FDA Introductory Remarks

NDA 209006 Solithromycin Capsules

NDA 209007 Solithromycin Injection

Antimicrobial Drugs Advisory Committee Meeting

November 4, 2016

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Director, Division of Anti-Infective Products

Introduction

- NDAs 209006 and 209007: Solithromycin capsules and injection
- Applicant: Cempra Pharmaceuticals, Inc.
- NDAs granted priority review as the product has (Qualified Infectious Diseases Product) QIDP designation
- Proposed Indication:
  - Treatment of community acquired bacterial pneumonia (CABP) caused by *S. pneumoniae, H. influenzae*, *M. catarrhalis,* methicillin-susceptible *S. aureus, L. pneumophila* and *M. pneumoniae* in patients ≥ 18 years of age
- Proposed Dosing Regimens:
  - Oral only: 800 mg once on day 1, followed by 400 mg once daily on days 2-5
  - Intravenous (IV) only: 400 mg once a day for 7 days
  - IV to oral switch: Loading dose of 800 mg orally, followed by 400 mg orally once daily to complete the 7-day course

Development Program

- One Phase 2 trial and two Phase 3 trials were conducted in patients with CABP
- The Phase 2 trial was a randomized, double-blind trial comparing oral solithromycin to oral levofloxacin in 132 patients
- The co-primary efficacy outcomes were investigator-assessment of clinical response at Test of Cure (TOC) in the Intent-to-Treat (ITT) and Clinically Evaluable (CE) populations
- Clinical Success:
  - ITT population: 84.6% in the solithromycin arm and 86.5% in the levofloxacin arm
  - CE population: 83.6% in the solithromycin arm and 93.1% in the levofloxacin arm

Development Program: Phase 3 trials

- Two randomized, double-blind, noninferiority trials comparing solithromycin to moxifloxacin; pre-specified noninferiority (NI) margin of 10%
- Study CE01-300 evaluated a 5-day oral solithromycin regimen and Study CE01-301 a 7-day IV to oral solithromycin regimen
- The primary efficacy endpoint was Early Clinical Response (ECR) based on the symptoms of cough, dyspnea, chest pain, and sputum production 72 (60-108) hours after initiation of treatment
- A responder for the primary endpoint should have met the following criteria:
  - improvement from baseline in at least 2 out of the 4 symptoms
  - no worsening of other symptoms
  - had not received an antibacterial drug for CABP from the first dose of study drug during the first 108 hours
  - alive through the late follow-up visit 28-35 days after the first dose of study drug

Efficacy Results: Phase 3 trials

- Both trials met the pre-specified NI margin of 10 % for the primary endpoint of ECR
- Study CE01-300:
  - Responder rates were 78.2% in the solithromycin arm and 77.9% in the moxifloxacin arm; treatment difference of 0.3% (95% CI -5.5% to 6.1%)
- Study CE01-301:
  - Responder rates were 79.3% in the solithromycin arm and 79.7% in the moxifloxacin arm; treatment difference of -0.5% (95% CI -6.1% to 5.2%)
  - Numerical increase in rates of investigator-assessed clinical failure at the Short-term Follow Up (SFU) visit, 5-10 days after End of Therapy (EOT), in the solithromycin arm compared to the moxifloxacin arm

Safety Assessment

- Safety database of 920 patients at the proposed dose and duration
- Hepatotoxicity
  - In studies CE01-300 and CE01-301, incidence of ALT elevations was higher in solithromycin-treated patients compared to moxifloxacin-treated patients; this difference was more pronounced in Study CE01-301
  - No cases of Hy's law were seen
  - ALT elevation was also seen in the COPD and NASH trials
  - One case of clinical hepatitis associated with eosinophilia was reported in the COPD trial
- Intravenous site reactions: Reported in ~31% of solithromycin recipients and in ~5% of moxifloxacin recipients
- Ketolide class adverse events:
  - No obvious signal for visual adverse effects identified so far; some reports of visual adverse reactions (blurry vision, tired eyes, black spots)
  - Patients with history of myasthenia gravis were excluded

Key Topic Areas

- Efficacy
  - In Study CE01-301, investigator assessed clinical failures were more common in the solithromycin arm at the SFU visit (5-10 days after EOT)
  - Limited clinical data are available in patients with CABP due to macrolide-resistant *S. pneumoniae*
- Safety
  - Hepatotoxicity was seen in the CABP trials; frequency of ALT elevations was higher in the solithromycin arm than in the moxifloxacin arm
  - Hepatotoxicity was also seen in the COPD trial, including a case of clinical hepatitis, as well as in the NASH trial
  - Exposure-response was seen for hepatotoxicity (AUC and ALT elevations)
  - Infusion site reactions
- Dosing Regimen
  - Proposed loading dose at the time of IV to oral switch

