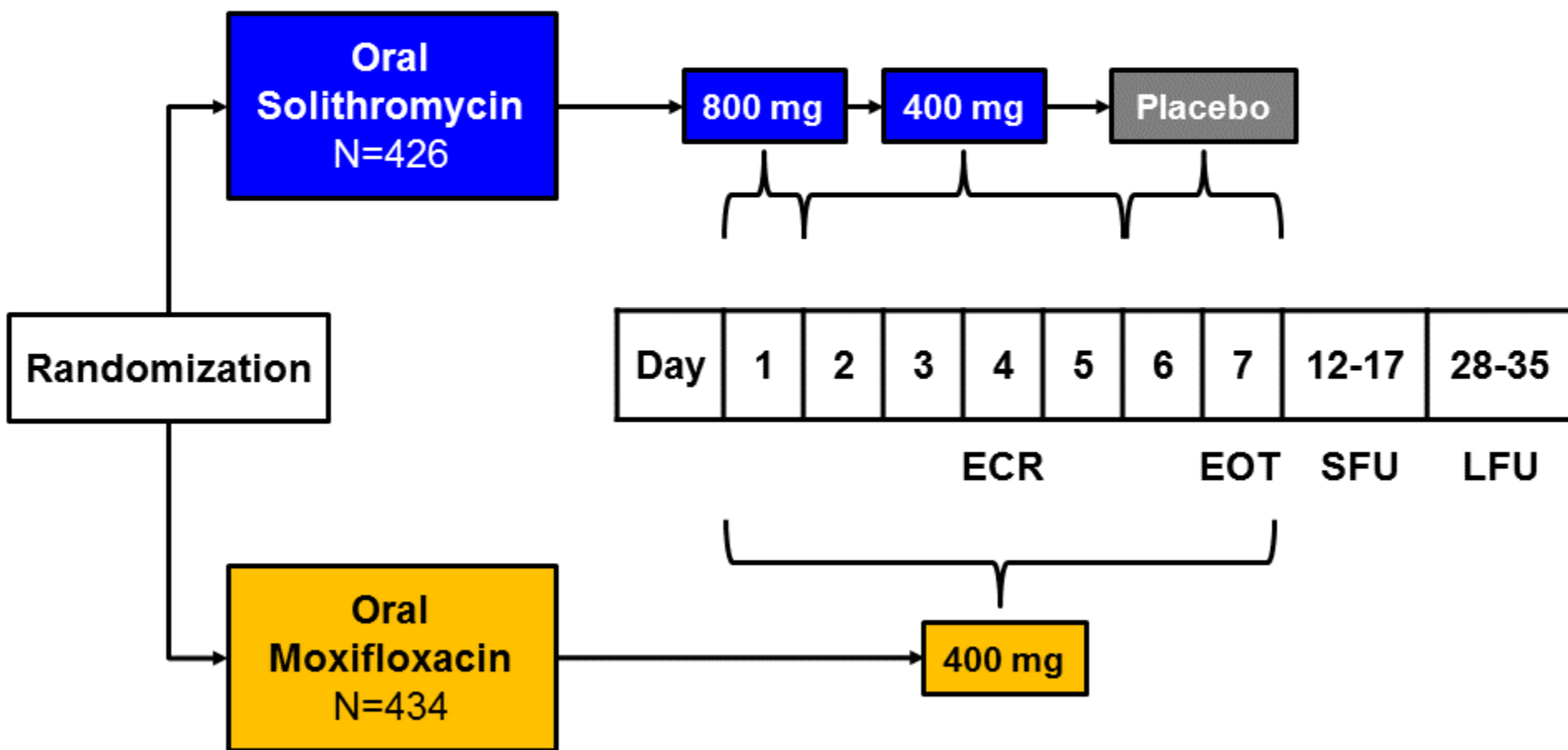
- Study 300: oral solithromycin
- Study 301: IV solithromycin with option to switch to oral
- Randomized, double-blind, active-controlled, multi-center, global, NI studies
- Comparator: moxifloxacin
- Same clinical assessments, outcomes measures and time points

# Randomization Stratification Factors

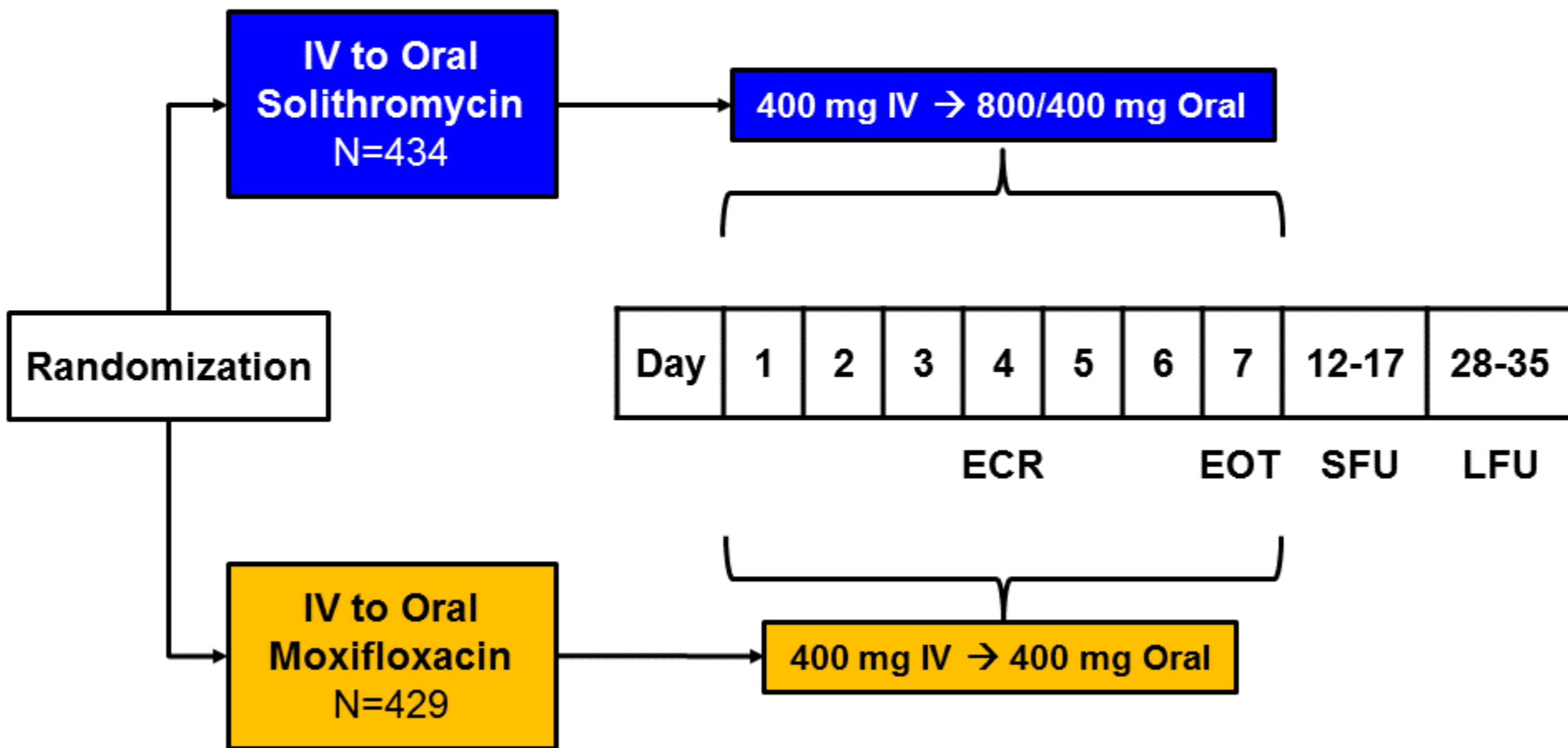
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- Geographic region
  - Study 300: N. America, Latin America, Europe, and S. Africa
  - Study 301: N. America, E. Europe, ROW
- History of asthma and / or COPD
- PORT II vs III / IV
  - Study 300: <50% PORT II
  - Study 301:  $\leq 25\%$  PORT II,  $\geq 25\%$  PORT IV

# Study 300: Oral Clinical Trial Design



# Study 301: IV to Oral Clinical Trial Design



# Key Inclusion Criteria Similar for Both Studies

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- $\geq 3$  cardinal symptoms of CABP
  - Cough, dyspnea, chest pain, sputum
- Fever, hypothermia, or pulmonary signs
- Radiographic confirmation of CABP
- Prior single dose, short half-life antibiotics allowed
  - $<25\%$  of patients

# Key Exclusion Criteria Similar for Both Studies

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- Severe COPD or bronchiectasis
- Mean QTcF >450 msec on screening
- AST or ALT >3×ULN
- Total bilirubin >2×ULN
- HIV, organ transplant, active cancers
- Myasthenia gravis

# Early Clinical Response (ECR) Primary Endpoint

---

- First prospective use of ECR as primary endpoint in CABP trial
- Improvement at Day 4 after first dose
- Programmatically defined as responder
  - Improvement in  $\geq 2$  cardinal symptoms
  - No worsening of any symptom
  - Did not receive another antibiotic for treatment of CABP
  - Survived for 30 days

# mITT Population Microbiological Diagnostic Methods

---

- Blood culture
- Sputum culture (Gram-stain: high PMN, low epi)
  - Routine and legionella media
- Urine antigen (*S. pneumoniae*, legionella)
- Nasopharyngeal *S. pneumoniae* qPCR
- Oropharyngeal mycoplasma culture and PCR
- Acute and convalescent serology
- Study 300 only: sputum multiplex PCR

## **Efficacy: Results**

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**Anita F. Das, PhD**  
Lead Biostatistician

## Endpoints in Studies 300 and 301

	<b>Study 300 (Oral)</b>	<b>Study 301 (IV to Oral)</b>
<b>ECR in ITT</b>	<b>Co-primary endpoint</b>	<b>Primary endpoint</b>
<b>ECR in mITT pooled</b>	<b>Co-primary endpoint</b>	<b>Secondary endpoint</b>

# Sample Size in ITT and Pooled mITT

---

- Assumptions for ECR in ITT
  - 73% response (based on Phase 2)
  - NI margin = 10% (2009 FDA CABP Guidance)
  - 1-sided  $\alpha = 0.025$
  - 90% power
  - Sample size:  $N = 860$
- Assumptions for ECR in pooled mITT
  - 73% response
  - NI margin = 15% (2009 FDA CABP Guidance)
  - >90% power
  - Microbiologic diagnosis in 25% of ITT

## Secondary and Additional Endpoints

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- Key secondary endpoint
  - Investigator's assessment of clinical response at short-term follow-up (SFU)
- Additional symptom based endpoints at SFU
  - Symptom response of cardinal CABP symptoms
  - Sustained ECR response
  - Resolution of all CABP symptoms
- Symptom improvement at each visit

# **Study 300: Phase 3 Oral Study**

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# Study 300: Balanced Demographics

	<b>Solithromycin N=426</b>	<b>Moxifloxacin N=434</b>
<b>Male</b>	<b>53.3%</b>	<b>52.8%</b>
<b>Age, mean (years)</b>	<b>58.5</b>	<b>56.7</b>
<b>≥ 65</b>	<b>36.4%</b>	<b>31.6%</b>
<b>≥ 75</b>	<b>14.6%</b>	<b>14.5%</b>
<b>Race</b>		
<b>White</b>	<b>81.5%</b>	<b>84.6%</b>
<b>Black or African American</b>	<b>10.8%</b>	<b>9.2%</b>
<b>Asian</b>	<b>0.9%</b>	<b>0.9%</b>
<b>Other</b>	<b>6.8%</b>	<b>5.3%</b>
<b>BMI, mean (kg/m<sup>2</sup>)</b>	<b>27.6</b>	<b>28.1</b>
<b>Patients enrolled in U.S.</b>	<b>21.6%</b>	<b>22.6%</b>

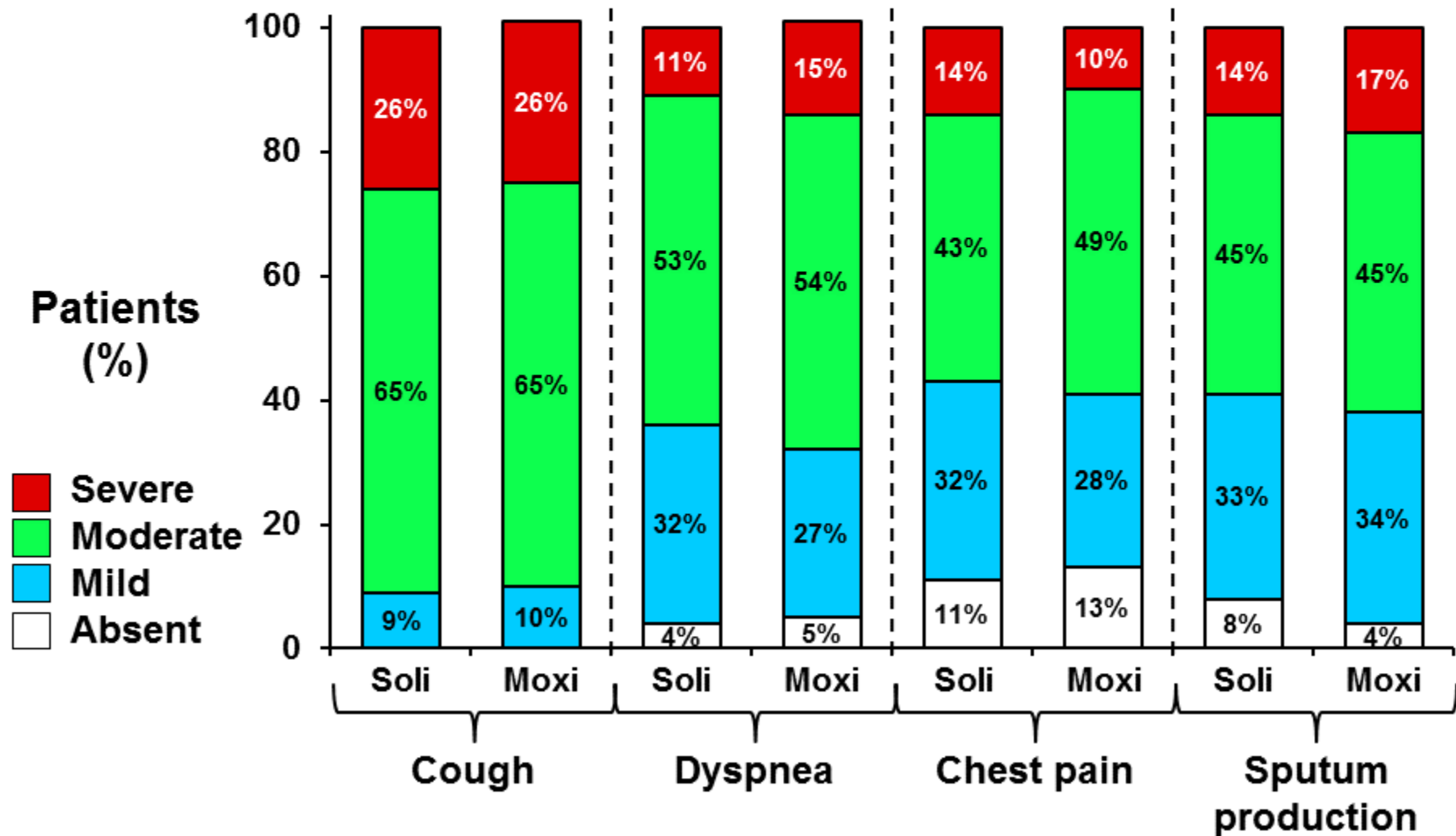
# Study 300: Balanced Disease Characteristics

	<b>Solithromycin N=426</b>	<b>Moxifloxacin N=434</b>
<b>History of asthma / COPD</b>	<b>14.6%</b>	<b>14.7%</b>
<b>PORT score, mean</b>	<b>71.7</b>	<b>71.2</b>
<b>PORT risk class</b>		
<b>II</b>	<b>49.3%</b>	<b>51.4%</b>
<b>III / IV</b>	<b>50.7%</b>	<b>48.6%</b>
<b>Met SIRS criteria</b>	<b>54.2%</b>	<b>60.4%</b>
<b>Met modified ATS severity criteria</b>	<b>5.6%</b>	<b>9.2%</b>
<b>Antibiotic use in prior 7 days</b>	<b>12.4%</b>	<b>10.1%</b>

SIRS = systemic inflammatory response syndrome

ATS = American Thoracic Society

# Study 300: Similar Symptom Severity at Baseline Between Treatment Groups



# Study 300: Baseline Pathogens (ITT)

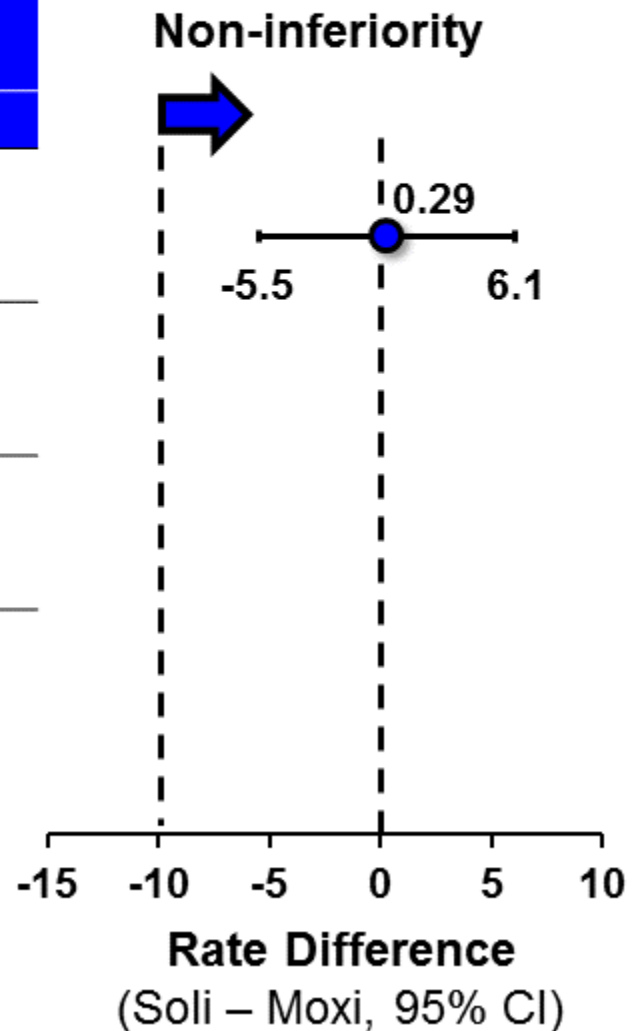
	Solithromycin N=426		Moxifloxacin N=434	
	n	%	n	%
Any pathogen (mITT)	235	55.2	226	52.1
<i>Streptococcus pneumoniae</i>	96	22.5	102	23.5
<i>Staphylococcus aureus</i>	22	5.2	14	3.2
<i>Haemophilus influenzae</i>	80	18.8	55	12.7
<i>Moraxella catarrhalis</i>	28	6.6	23	5.3
<i>Mycoplasma pneumoniae</i>	37	8.7	42	9.7
<i>Legionella pneumophila</i>	61	14.3	63	14.5

# Study 300: Disposition

	Solithromycin N=426		Moxifloxacin N=434	
	n	%	n	%
Completed study	406	95.3	413	95.2
Premature withdrawal from study	20	4.7	21	4.8
Withdrew consent	11	2.6	5	1.2
Death	6	1.4	6	1.4
Lost to follow-up	2	0.5	5	1.2
Unwilling to comply with protocol procedures	0	0	1	0.2
Other	1	0.2	4	0.9

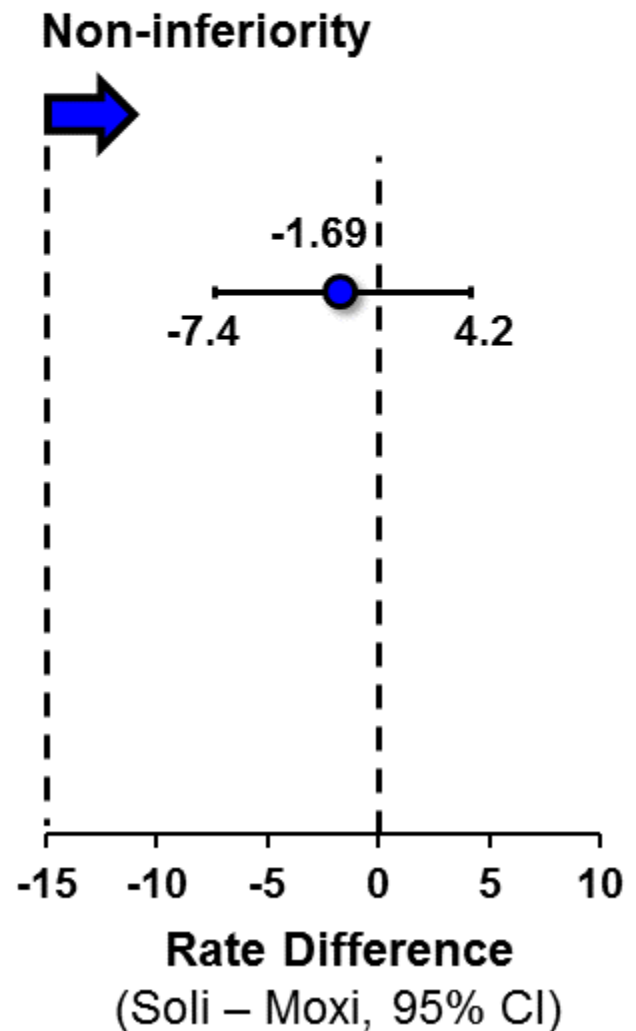
# Study 300: Co-Primary Endpoint Early Clinical Response Met (ITT)

ECR, ITT	Solithromycin N=426		Moxifloxacin N=434	
	n	%	n	%
Responder	333	78.2	338	77.9
Non-responder	81	19.0	84	19.4
Indeterminate	12	2.8	12	2.8



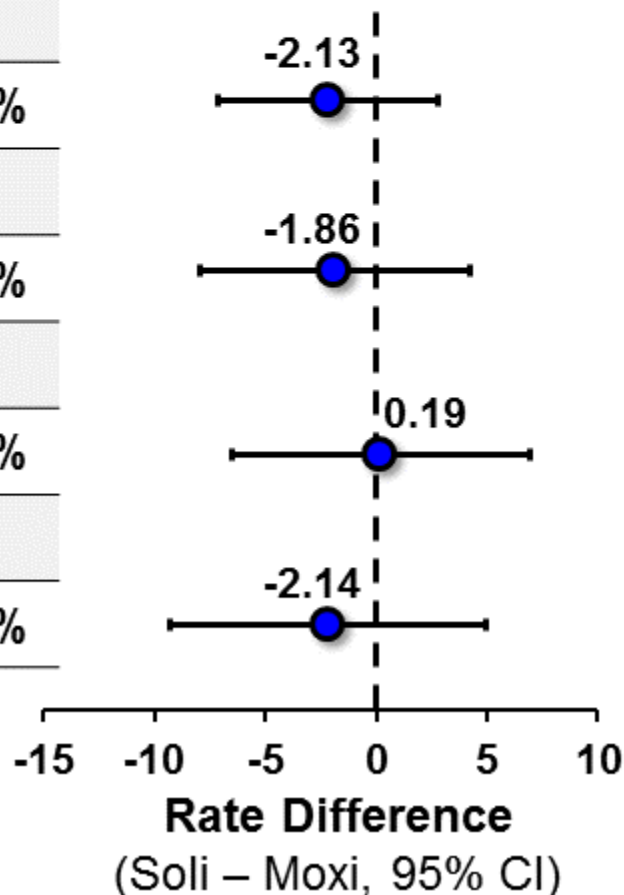
# Pooled Studies: Co-Primary Endpoint Early Clinical Response Met (mITT)

ECR, Pooled mITT	Solithromycin Pooled N=408		Moxifloxacin Pooled N=379	
	n	%	n	%
Responder	315	77.2	299	78.9
Non-responder	81	19.9	72	19.0
Indeterminate	12	2.9	8	2.1

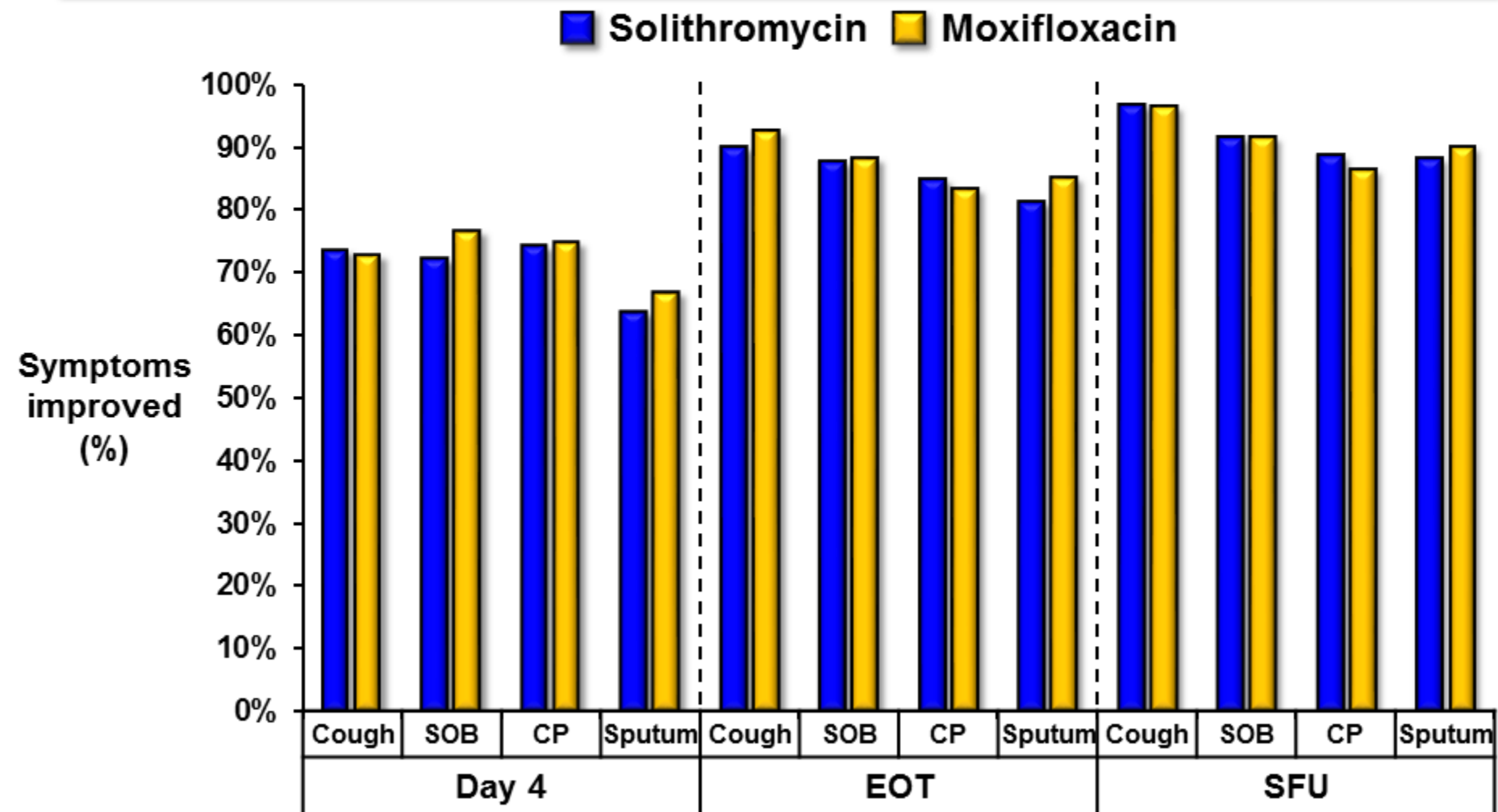


# Study 300: Analyses at SFU Support Primary Endpoints Results (ITT)

Efficacy Outcome, ITT	Solithromycin		Moxifloxacin	
	n/N	%	n/N	%
<b>Investigator Assessment at SFU</b>				
Success	360/426	84.5%	376/434	86.6%
<b>Symptom Response by Major CABP Symptoms</b>				
Responder	315/426	73.9%	329/434	75.8%
<b>Sustained ECR</b>				
Responder	273/426	64.1%	277/434	63.8%
<b>Resolution of All CABP Symptoms</b>				
Responder	219/394	55.6%	232/404	57.4%



# Study 300: Similar Improvement in CABP Symptoms at Day 4, EOT, SFU



SOB = Dyspnea / shortness of breath

CP = Chest pain due to pneumonia

## **Study 301: Phase 3 IV to Oral**

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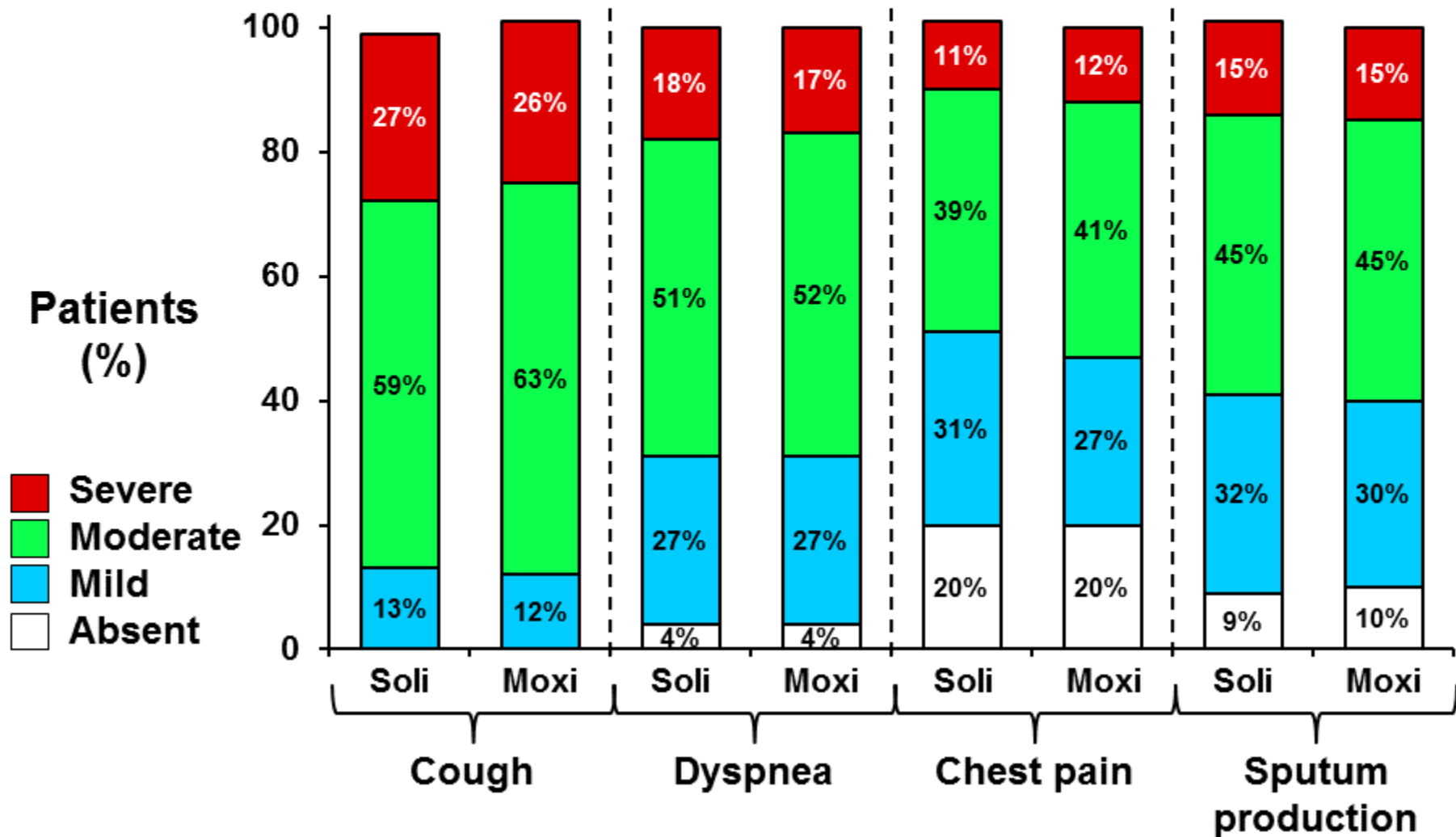
# Study 301: Balanced Demographics