Outline for the Day

- Presentations by the Applicant
- Presentations by the FDA
  - Daniel Rubin, PhD: Efficacy
  - Ramya Gopinath, MD: Safety
  - Yongheng Zhang, PhD: Clinical Pharmacology
- Clarifying questions
- Lunch
- Open Public Hearing
- Questions for the committee

Question 1

- Has the Applicant provided substantial evidence of the efficacy of solithromycin for the treatment of community acquired bacterial pneumonia (CABP)?
  - If yes, please provide any recommendations for labeling.
  - If no, please discuss additional studies/analyses that are needed.

Question 2

- Has the risk of hepatotoxicity with solithromycin been adequately characterized?
  - If yes, please provide any recommendations for labeling.
  - If no, please discuss additional studies that are needed to further characterize the risk.

Question 3

- Do the efficacy results of solithromycin for the treatment of CABP, outweigh the risks including hepatotoxicity?
  - If yes, please provide any recommendations for labeling.
  - If no, please discuss additional studies/analyses that are needed.

Presentation of Clinical Efficacy

Antimicrobial Drugs Advisory Committee Meeting
November 4, 2016

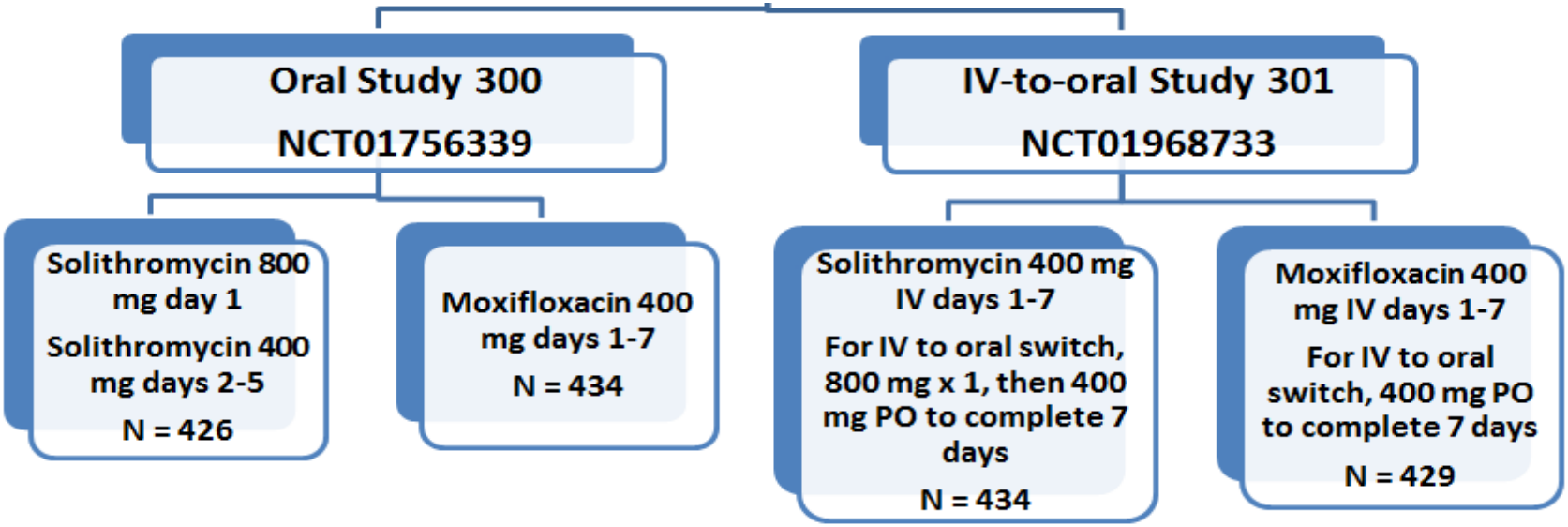
Daniel Rubin, PhD
Statistical Reviewer
Division of Biometrics IV, Office of Biostatistics,
Office of Translational Sciences, CDER, FDA

Outline

- Phase 3 trial designs
- Study populations
- Efficacy results
- Efficacy conclusions

Phase 3 Trial Designs

- Randomized, active controlled, double blind, non-inferiority trials comparing solithromycin versus moxifloxacin