	<b>Solithromycin (IV to Oral) N=434</b>	<b>Moxifloxacin (IV to Oral) N=429</b>
<b>Male</b>	<b>48.8%</b>	<b>55.0%</b>
<b>Age, mean (years)</b>	<b>60.5</b>	<b>61.1</b>
<b>≥ 65</b>	<b>43.3%</b>	<b>45.9%</b>
<b>≥ 75</b>	<b>19.1%</b>	<b>17.9%</b>
<b>Race</b>		
<b>White</b>	<b>79.3%</b>	<b>77.9%</b>
<b>Black or African American</b>	<b>5.1%</b>	<b>5.1%</b>
<b>Asian</b>	<b>14.1%</b>	<b>14.7%</b>
<b>Other (mixed)</b>	<b>1.6%</b>	<b>2.4%</b>
<b>BMI, mean (kg/m<sup>2</sup>)</b>	<b>26.8</b>	<b>27.4</b>
<b>Patients enrolled in U.S.</b>	<b>10.6%</b>	<b>11.7%</b>

# Study 301: Similar Disease Characteristics

	<b>Solithromycin (IV to Oral) N=434</b>	<b>Moxifloxacin (IV to Oral) N=429</b>
<b>History of asthma / COPD</b>	<b>21.9%</b>	<b>21.4%</b>
<b>PORT score, mean</b>	<b>81.8</b>	<b>82.6</b>
<b>PORT risk class</b>		
II	24.4%	22.4%
III / IV	75.6%	77.6%
<b>Met SIRS criteria</b>	<b>72.1%</b>	<b>68.5%</b>
<b>Met modified ATS severity criteria</b>	<b>5.5%</b>	<b>4.2%</b>
<b>Antibiotics in prior 7 days</b>	<b>23.5%</b>	<b>25.6%</b>

# Study 301: Similar Symptoms of CABP at Baseline Between Treatment Groups



# Study 301: Balanced Baseline Pathogens (ITT)

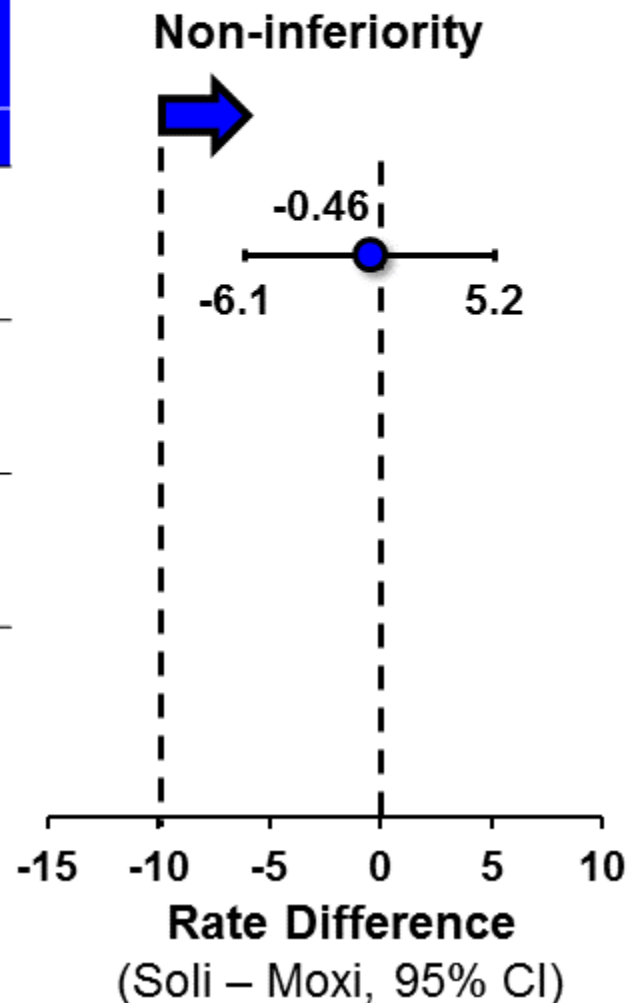
	Solithromycin (IV to Oral) N=434		Moxifloxacin (IV to Oral) N=429	
	n	%	n	%
Any pathogen (mITT)	173	39.9	153	35.7
<i>Streptococcus pneumoniae</i>	79	18.2	76	17.7
<i>Staphylococcus aureus</i>	21	4.8	16	3.7
<i>Haemophilus influenzae</i>	18	4.1	20	4.7
<i>Moraxella catarrhalis</i>	4	0.9	3	0.7
<i>Mycoplasma pneumoniae</i>	39	9.0	30	7.0
<i>Legionella pneumophila</i>	18	4.1	17	4.0

# Study 301: Disposition

	Solithromycin (IV to Oral) N=434		Moxifloxacin (IV to Oral) N=429	
	n	%	n	%
Completed study	407	93.8	408	95.1
Premature withdrawal from study	27	6.2	21	4.9
Withdrew consent	15	3.5	8	1.9
Death	5	1.2	7	1.6
Adverse events	5	1.2	1	0.2
Unwilling to comply with protocol procedures	0	0	1	0.2
Lost to follow-up	0	0	0	0
Other	2	0.5	4	0.9

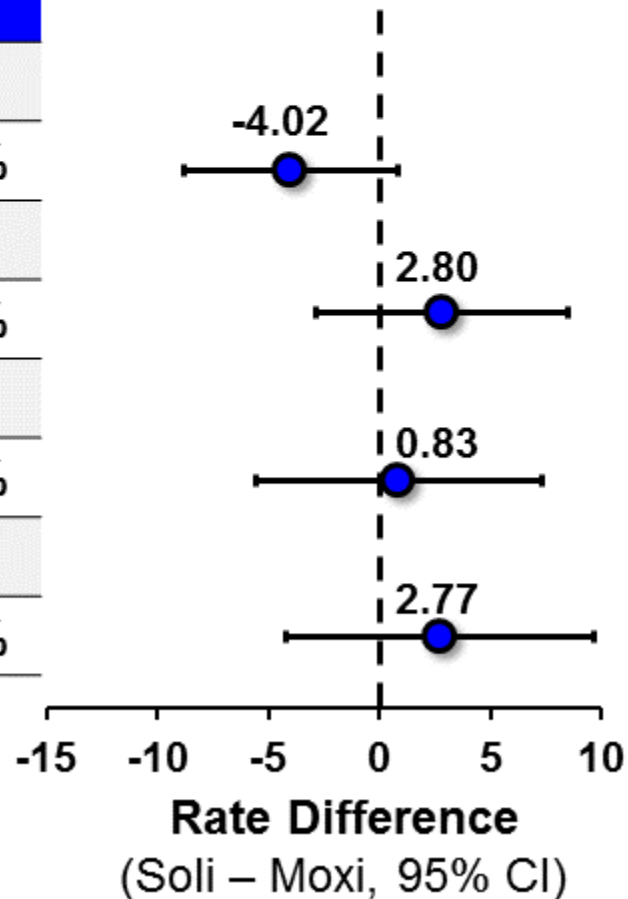
# Study 301: Primary Endpoint ECR Met Non-Inferiority (ITT)

ECR, ITT	Solithromycin (IV to Oral) N=434		Moxifloxacin (IV to Oral) N=429	
	n	%	n	%
Responder	344	79.3	342	79.7
Non-responder	76	17.5	78	18.2
Indeterminate	14	3.2	9	2.1



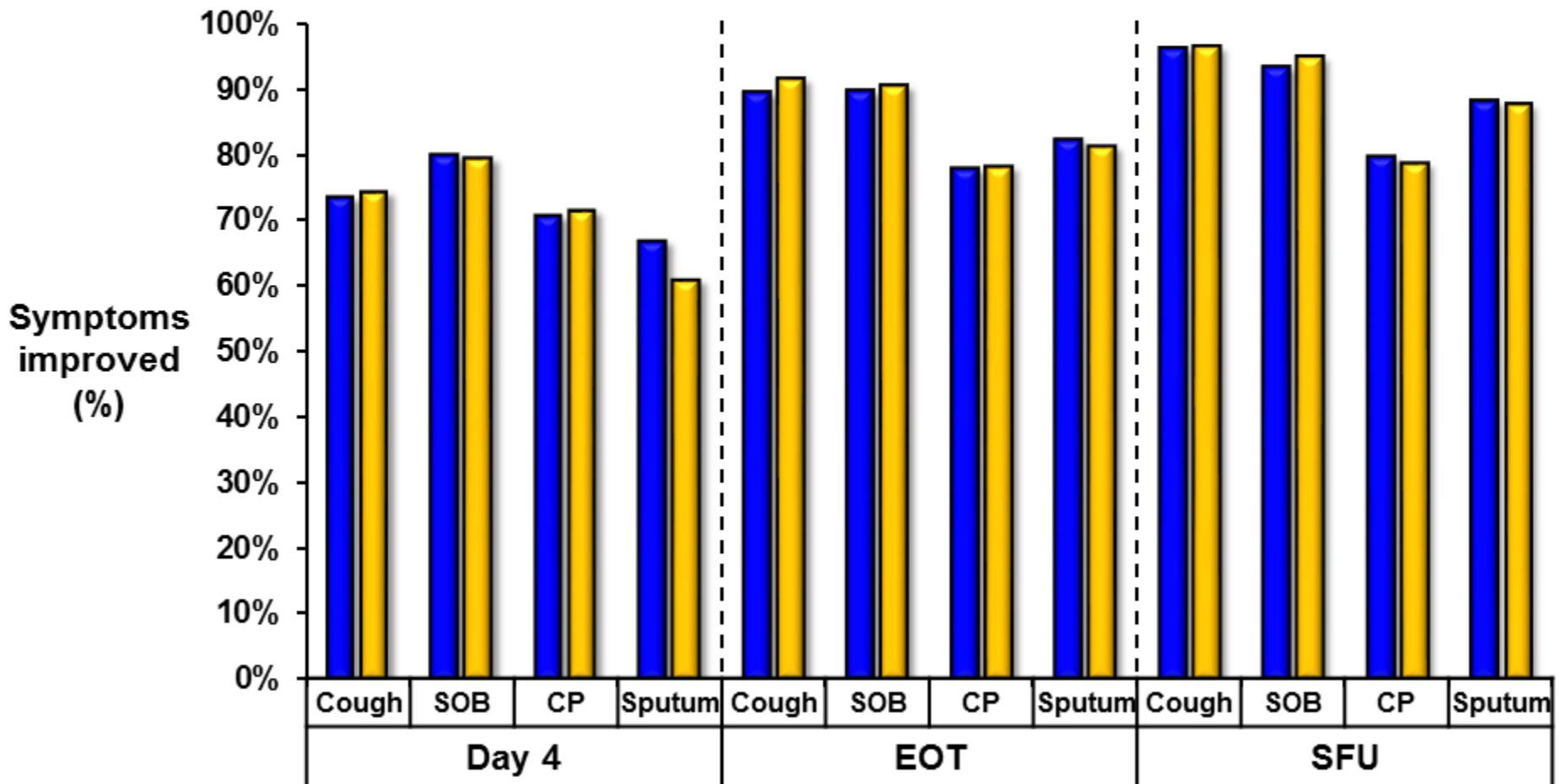
# Study 301: Additional Analyses at SFU Support Primary Endpoint Results (ITT)

Efficacy Outcome, ITT	Solithromycin (IV to Oral)		Moxifloxacin (IV to Oral)	
	n/N	%	n/N	%
<b>Investigator Assessment at SFU</b>				
Success	367/434	84.6%	380/429	88.6%
<b>Symptom Response by Major CABP Symptoms</b>				
Responder	346/434	79.7%	330/429	76.9%
<b>Sustained ECR</b>				
Responder	297/434	68.4%	290/429	67.6%
<b>Resolution of All CABP Symptoms</b>				
Responder	253/405	62.5%	240/402	59.7%



# Study 301: Comparable Cardinal Symptom Improvement at Each Time Point

■ Solithromycin ■ Moxifloxacin



SOB = Dyspnea/shortness of breath  
CP = Chest pain due to pneumonia

# Pooled Analyses for Studies 300 and 301

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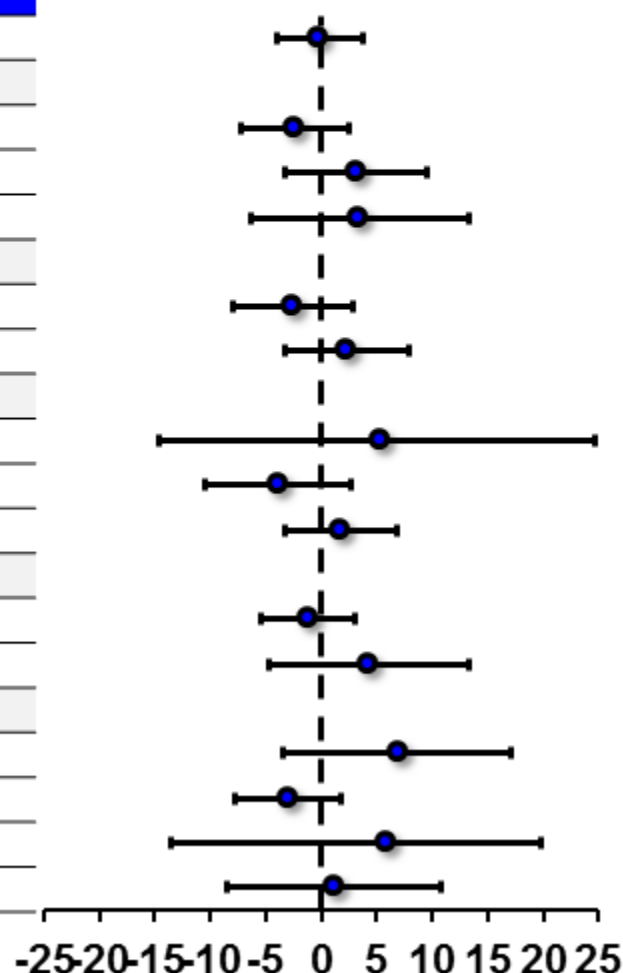
# Pooled Studies: ECR in ITT

## Demographic Subgroup Analyses

Subgroup	Solithromycin		Moxifloxacin	
	n/N	%	n/N	%
ITT population (overall)	676/859	78.7	678/860	78.8
<b>Age</b>				
<65 years	407/517	78.7	426/526	81.0
≥ 65 years	269/342	78.7	252/334	75.4
≥ 75 years	115/145	79.3	106/140	75.7
<b>Gender</b>				
Male	337/439	76.8	367/463	79.3
Female	339/420	80.7	311/397	78.3
<b>BMI</b>				
Underweight	29/38	76.3	27/37	73.0
Normal Weight	234/300	78.0	236/288	81.9
Overweight	412/520	79.2	412/532	77.4
<b>Race</b>				
White	541/690	78.4	555/698	79.5
Non-White	135/169	79.9	123/162	75.9
<b>Geographic Region</b>				
North America	110/151	72.8	103/156	66.0
Europe	420/523	80.3	418/502	83.3
Latin America	42/57	73.7	48/65	73.8
Rest of World	104/128	81.3	109/137	79.6

Difference (Soli – Moxi, 95% CI)\*

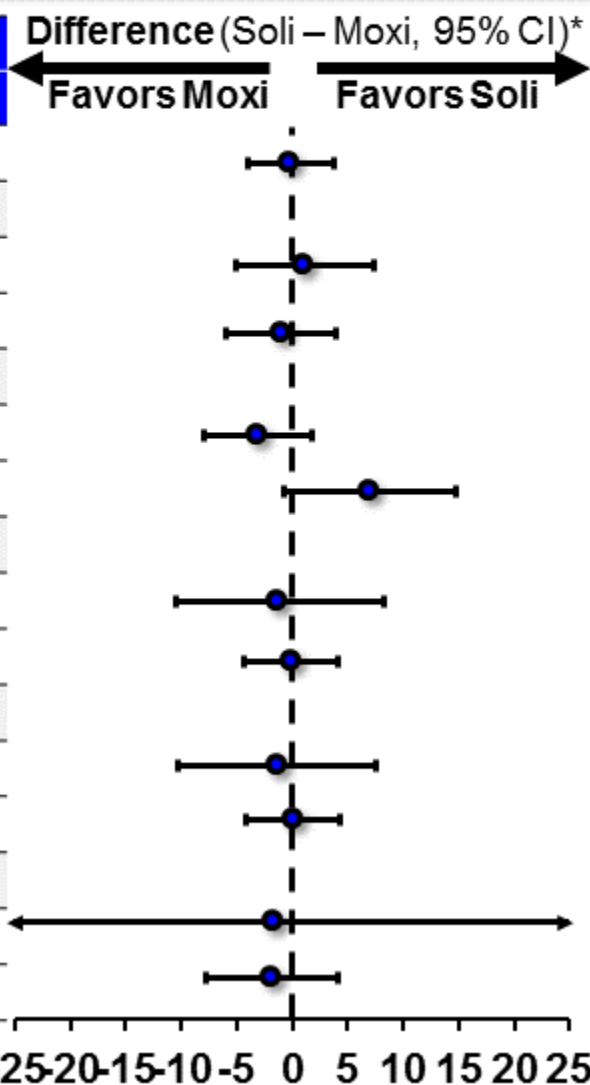
Favors Moxi      Favors Soli



\*Difference and 95% CI weighted by study

# Pooled Studies: Similar ECR in Disease Severity and Prior Antibiotic Subgroups

Subgroup	Solithromycin		Moxifloxacin	
	n/N	%	n/N	%
ITT population (overall)	676/859	78.7	678/860	78.8
<b>PORT Risk Class</b>				
PORT Class II	256/315	81.3	254/317	80.1
PORT Class III / IV	420/544	77.2	424/543	78.1
<b>SIRS Criteria</b>				
Yes	420/544	77.2	445/555	80.2
No	191/232	82.3	156/207	75.4
<b>History of COPD or Asthma</b>				
Yes	119/157	75.8	119/156	76.3
No	557/702	79.3	559/704	79.4
<b>Prior Antibiotic Use</b>				
Yes	124/155	80.0	125/154	81.2
No	552/704	78.4	553/706	78.3
<b>Bacteremia (mITT)</b>				
Yes	13/20	65.0	14/21	66.7
No	302/388	77.8	285/356	79.6



\*Difference and 95% CI weighted by study

# Pooled Studies: Early Clinical Response by Pathogen (mITT)

Selected Pathogens, Pooled mITT	Soli Pooled N=408		Moxi Pooled N=377	
	n/N	%	n/N	%
<i>S. pneumoniae</i>	135/175	77.1	148/177	83.6
Macrolide-resistant	17/24	70.8	17/22	77.3
<i>S. aureus</i>	31/43	72.1	22/30	73.3
<i>H. influenzae</i>	78/98	79.6	61/75	81.3
<i>M. catarrhalis</i>	26/32	81.3	20/26	76.9
<i>M. pneumoniae</i>	65/76	85.5	55/71	77.5
<i>L. pneumophila</i>	61/79	77.2	64/80	80.0

# Pooled Studies: Clinical Success at SFU by Pathogen (mITT)

Selected Pathogens, Pooled mITT	Soli Pooled N=408		Moxi Pooled N=377	
	n/N	%	n/N	%
<i>S. pneumoniae</i>	146/175	83.4	154/177	87.0
Macrolide-resistant	22/24	91.7	19/22	86.4
<i>S. aureus</i>	32/43	74.4	27/30	90.0
<i>H. influenzae</i>	79/98	80.6	68/75	90.7
<i>M. catarrhalis</i>	27/32	84.4	23/26	88.5
<i>M. pneumoniae</i>	65/76	85.5	64/71	90.1
<i>L. pneumophila</i>	71/79	89.9	75/80	93.8

# Efficacy Conclusion: Solithromycin Effective for Treatment of CABP

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- Primary outcome of Early Clinical Response
- High investigator assessed success rates at Short-term Follow-Up
- Similar response rates for all symptom based endpoints
- Consistently observed across subpopulations
- Comparable by-pathogen early clinical response and success rates for target CABP pathogens

## Safety

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**David Oldach, MD, FIDSA**

Chief Medical Officer

Cempra Pharmaceuticals, Inc.

# Development Program Safety Populations

Clinical Phase	N
Overall	>2000
Integrated safety	1474
Phase 1 (healthy adults)	554
Phase 2 CABP	64
Phase 3 CABP	856

Overall includes: gonorrhea patients, pediatric populations, longer-term dosing (COPD, NASH), non-Cempra sponsored studies

# Safety Profile: Pooled Phase 3 Trials

	Solithromycin N=856		Moxifloxacin N=858	
	n	%	n	%
<b>AEs</b>	<b>378</b>	<b>44.2</b>	<b>302</b>	<b>35.2</b>
<b>AEs (excluding IV site events)</b>	<b>304</b>	<b>35.5</b>	<b>294</b>	<b>34.3</b>
<b>Severe AEs</b>	<b>49</b>	<b>5.7</b>	<b>39</b>	<b>4.5</b>
<b>AEs leading to discontinuation</b>	<b>41</b>	<b>4.8</b>	<b>29</b>	<b>3.4</b>
<b>SAEs</b>	<b>58</b>	<b>6.8</b>	<b>50</b>	<b>5.8</b>
<b>Deaths</b>	<b>11</b>	<b>1.3</b>	<b>13</b>	<b>1.5</b>

# AEs $\geq 1\%$ : Comparable Between Solithromycin and Moxifloxacin

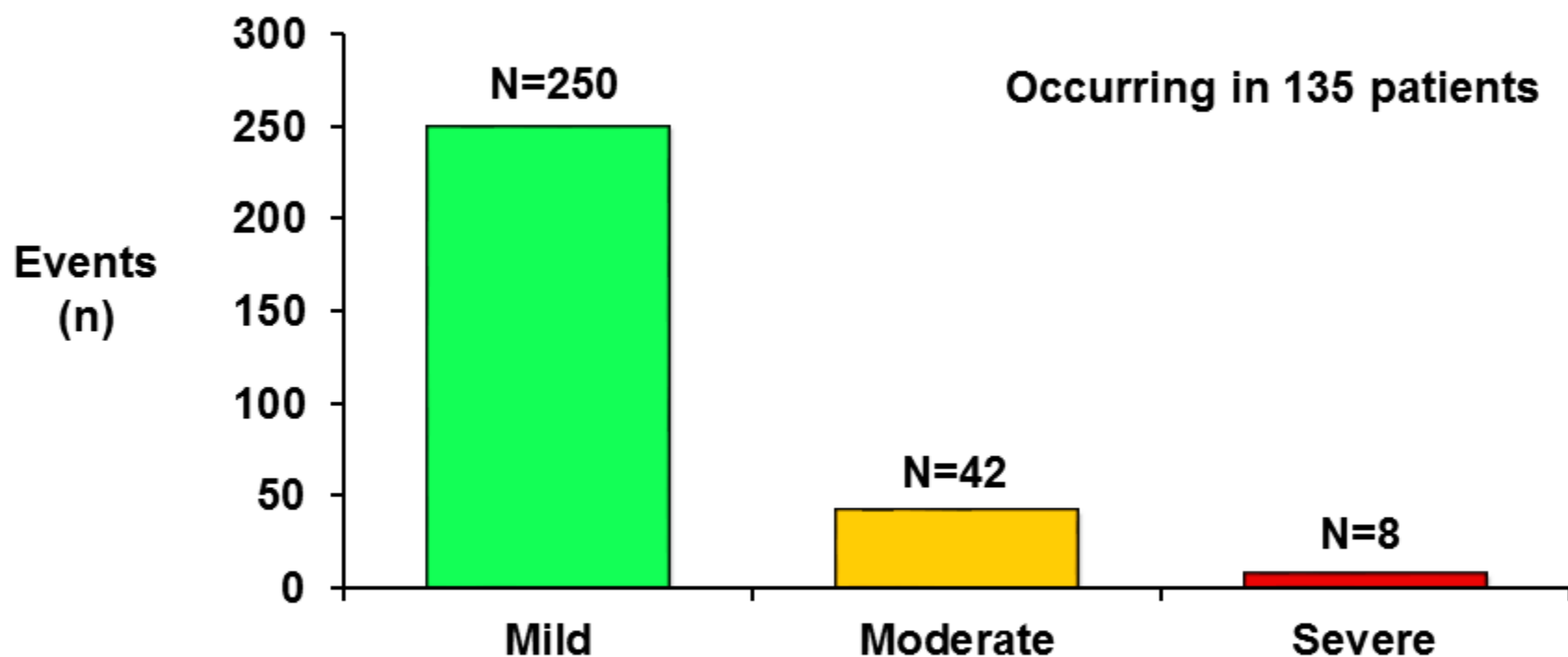
MedDRA Preferred Term	Solithromycin N=856		Moxifloxacin N=858	
	n	%	n	%
Diarrhea	37	4.3	53	6.2
<i>C. difficile</i> associated diarrhea	0	0	3	0.3
Headache	34	4.0	29	3.4
Nausea	29	3.4	24	2.8
Dizziness	20	2.3	12	1.4
Pneumonia	18	2.1	10	1.2
Vomiting	14	1.6	13	1.5
Hypokalemia	13	1.5	12	1.4
Hypertension	12	1.4	15	1.7
Insomnia	11	1.3	9	1.0

## IV-Related Reactions

<b>Study 301</b>	<b>Solithromycin N=432</b>		<b>Moxifloxacin N=426</b>	
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
<b>Any IV related reaction</b>	<b>135</b>	<b>31.3</b>	<b>23</b>	<b>5.4</b>
<b>Severe AEs</b>	<b>8</b>	<b>1.9</b>	<b>0</b>	<b>0</b>
<b>SAEs</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>AEs leading to drug discontinuation</b>	<b>10</b>	<b>2.3</b>	<b>1</b>	<b>0.2</b>

## Infusion Site AE Severity: Majority Were Mild or Moderate and Recovered Rapidly

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- Severe symptoms
  - Pain or paresthesia in 7 patients resolved on same or next day
  - Phlebitis in 1 patient resolved by SFU visit
- No IV-related reactions resulted in long-term sequelae

# AEs Leading to Discontinuation of Study Drug in $\geq 2$ Patients

System Organ Class	Solithromycin N=856		Moxifloxacin N=858	
	n	%	n	%
<b>Patients with <math>\geq 1</math> AE</b>	<b>41</b>	<b>4.8</b>	<b>29</b>	<b>3.4</b>
Infusion site reactions	10/432	2.3	1/426	0.2
Infections	9	1.1	6	0.7
Respiratory, thoracic disorders	5	0.6	5	0.6
Cardiac disorders	4	0.5	4	0.5
Laboratory abnormalities	4	0.5	2	0.2
Skin disorders	4	0.5	5	0.6
Gastrointestinal disorders	2	0.2	5	0.6
Nervous system disorders	2	0.2	0	0

# SAEs by Preferred Term in $\geq 2$ Patients

MedDRA Preferred term	Solithromycin N=856		Moxifloxacin N=858	
	n	%	n	%
<b>Patients with <math>\geq 1</math> SAE</b>	<b>58</b>	<b>6.8</b>	<b>50</b>	<b>5.8</b>
Pneumonia	13	1.5	6	0.7
Pleural effusion or empyema	5	0.6	3	0.3
Acute respiratory failure	5	0.6	9	1.0
Acute myocardial infarction	4	0.5	1	0.1
Congestive heart failure	2	0.2	5	0.6
COPD	2	0.2	2	0.2
Pulmonary tuberculosis	2	0.2	1	0.1
Septic shock	2	0.2	1	0.1
Cardiac arrest	2	0.2	1	0.1
Cerebrovascular accident	2	0.2	0	0

# Deaths

	Solithromycin N=856		Moxifloxacin N=858	
	n/N	%	n/N	%
<b>Overall deaths</b>	11/856	1.3	13/858	1.5
<b>Study 300</b>	6/424	1.4	6/432	1.4
<b>Study 301</b>	5/432	1.2	7/426	1.6