- Design principles were consistent with the current FDA draft guidance for community-acquired bacterial pneumonia (CABP) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm123686.pdf

Phase 3 Trial Designs

- Key inclusion criteria: Adults ≥18 years old, CABP diagnosed with signs, symptoms, and radiographic evidence

- Key exclusion criteria: renal failure, severe hepatic impairment, myasthenia gravis, previous hypersensitivity to macrolides, QT prolongation or QT-prolonging drugs

- Enrollment restrictions:
  - At most 25% of subjects could have a single dose of a short-acting prior antibacterial CABP treatment
  - Pneumonia Patient Outcomes Research Team (PORT) Risk Class II-IV, with Risk Class II subjects limited to 50% of Oral Study 300 and 25% of IV-to-oral Study 301
  - At most 80% of enrolled subjects could be <65 years old
  - Enrollment target of ≤75% of subjects outside North America. [Target not achieved in IV-to-oral Study 301.]

Primary Efficacy Endpoint

- Early clinical response (ECR) at the 72 (-12/+36) hour visit:
  - Improvement from baseline on ≥2 of the 4 symptoms of cough, dyspnea, chest pain, and sputum production
  - Symptoms were scored as absent, mild, moderate, or severe
  - No worsening from baseline on any of the 4 symptoms at ECR visit
  - No receipt of an alternate CABP antibiotic during the first 108 hours (4.5 days)

    [Criterion affected ≤4% of subjects in each arm of each trial.]
  - Survival through the late follow-up visit on Day 28-35

    [Criterion affected ≤2% of subjects in each arm of each trial.]

This endpoint was consistent with the FDA draft guidance and was based on recommendations from the Foundations for the National Institutes of Health

Important Secondary Endpoints and Additional Pre-specified Endpoints

- Investigator assessed clinical response at the short-term follow-up (SFU) visit on Day 12-17
- Investigator assessed clinical response at the end of therapy (EOT) visit
- Early clinical response with improvement in vital signs at the 72 (-12/+36) hour visit
- Symptom response at the Day 12-17 visit: absence of chest pain and sputum production, and absence or improvement from baseline in cough and dyspnea
- Symptom response at both the 72 (-12/+36) hour visit and the Day 12-17 visit

Statistical Analysis

- Primary efficacy analysis for each Phase 3 trial:
  - Comparison of the (solithromycin – moxifloxacin) difference in early clinical response rates with a non-inferiority margin of 10% in the intent-to-treat (ITT) population of all randomized subjects

- Protocol-defined co-primary efficacy analysis from pooled trials:
  - Comparison of the (solithromycin – moxifloxacin) difference in early clinical response rates with a non-inferiority margin of 15% in the microbiological intent-to-treat (mITT) population
  - The mITT population included patients with a baseline pathogen in sputum, pleural fluid, bronchoalveolar lavage, blood, oropharyngeal and/or nasopharyngeal swabs identified with culture, urinary antigen test, serology, and/or unapproved molecular diagnostic assays (PCR)
  - Note: The mITT-2 population was a post-hoc analysis population and included baseline pathogens identified by culture or urinary antigen tests.

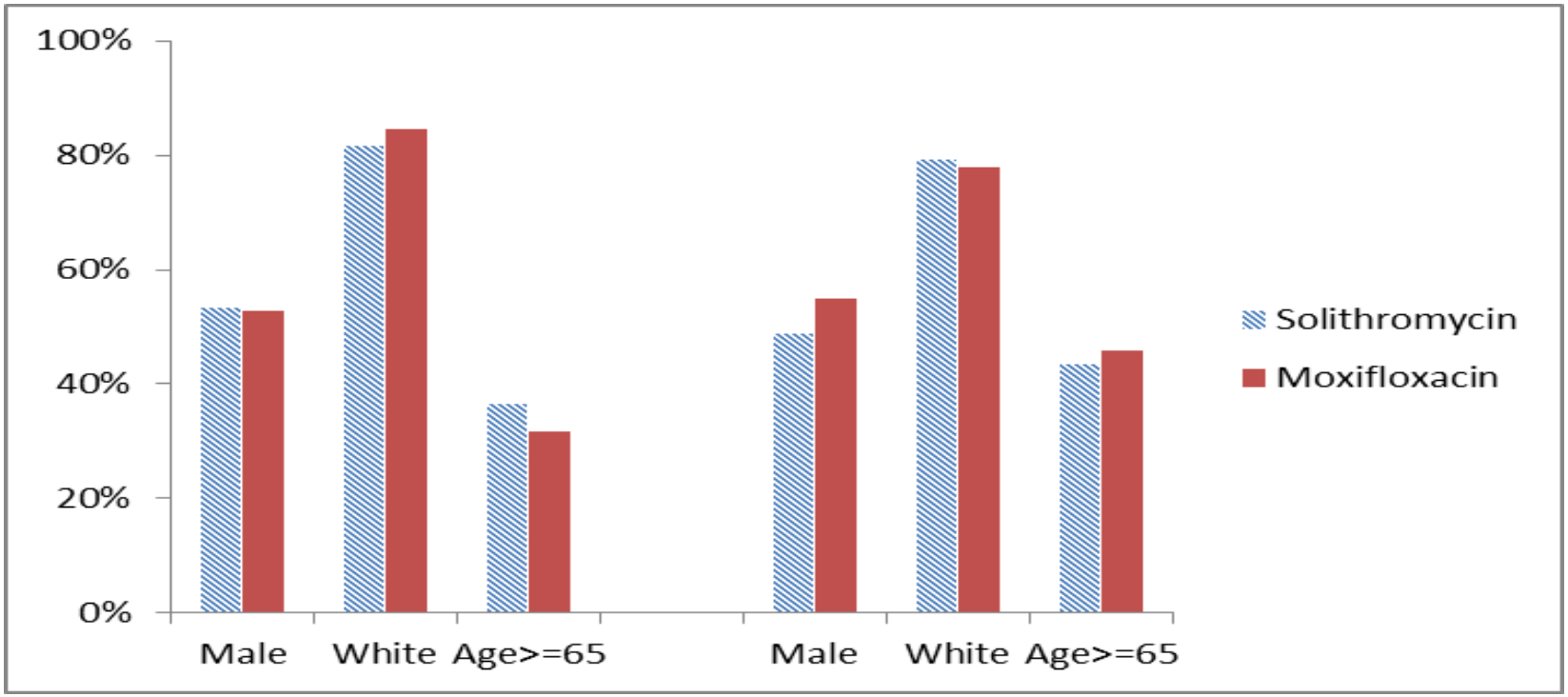
Trial Conduct

- There was approximately 3% missing or indeterminate data in each arm of each trial for the primary endpoint of early clinical response
- The total premature subject withdrawal rate was approximately 5%
- The total premature study drug discontinuation rate was approximately 8%. The most common reason was an adverse event.
- Protocol violations largely related to baseline covariate measurements and were unlikely to have changed overall conclusions
- An audit from the Applicant found incomplete documentation for a study site in Russia and implausible drug concentrations from a study site in Bulgaria. Together the sites enrolled 30 subjects, but results are qualitatively unchanged if excluding these sites.