- Most attributed to underlying respiratory or cardiac diseases

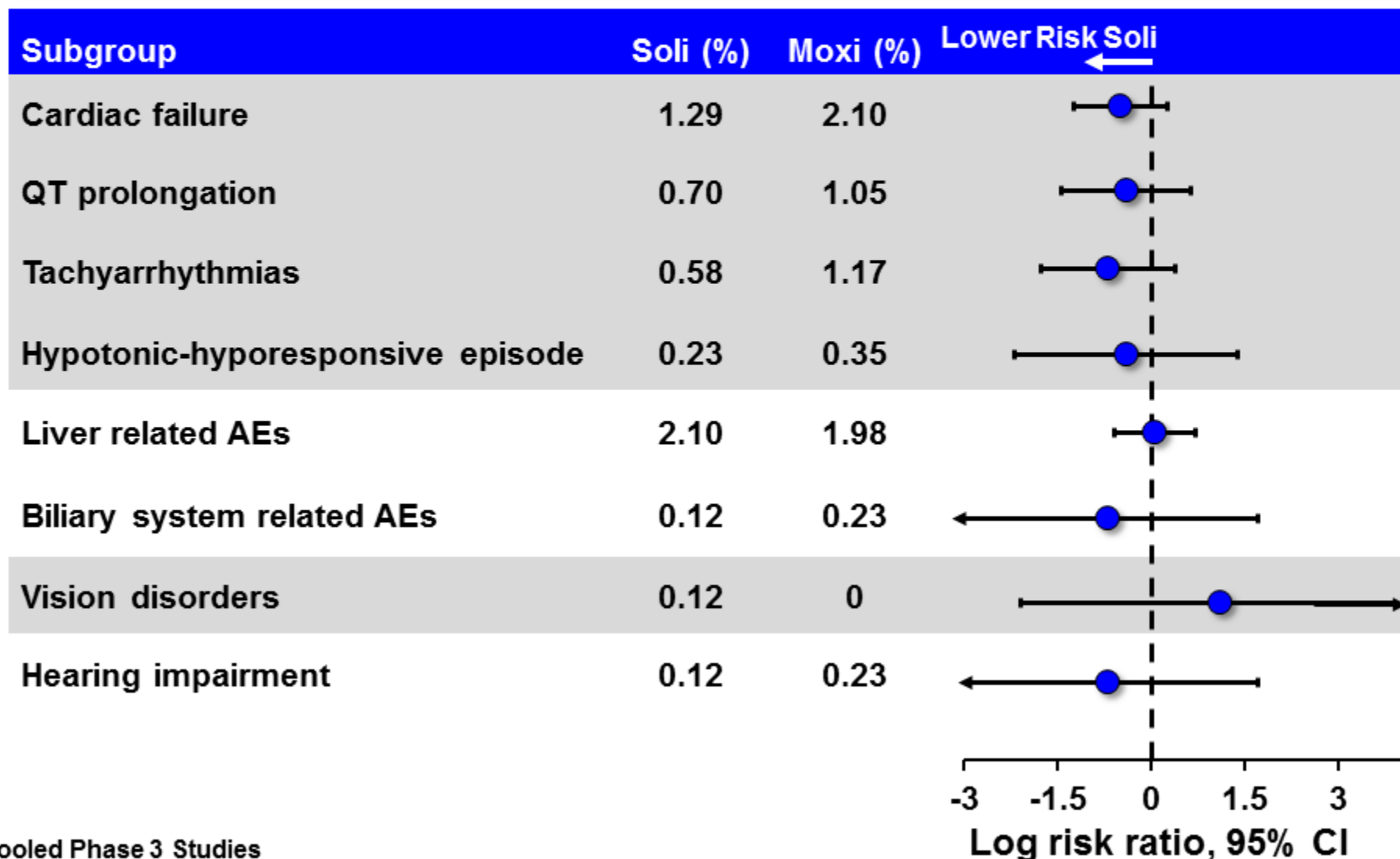
## **AEs of Special Interest (AESI)**

## Rationale for AESI

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- AEs observed with macrolides
  - Cardiac, hearing, liver
- AEs observed with telithromycin
  - Liver, loss of consciousness, vision and myasthenia gravis

# AESI Overview



# Eye Disorder AEs in Solithromycin Recipients: Integrated Studies

	Phase 1 N=554	Phase 2/3 N=920	Total N=1474
<b>SOC / Preferred Term</b>	<b>n</b>	<b>n</b>	<b>n</b>
<b>Eye disorders</b>	<b>6</b>	<b>1</b>	<b>7</b>
Eye irritation	2	0	2
Vision blurred	2	0	2
Asthenopia	1	0	1
Eye pain	1	0	1
Eyelids pruritus	1	0	1
Lacrimation increased	1	0	1
Floaters	0	1	1

# Syncope or Falls Occurred Well After Completion of Solithromycin Dosing

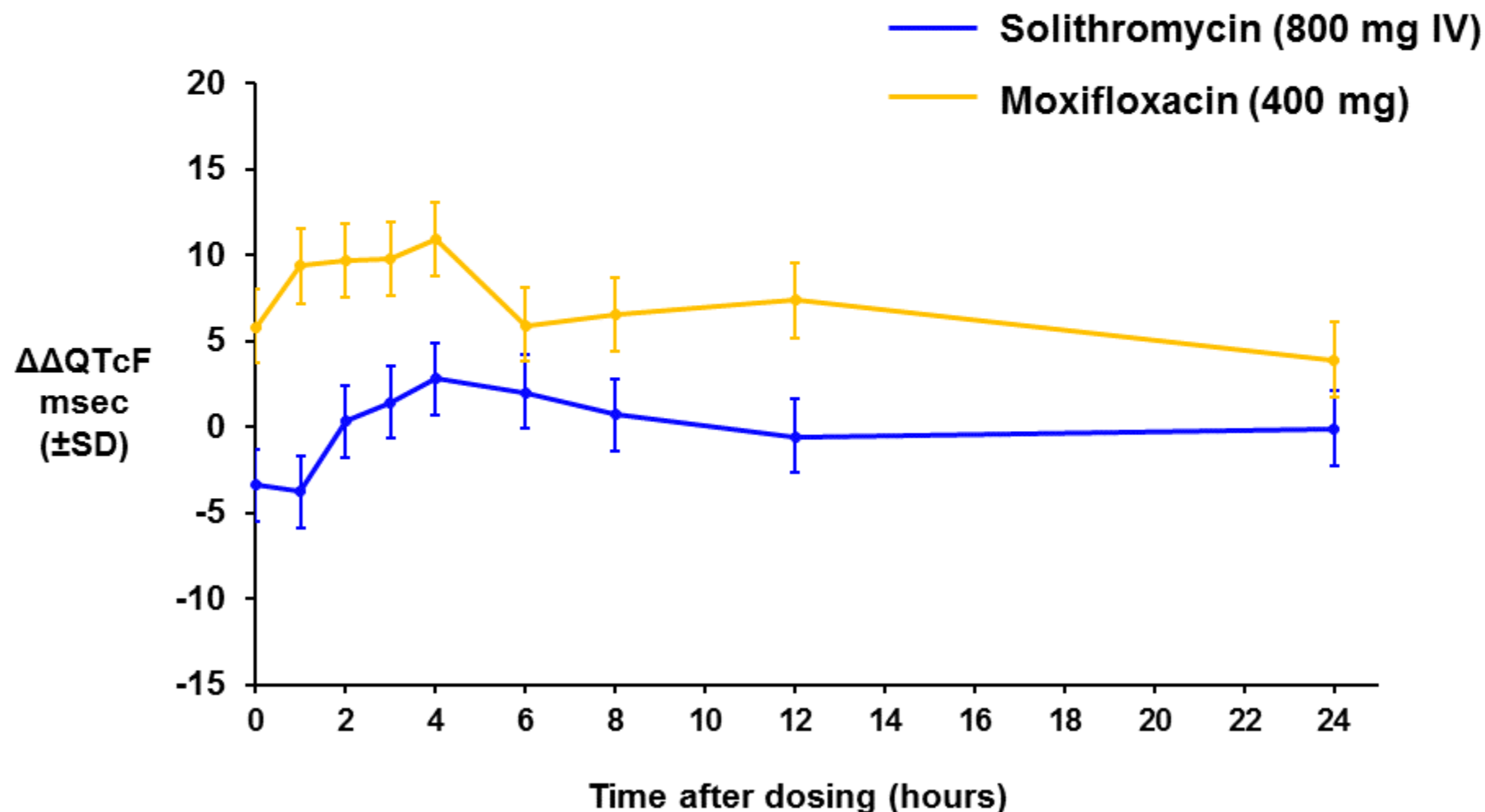
	AE term	Treatment duration	Day of event
Phase 2 CABP	Syncope	5	10
	Syncope	5	26
	Fall	5	10
Phase 3 CABP	Syncope	5	28

- Hypotonia
  - Miscoded event
  - Actually hypotension on Day 1

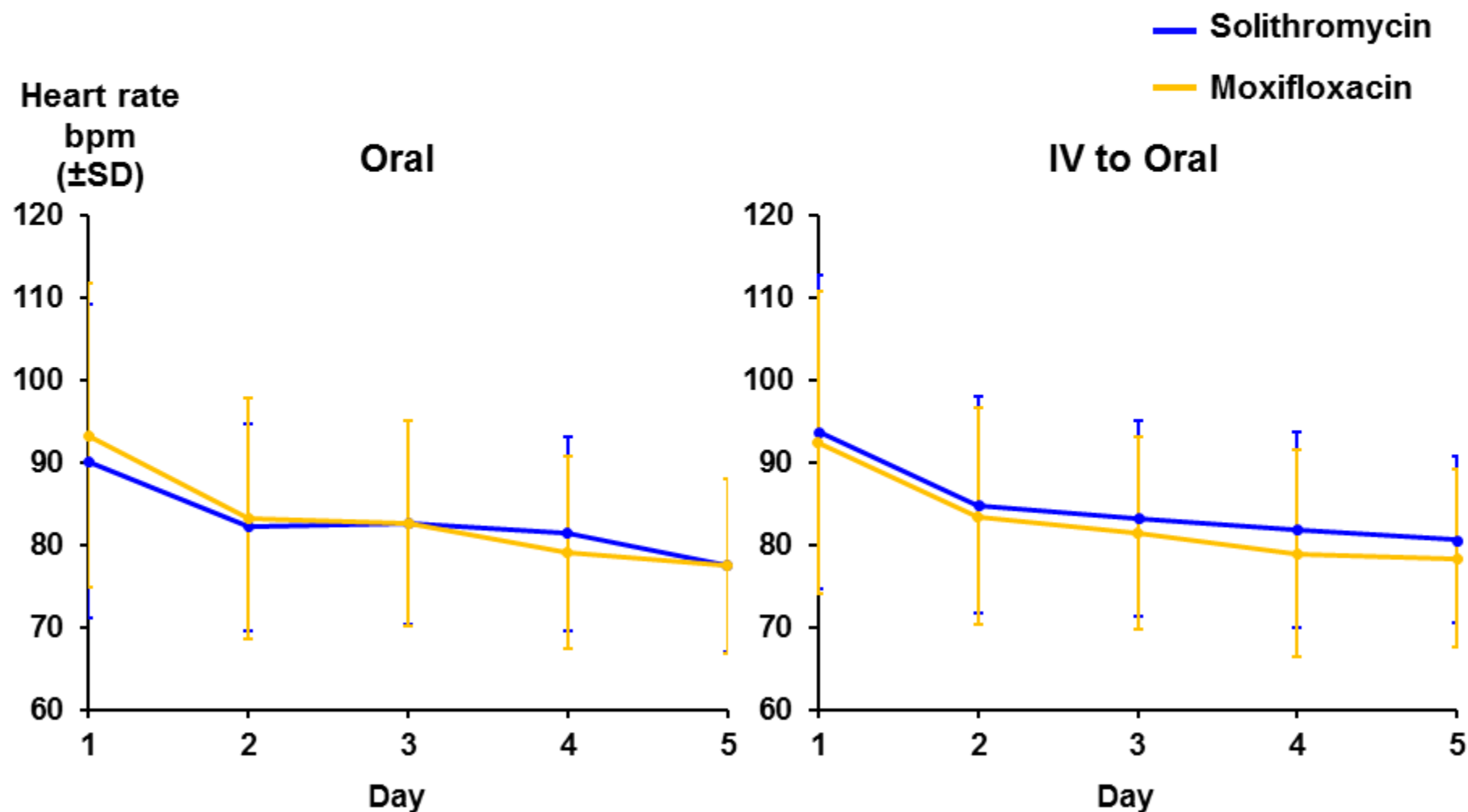
## CV AEs in $\geq 2$ Patients in Either Group

	Solithromycin N=856		Moxifloxacin N=858	
	n	%	n	%
<b>Patients with any cardiac AESI</b>	<b>26</b>	<b>3.0</b>	<b>40</b>	<b>4.7</b>
Acute myocardial infarction	4	0.5	3	0.3
Atrial fibrillation	3	0.4	7	0.8
Congestive heart failure	3	0.4	8	0.9
QT prolonged	3	0.4	6	0.7
Tachycardia	3	0.4	3	0.3
Cardiac arrest	2	0.2	1	0.1
Extrasystoles	2	0.2	0	0
Myocardial ischemia	1	0.1	4	0.5
Pulmonary congestion	1	0.1	2	0.2
Mitral valve incompetence	1	0.1	2	0.2

# Solithromycin Thorough QT Study: $\Delta\Delta QTcF$ Data



# Change in Mean Heart Rate Studies 300 and 301



# Rates of Transaminase and Bilirubin Elevation at Any Post-Baseline Time Point

Outcome Measure		Pooled Phase 3 CABP Studies			
		Solithromycin		Moxifloxacin	
		n/N	%	n/N	%
ALT	>ULN	370/828	44.7	263/835	31.5
	>3×ULN	60/828	7.2	30/835	3.6
	>10×ULN	1/828	0.1	2/835	0.2
AST	>ULN	284/822	34.5	209/825	25.3
	>3×ULN	30/822	3.6	18/825	2.2
	>10×ULN	4/822	0.5	2/825	0.2
ALT or AST	>ULN	412/829	49.7	302/835	36.2
	>3×ULN	67/829	8.1	36/835	4.3
	>10×ULN	4/829	0.5	3/835	0.4
ALT or AST Total Bilirubin	>3×ULN >2.0×ULN	2/828	0.2	1/835	0.1