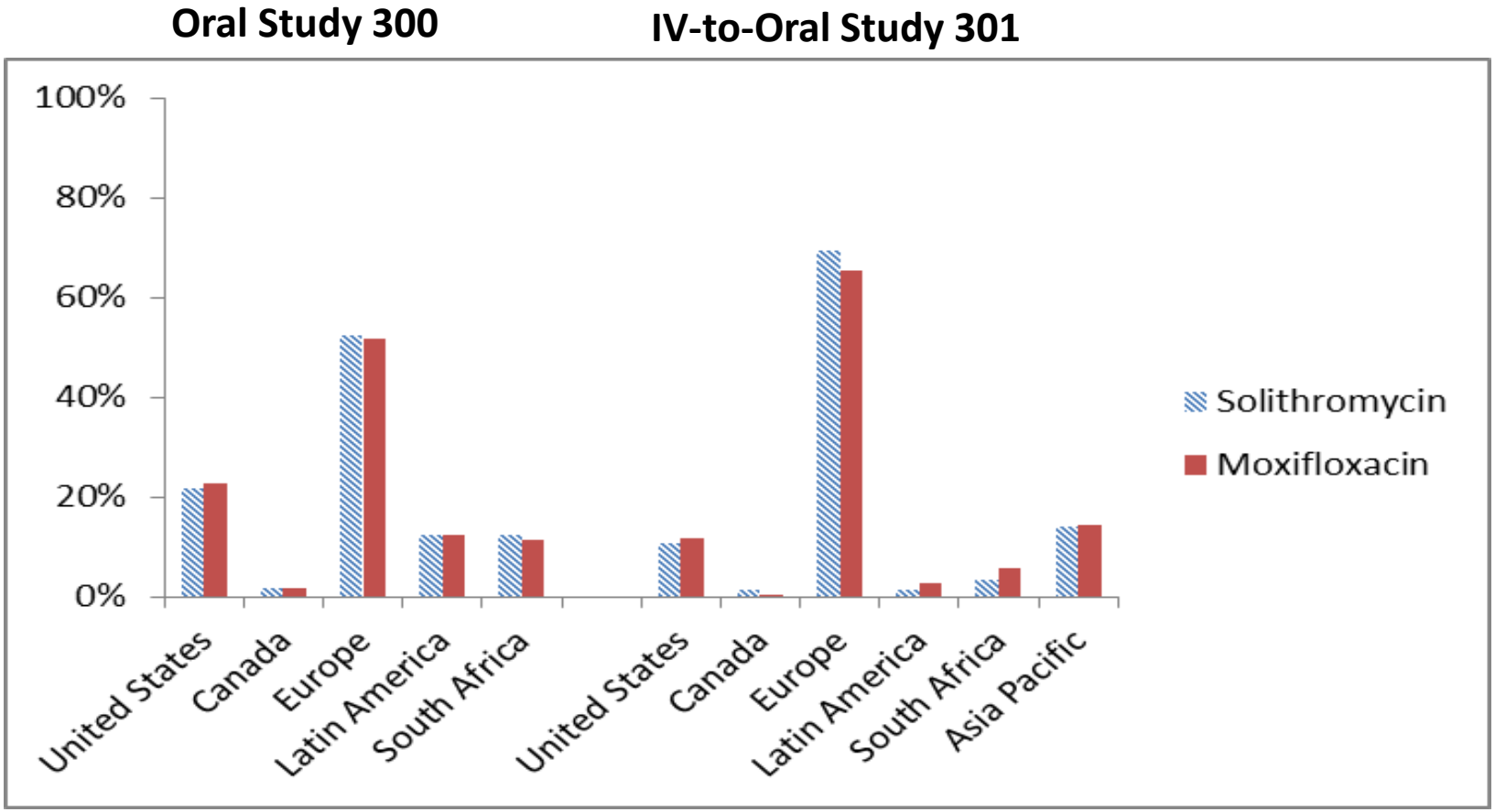
Baseline Demographics – ITT Population

Oral Study 300
(N = 860 total subjects)

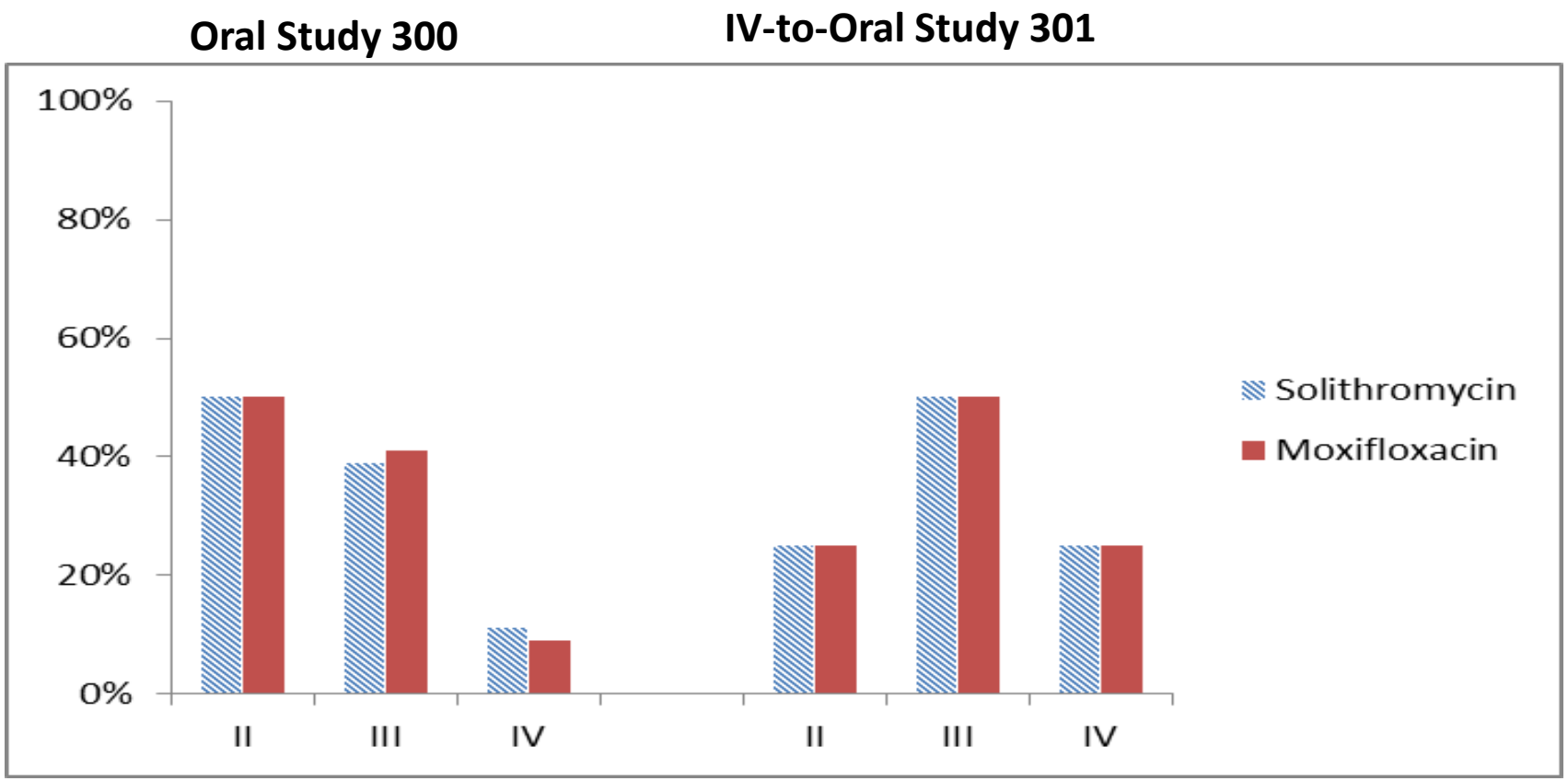
IV-to-Oral Study 301
(N = 863 total subjects)