# Rates of Transaminase Elevations by Study in Solithromycin Patients

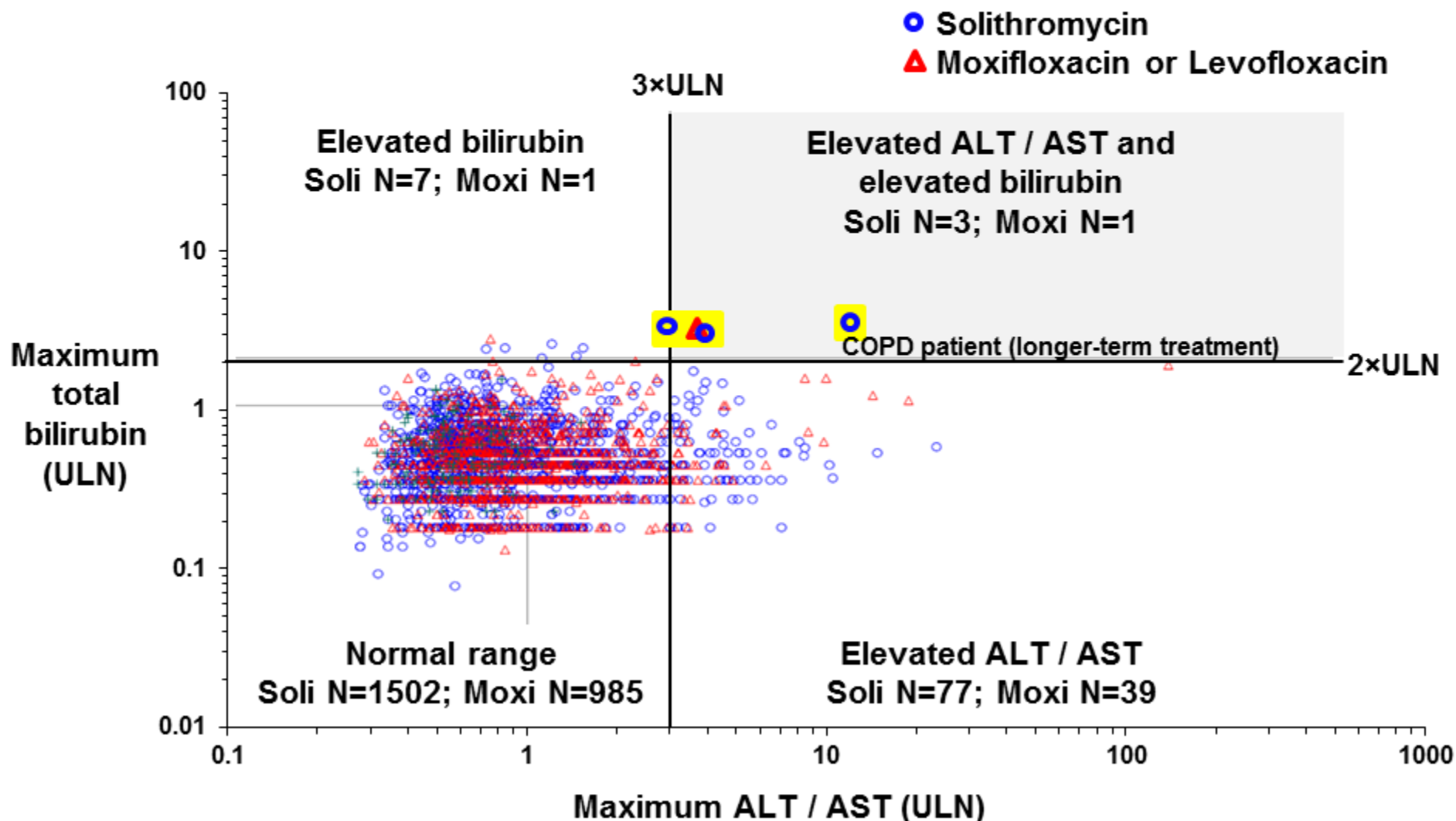
Enzyme	Peak Elevation	Study 300 (Oral)	Study 301 (IV to Oral)
		Solithromycin N=424 %	Solithromycin N=432 %
ALT	>ULN	41.8	47.5
	>3×ULN	5.4	9.1
	>5×ULN	1.7	3.1
	>10×ULN	0.2	0
AST	>ULN	32.0	37.0
	>3×ULN	2.5	4.8
	>5×ULN	1.0	2.2
	>10×ULN	0.5	0.5

# Hy's Law: Predictive Tool to Identify Drugs With High Risk for Fatal DILI

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- Hy's Law case definition
  - Treatment emergent hepatocellular injury
    - ALT or AST  $>3\times$ ULN and total bilirubin  $>2\times$ ULN
    - Alkaline phosphatase  $<2\times$ ULN
  - No alternative clinical explanation
- No Hy's Law cases were observed

# eDISH Plot: Solithromycin and Comparator



# Difference Between Sponsor and FDA eDISH Plots

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- FDA: 5 patients in right upper quadrant
- FDA eDISH analysis dataset
  - Limited to ALT vs bilirubin
  - Included baseline laboratory values
- Additional patients bilirubin baseline elevations declined on therapy
- None met Hy's Law criteria on study drug

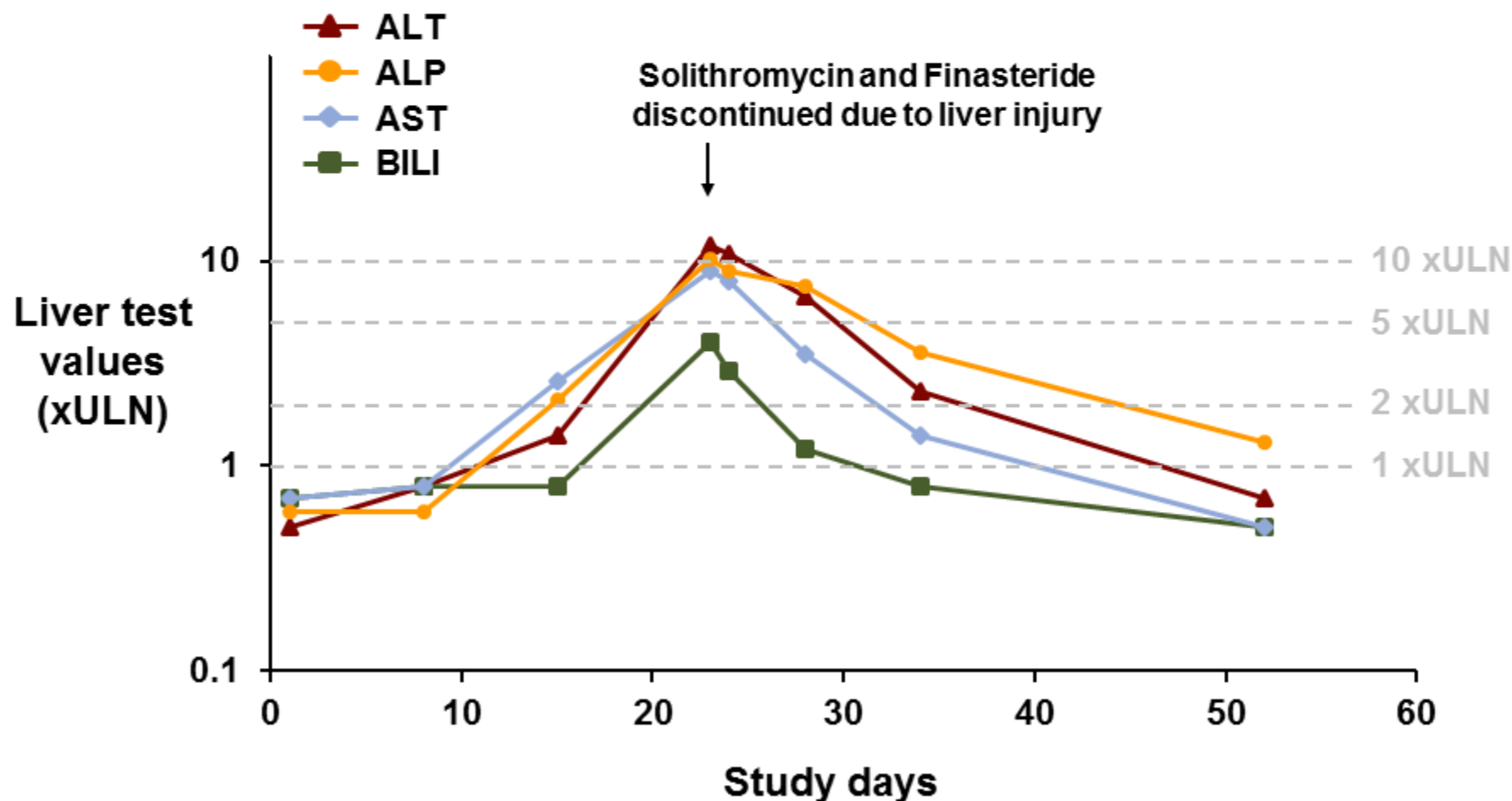
## Sponsor eDISH Plot: CABP Patients of Interest

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- 58-year old female (Study 300)
  - Multi-organ failure due to sepsis
  - Death at Day 13
  - Not Hy's Law case
- 34-year old female (Study 301)
  - Mild ALT elevation ( $3.8 \times \text{ULN}$ ) Day 12
    - Normalized at Day 26
  - Normal bilirubin at Day 12
    - Mild elevation ( $2.4 \times \text{ULN}$ ) at Day 26
  - Not Hy's Law case

# Rapidly Resolving Cholestatic Hepatitis in Longer-Term Dosing Patient

- 69-year COPD patient received 400 mg QD solithromycin x 23 days



# Solithromycin: IV and Oral has Acceptable Safety Profile for CABP

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- Liver safety profile
  - Exposure related ALT elevations typically asymptomatic, without bilirubin elevation
- Low *C. difficile* associated diarrhea risk
- Infusion-related AEs typically mild or moderate
- No QT signal
- No vision or hearing AE signal

## Ongoing and Planned Trials

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- Pediatric CABP study
  - ~300 pediatric patients
- Phase 3 gonorrhea study
- Exploratory studies in NASH and COPD
- Toyama Phase 3 CABP study

# Proposed Pharmacovigilance: Hepatic Safety Advisory Board

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- Independent panel of liver safety experts will regularly review all potential cases of interest
  - Ongoing clinical trials
  - Medical literature
  - Direct reporting by clinicians
  - MedWatch reports

# Enhanced Pharmacovigilance

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- Prospective program to identify rare or idiosyncratic hepatic events
- In discussion with healthcare systems
  - VA, Harvard Pilgrim, and Kaiser
  - Cover millions of U.S. lives
- Using Centralized Data Warehouse with weekly updates
- Establish an algorithm to identify ICD-10 hepatic outcomes of interest

# Liver Safety

**Paul B. Watkins, MD**

Howard Q. Ferguson Distinguished Professor

Hepatologist

Director, Institute for Drug Safety Sciences

University of North Carolina at Chapel Hill

# Table 2. Top 10 Therapeutic Classes and Individual Agents to Cause Drug-Induced Liver Injury in the DILIN Prospective Study

Therapeutic Classes	n	Individual Agents	n
1. Antimicrobials	408	1. Amoxicillin-clavulanate	91
2. Herbal and dietary supplements	145	2. Isoniazid	48
3. Cardiovascular agents	88	3. Nitrofurantoin	42
4. Central nervous system agents	82	4. Sulfamethoxazole/trimethoprim	31
5. Anti-neoplastic agents	49	5. Minocycline	28
6. Analgesics	33	6. Cefazolin	20
7. Immunomodulatory	27	7. Azithromycin	18
8. Endocrine	20	8. Ciprofloxacin	16
9. Rheumatologic	13	9. Levofloxacin	13
10. Gastrointestinal	12	10. Diclofenac	12

# Two Issues with Solithromycin

- ALT elevations
  - Imbalance compared to other macrolides
  - Asymptomatic and transient
- Legacy of telithromycin (Ketek)
  - Extremely rare, severe, idiosyncratic DILI
  - Not predicted in very large clinical trial database

# DILIsym®

Software designed to understand and  
predict liver safety liabilities in new drug  
candidates

# DILIsym<sup>®</sup> Mechanism-Based Modeling

## Drug Properties

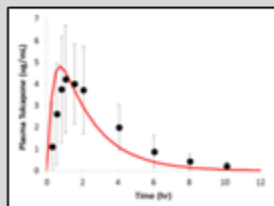
- Oxidative stress
- Mitochondrial dysfunction
- Bile acid transporter inhibition



## Liver Exposure

### PBPK\* Modeling

- Compound properties
- Tissue penetration studies
- Pharmacokinetic data
- *in vitro* data



## Simulated Patient Population



SimPops<sup>®</sup>

\*Physiologically based pharmacokinetic

# Rates of Serum ALT > 3X ULN in Clinical Trials Reasonably Predicted by DILIsym

Compound	Protocol	Peak ALT > 3X ULN	
		Observed	Simulated
Solithromycin	Oral (Study 300)	5.4% (2.8%)**	3.9%
	IV to Oral (Study 301)	9.1% (6.6%)**	6.0%
Erythromycin	500 mg QD 10 days	1-2%	2.8%
Clarithromycin	500 mg BID 7 days	1-2%	2.8%
Telithromycin	800 mg QD 10 days	0-0.7%*	0%

Simulation Results and Clinical Data

\* FDA Briefing Book for 2006 Ketek Advisory Committee

\*\* Normal ALT at baseline

# Contribution to Predicted ALT Elevations in Simulated Human Population

<b>DILI Mechanism</b>	<b>Solithromycin</b>	<b>Telithromycin</b>	<b>Erythromycin</b>	<b>Clarithromycin</b>
<b>Mitochondrial Respiration Inhibition</b>	Predominant	None	None	Predominant
<b>Oxidative Stress</b>	None	None	Minor	None
<b>Bile Acid Transporter Inhibition</b>	Minor	(Predominant)	Predominant	Minor

# Summary

- ALT elevations
  - Well-characterized clinically and mechanistically for Solithromycin
  - Within class no correlation with severe DILI
- Legacy of telithromycin (Ketek)
  - Soli liver effects differ from telithromycin
  - Liability unlikely detected in large clinical trial

## Primary Care Perspective

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**Steve Vacalis, DO**

Family Medicine Physician

CaroMont Family Medicine

North Carolina

# Pneumonia Prevalent and Deadly: U.S. Burden of Pneumonia

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- Pneumonia places significant burden on healthcare system
  - 4.5 million ambulatory visits<sup>1</sup>
  - >80% treated outpatient

# ***S. pneumoniae* Macrolide Resistance**

## **National Issue**

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- Susceptibility rates decreased across most antibiotics since 2010
- Macrolides less effective
  - National resistance levels near 50%
  - North Carolina resistance >53%
- No longer macrolide monotherapy option due to risk of failures

## Outpatient Treatment in Light of Regions with >25% Macrolide Resistance (MIC $\geq$ 16 $\mu$ g/mL)

---

- Special considerations in IDSA / ATS Guidelines<sup>1</sup>
  - Fluoroquinolone or  $\beta$ -lactam + Doxycycline
- Leads to overuse of fluoroquinolones
  - Increases risk of serious disabling and potentially permanent side effects
- Need new antibiotic therapies
- Solithromycin may restore macrolide monotherapy as suggested in guidelines

# Goal of Therapy: Decrease Hospitalizations and Eliminate Clinical Failures

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- Clinical failure defined as
  - Second course of same antibiotic
  - Starting different antibiotic during therapy
  - Admittance to UC or ER on antibiotic
  - Admittance to hospital
  - Death

# Solithromycin to Provide Macrolide Monotherapy Option

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- Simplifies hospital to outpatient transition
  - Convenient IV to Oral switch
- No episodes of *C. difficile* associated diarrhea
- Provides coverage of both typical and atypical pathogens of CABP
  - Macrolide susceptible strains
  - Macrolide resistant strains

# Solithromycin Provides Efficacy of Fluoroquinolones and Acceptable Safety

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- Efficacy data demonstrated non-inferiority to moxifloxacin
- Well-tolerated drug
  - Infusion site AEs observed with Solithromycin typical for macrolides
  - Liver enzyme elevations asymptomatic and transient
- Post-approval plan important
  - Monitor potential rare liver injury events

# **Totality of Data Supports Positive Benefit-Risk Profile for Solithromycin**

---

- Will provide clinicians with robust clinical option within macrolide class
- Activity against many pathogens
- Acceptable safety profile
- Addresses critical antibiotic stewardship needs

# **Solithromycin for the Treatment of Community-Acquired Bacterial Pneumonia (CABP)**

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**November 4, 2016**

Cempra Pharmaceuticals, Inc.