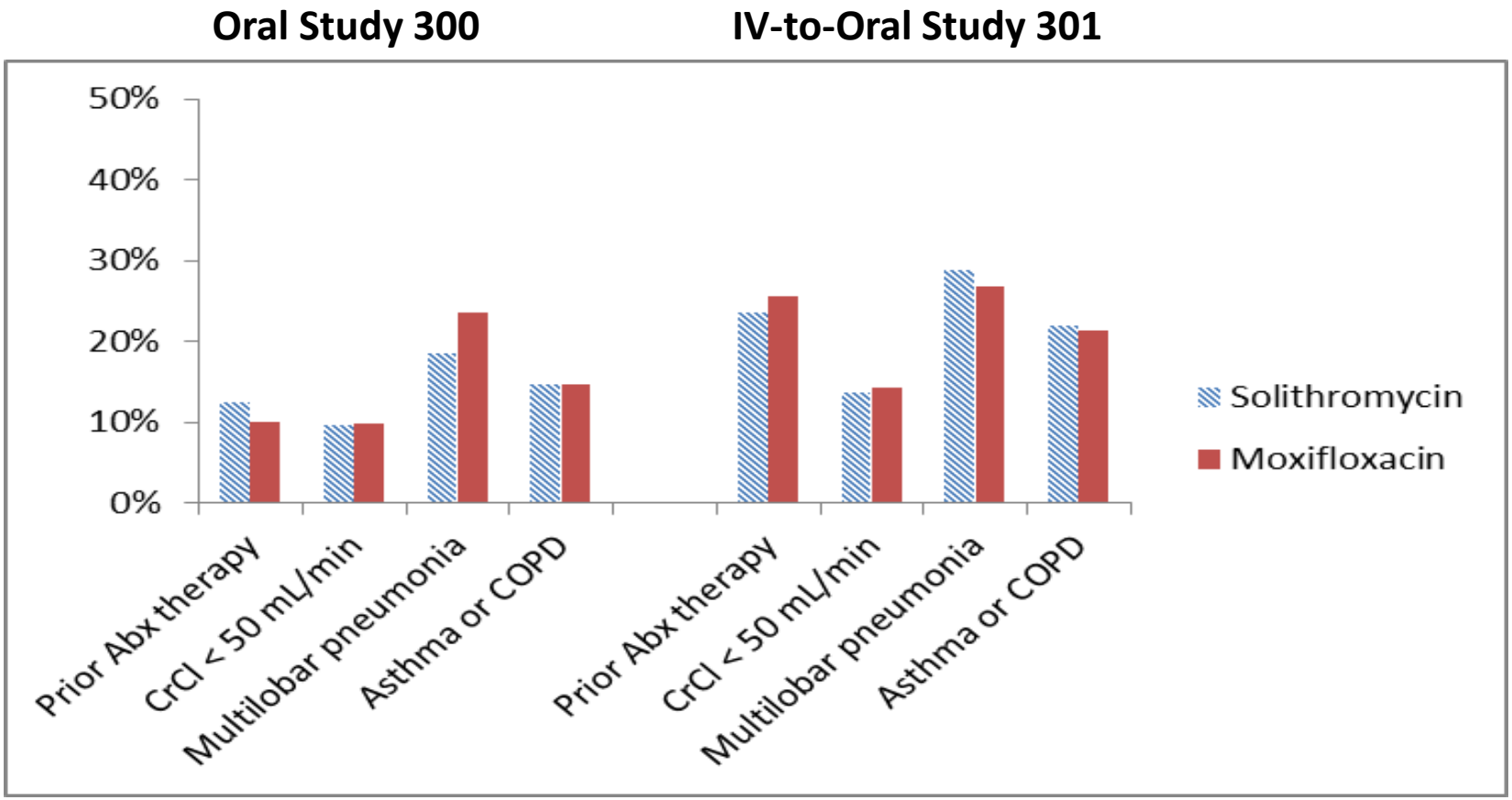
Region of Enrollment – ITT Population



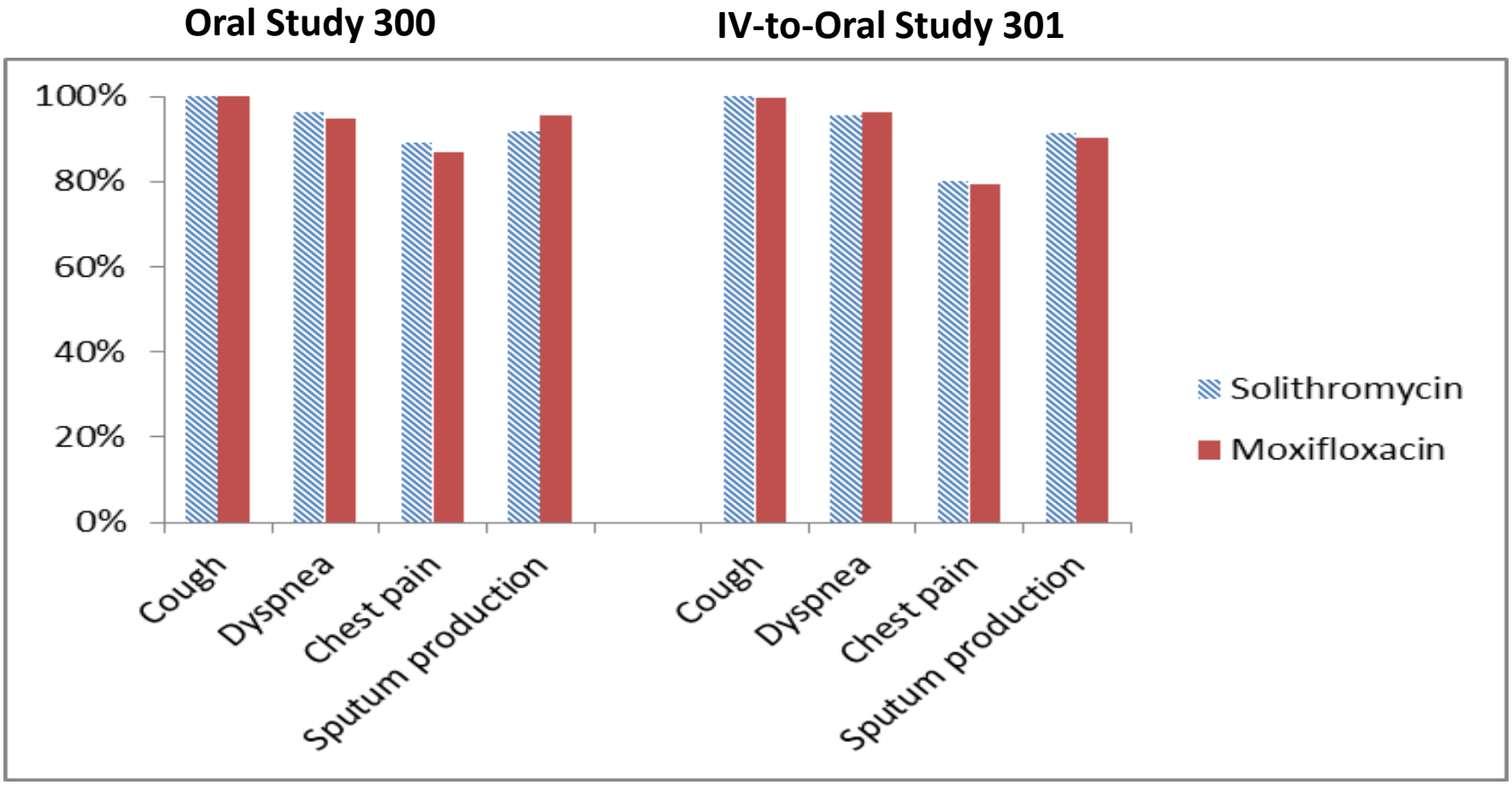
Baseline PORT Risk Class – ITT Population