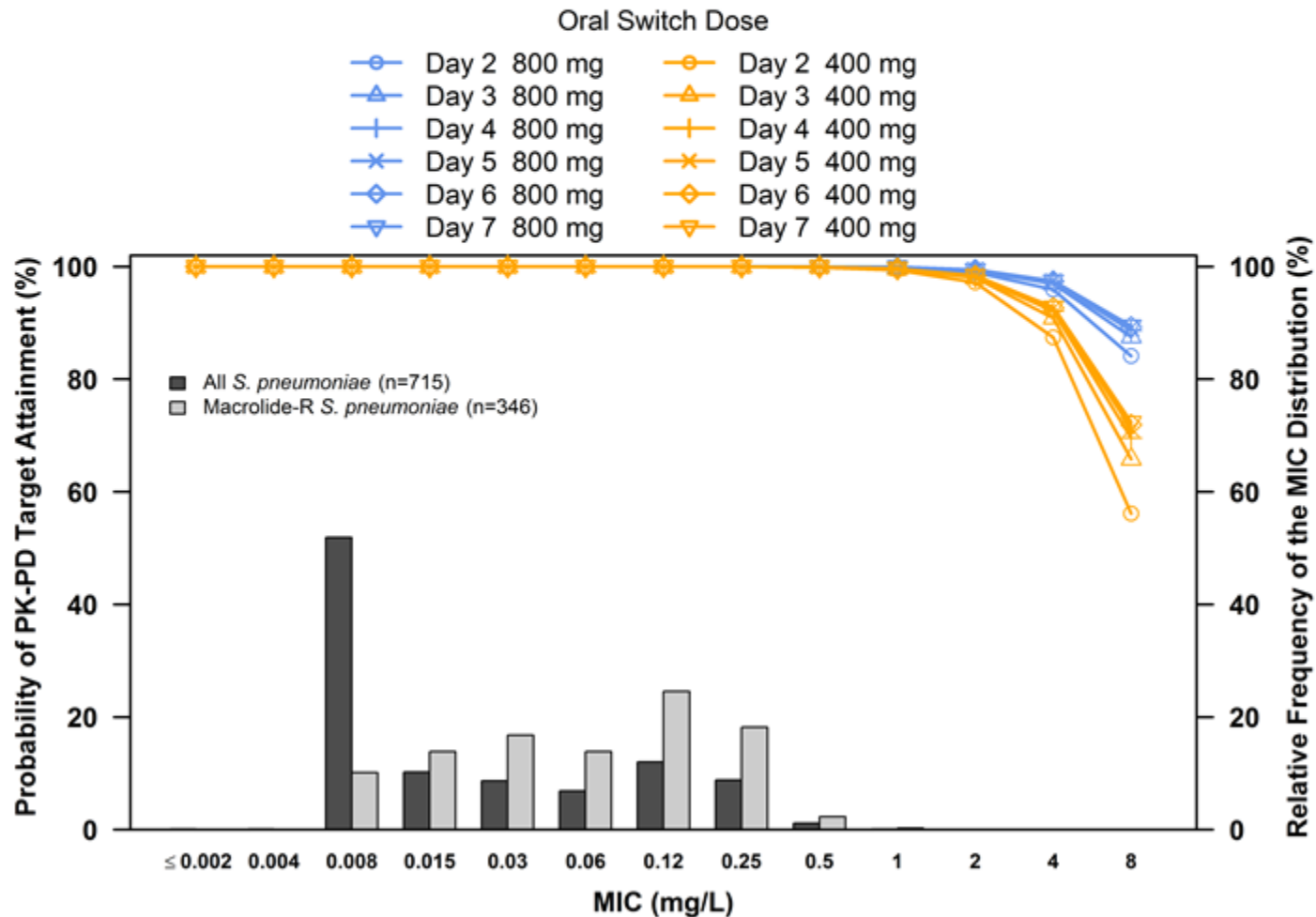
Antimicrobial Drugs Advisory Committee

BACK-UP SLIDES SHOWN  
ONSCREEN

# ECR by Macrolide-Resistance Gene: *S. pneumoniae* (mITT)

	Pooled mITT	
	Soli n/N (%)	Moxi n/N (%)
All <i>S. pneumoniae</i> Genotyped for Macrolide-Resistance	16/22 (72.7)	17/22 (77.3)
<i>ermB</i>	10/12 (83.3)	9/13 (69.2)
<i>mefA</i>	0/0	1/1 (100)
<i>mefE</i>	2/3 (66.7)	3/3 (100)
<i>ermB</i> & <i>mefA</i>	0/0	1/1 (100)
<i>ermB</i> & <i>mefE</i>	4/6 (66.7)	2/2 (100)
Negative	0/1 ( 0.0)	1/2 (50.0)

# Dose and PK/PD Target Attainment (ELF)





# DILIsym Performance Review – Prediction of serum ALT > 3 X ULN

Color Key – Accuracy of DILIsym	
Good	
Bad	

Drug	Predicted in Humans
Tolcapone (ALT)*	
Entacapone (Clean)*	
Bosentan (ALT)*	
Telmisartan (Clean)	
Troglitazone (ALT)*	
Pioglitazone (Clean)*	
AMG009 (ALT)**	
AMG 853 (Clean)**	
Compound G (ALT)	
Compound H (Clean)	
CKA (Clean)**	
Methapyrilene (Clean)*	

Drug	Predicted in Humans
Tolvaptan (ALT)*	
Compound B (ALT)**	
Compound C (ALT)**	
Compound E (ALT)	
Compound F (ALT)	
Etomoxir (ALT)*	
Solithromycin (ALT)	
Erythromycin (ALT)	
Clarithromycin (ALT)	
Compound A (ALT)	
Telithromycin (ALT)	

\* Published

\*\* Manuscript submitted

# DILIsym Performance Review

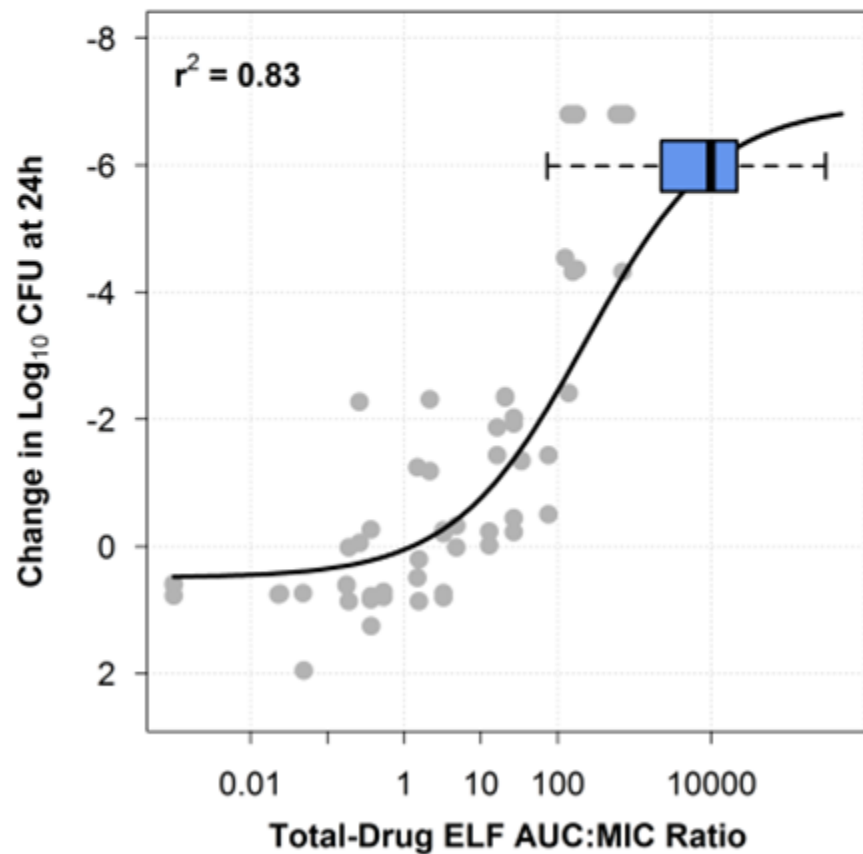
Drug	Injury Frequency	Injury Dose-Response	Injury Severity	Injury Timing	Injury Mechanism
Entacapone (Clean)					
Tolcapone (DILI)					
Methapyrilene (Clean)					
Troglitazone (DILI)					
Pioglitazone (Clean)					
AMG009 (DILI)					
Compound A (DILI)					
Bosentan (DILI)					
Telmisartan (Clean)					
Tolvaptan (DILI)					
Compound B (DILI)					
Compound C (DILI)					
Etomoxir (DILI)					
Compound E (DILI)					
Compound F (DILI)					
AMG 853 (Clean)					
Compound G (DILI)					
Compound J (DILI)					
CKA (Clean)					
Compound H (Clean)					
Compound I (DILI)					

**Color Key – Accuracy of DILIsym**

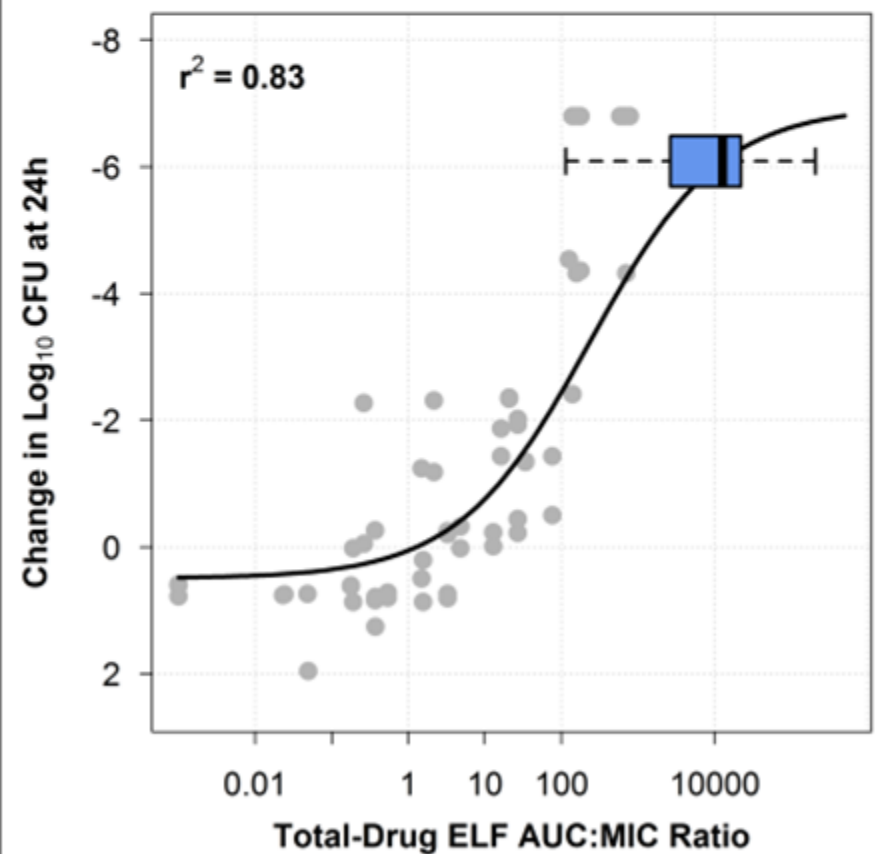
Excellent	
Good	
Fair	
Poor	
Unavailable or not applicable	

# Clinical Solithromycin ELF Exposures Relative to Murine PK-PD

## SOLI PO Regimen

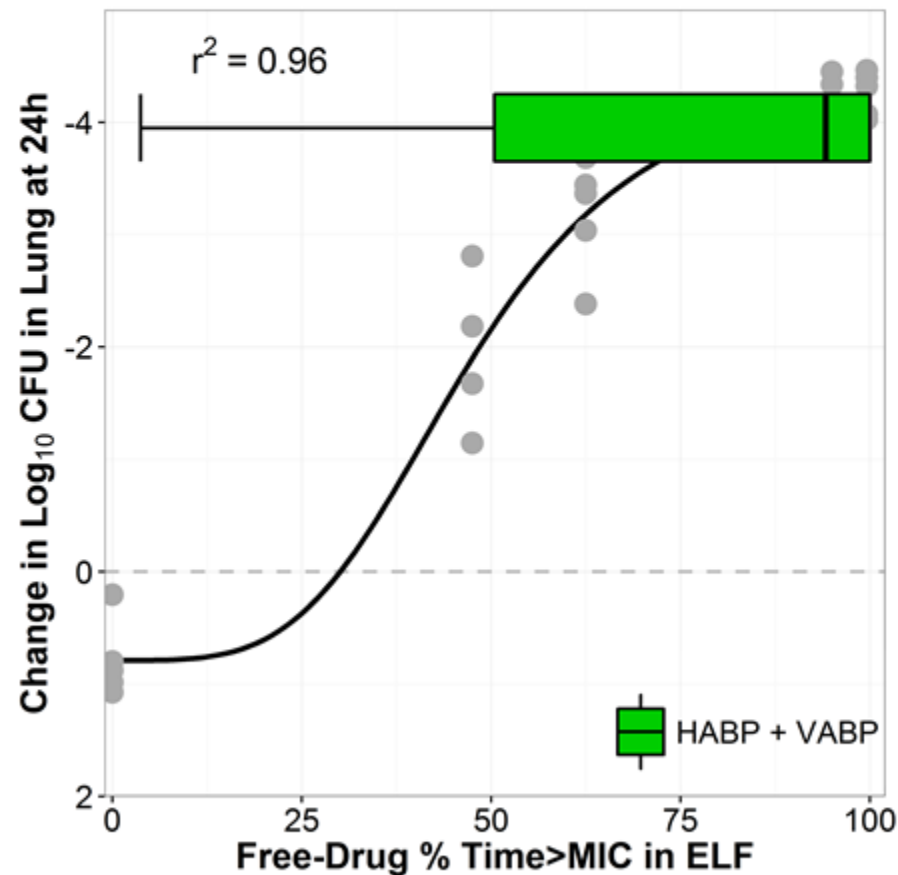


## SOLI IV to PO Regimen

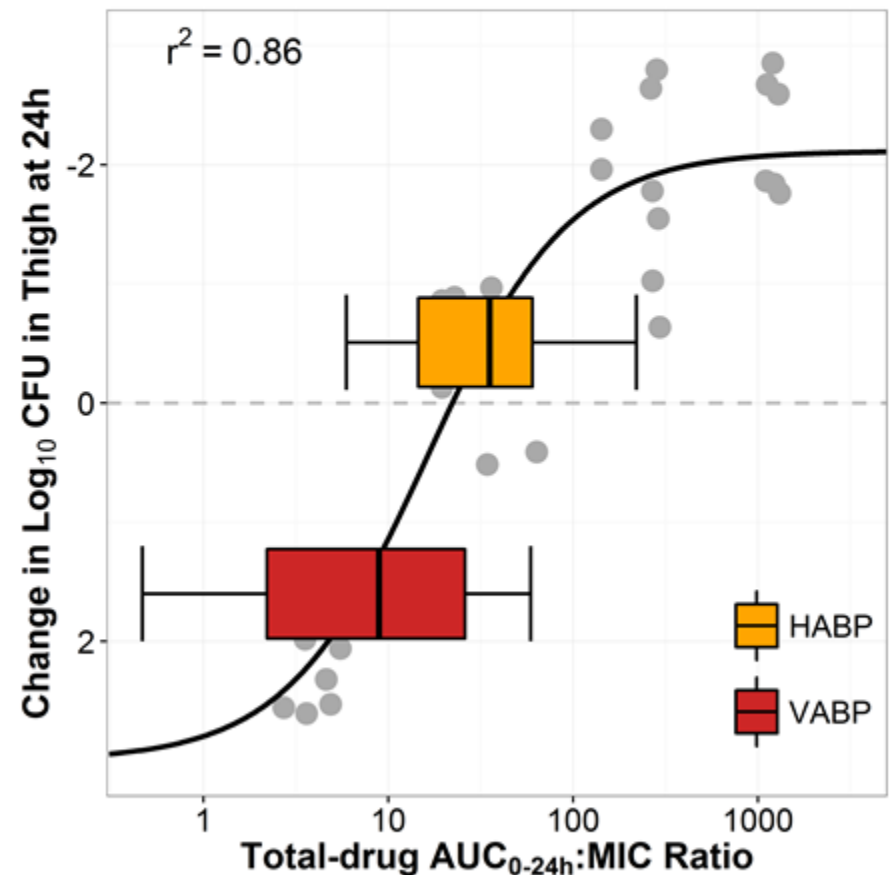


# Optimized Pneumonia Dosing vs Not

## Meropenem

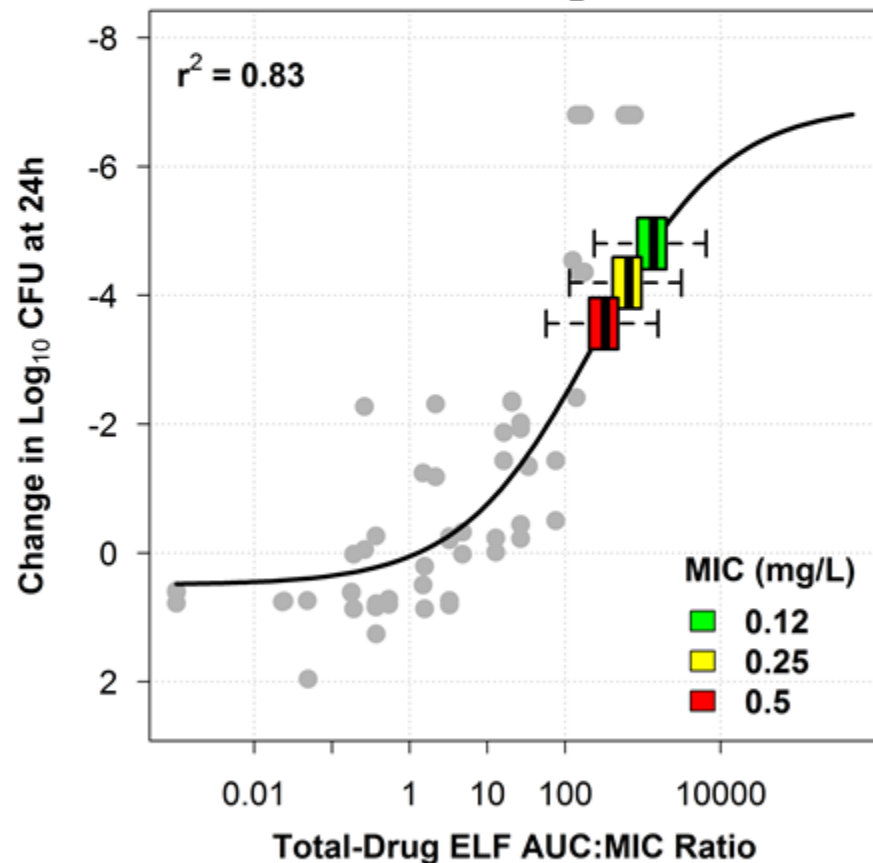


## Tigecycline

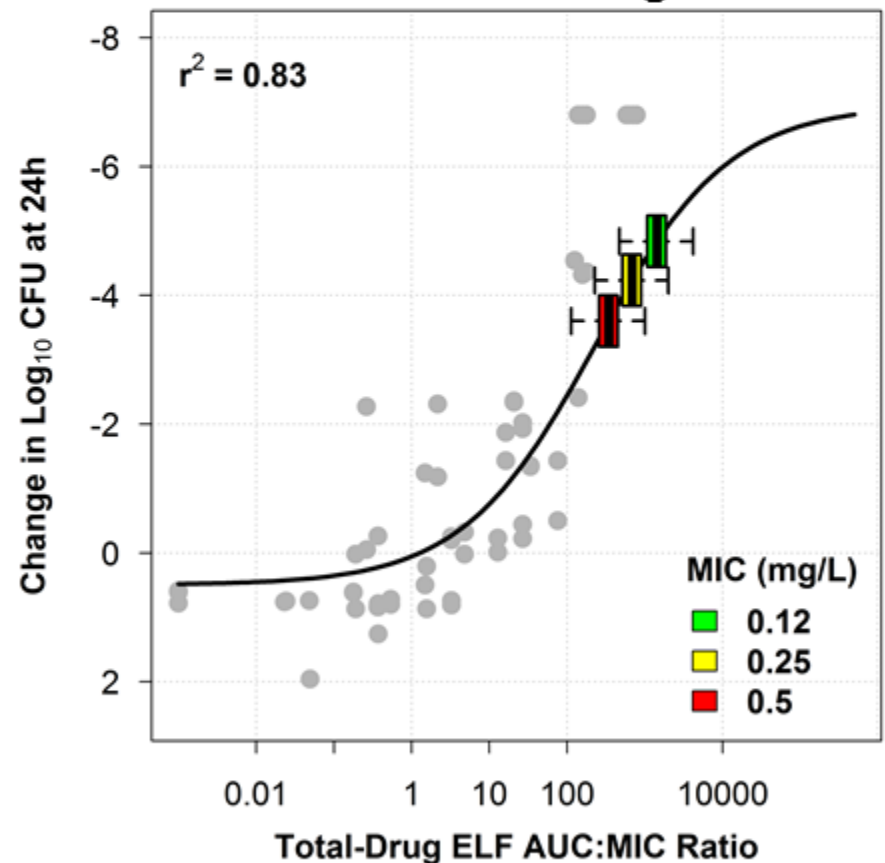


# Clinical Solithromycin ELF Exposures by MIC Relative to Murine PK-PD

## SOLI PO Regimen



## SOLI IV to PO Regimen



## **Solithromycin PO Only Dose Selection: % Probabilities of Target Attainment (Plasma)**

<b>Dosing Regimen</b>	<b>Day</b>	<b>MIC (<math>\mu\text{g/mL}</math>)</b>	
		<b>0.12</b>	<b>0.25</b>
<b>800 mg PO on D1, 400 mg PO on D2-7</b>	<b>1</b>	<b>97.6</b>	<b>68.5</b>
	<b>5</b>	<b>85.9</b>	<b>53.9</b>
<b>600 mg PO on D1, 300 mg PO on D2-7</b>	<b>1</b>	<b>86.1</b>	<b>41.7</b>
	<b>5</b>	<b>59.1</b>	<b>28.0</b>
<b>400 mg PO on D1, 200 mg PO on D2-7</b>	<b>1</b>	<b>47.1</b>	<b>9.6</b>
	<b>5</b>	<b>14.3</b>	<b>2.8</b>

# Phase 3 CABP Studies: Time to Peak Elevation

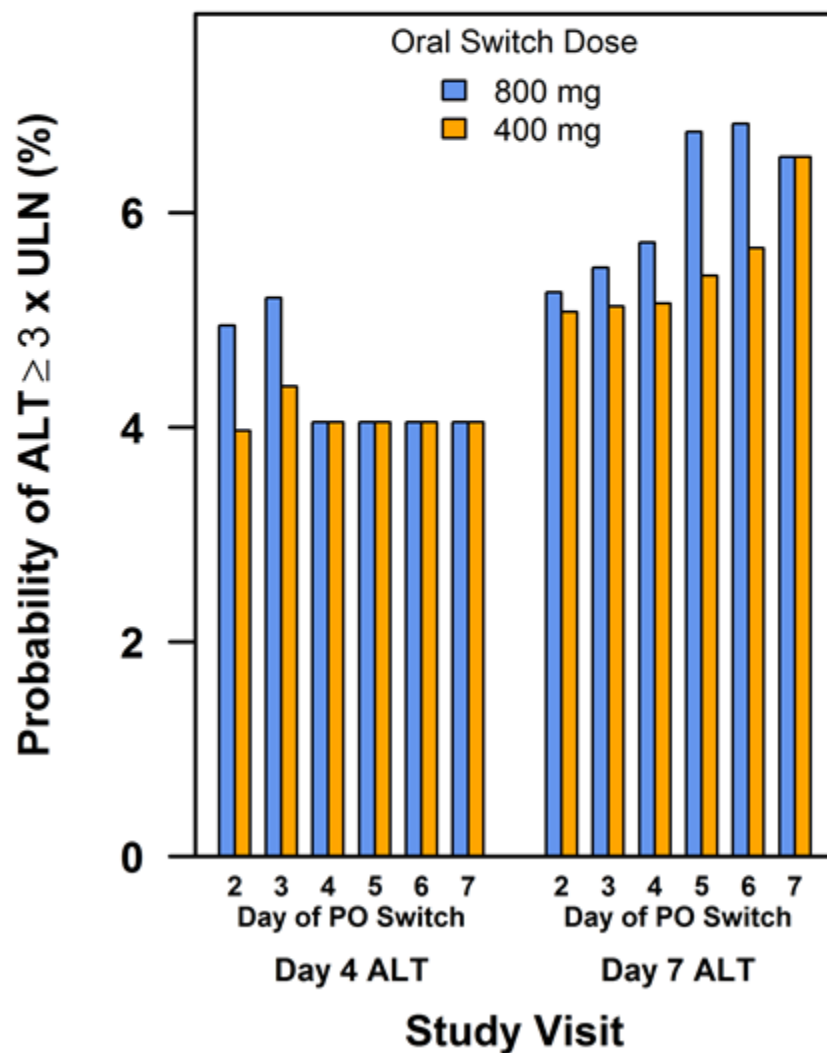
Outcome Measure	Day	Solithromycin		Moxifloxacin	
		n/N	%	n/N	%
ALT $\uparrow > 3 \times \text{ULN}$	1-5	35/60	58.3	14/30	46.7
	6-10	22/60	36.7	12/30	40.0
	11-15	3/60	5.0	4/30	13.3
	After Day 15	0/60	0	0/30	0
ALT $\uparrow > 5 \times \text{ULN}$	1-5	16/20	80	2/8	25
	6-10	3/20	15	5/8	62.5
	11-15	1/20	5	1/8	12.5
	After Day 15	0/20	0	0/8	0
AST $\uparrow > 3 \times \text{ULN}$	1-5	24/30	80	10/18	55.6
	6-10	5/30	16.7	7/18	38.9
	11-15	1/30	3.3	1/18	5.6
	After Day 15	0/30	0	0/18	0
AST $\uparrow > 5 \times \text{ULN}$	1-5	13/13	100	1/6	16.7
	6-10	0/13	0	4/6	66.7
	11-15	0/13	0	1/6	16.7
	After Day 15	0/13	0	0/6	0

# Frequency of ALT Elevation by Quartiles of Peak Plasma Solithromycin Exposure

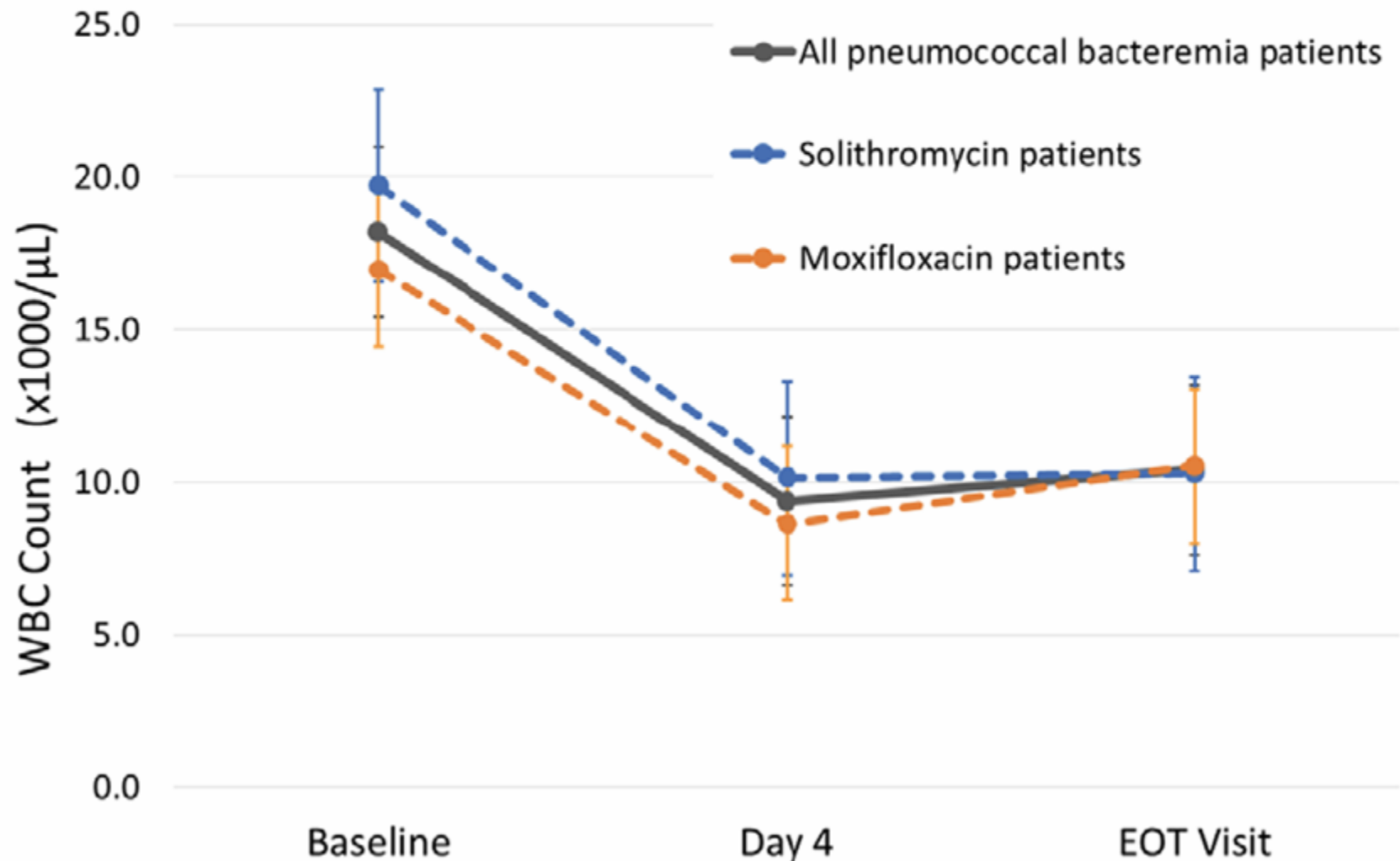
Study 300	AUC ( $\mu\text{g/mL}\cdot\text{h}$ )			
	$\leq 13.451$	$>13.451 - \leq 21.803$	$>21.803 - \leq 31.266$	$>31.266$
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
ALT Elevation				
>ULN	42/97 (43.3)	34/95 (35.8)	33/97 (34.0)	49/95 (51.6)
>3xULN	6/97 (6.2)	5/95 (5.3)	7/97 (7.2)	4/95 (4.2)
>5xULN	2/97 (2.1)	2/95 (2.1)	1/97 (1.0)	2/95 (2.1)

Study 301	AUC ( $\mu\text{g/mL}\cdot\text{h}$ )			
	$\leq 20.484$	$>20.484 - \leq 28.032$	$>28.032 - \leq 39.001$	$>39.001$
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
ALT Elevation				
>ULN	39/99 (39.4)	45/99 (45.5)	51/98 (52.0)	49/101 (48.5)
>3xULN	7/99 (7.1)	6/99 (6.1)	12/98 (12.2)	11/101 (10.9)
>5xULN	2/99 (2.0)	2/99 (2.0)	6/98 (6.1)	3/101 (3.0)

# Impact Oral Switch Day on ALT



# Pneumococcal Bacteremia Patients: WBC Counts by Study Visit



# Pneumococcal Bacteremia Patients: Body Temperature by Study Visit