Baseline Characteristics – ITT Population

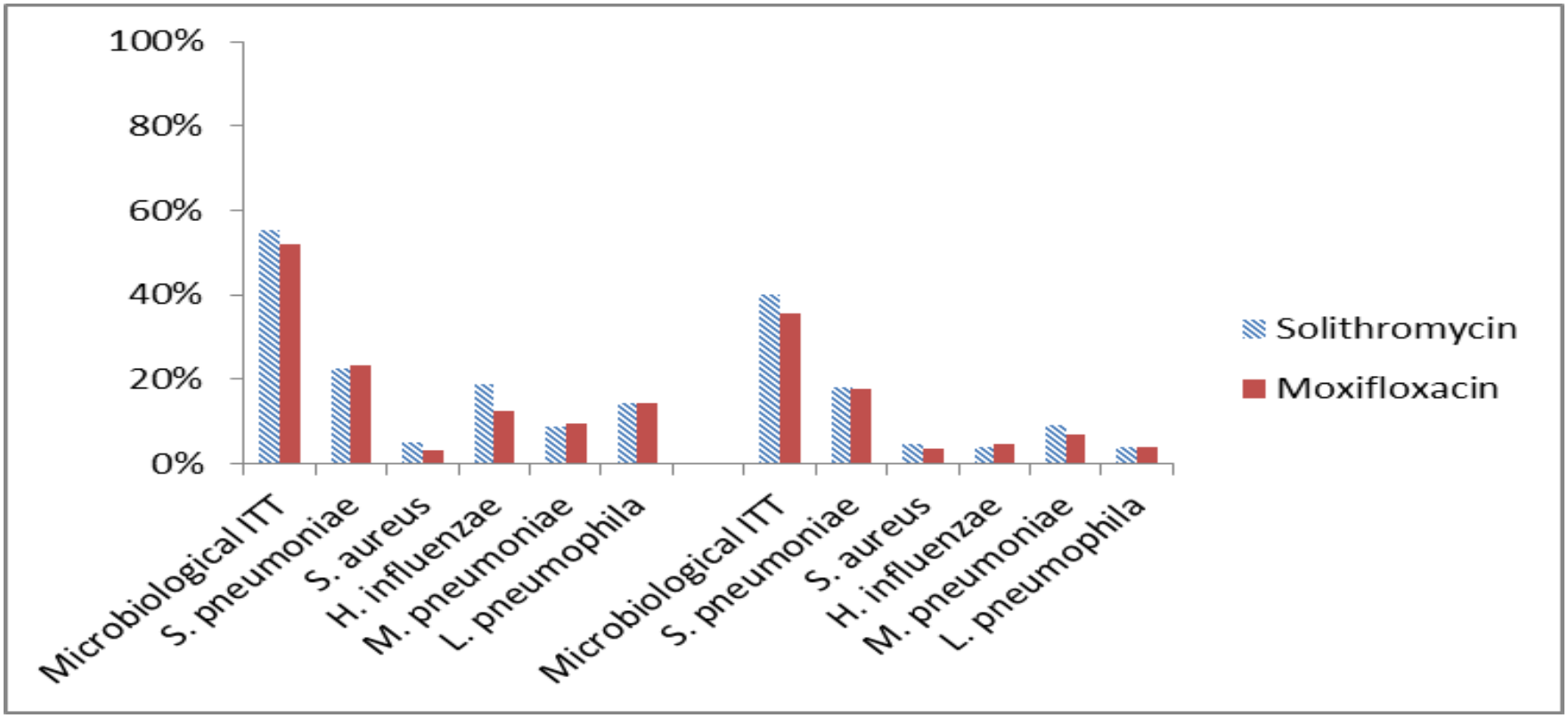


Baseline Symptoms – ITT Population



Baseline Pathogens – ITT Population

Oral Study 300 **IV-to-Oral Study 301**

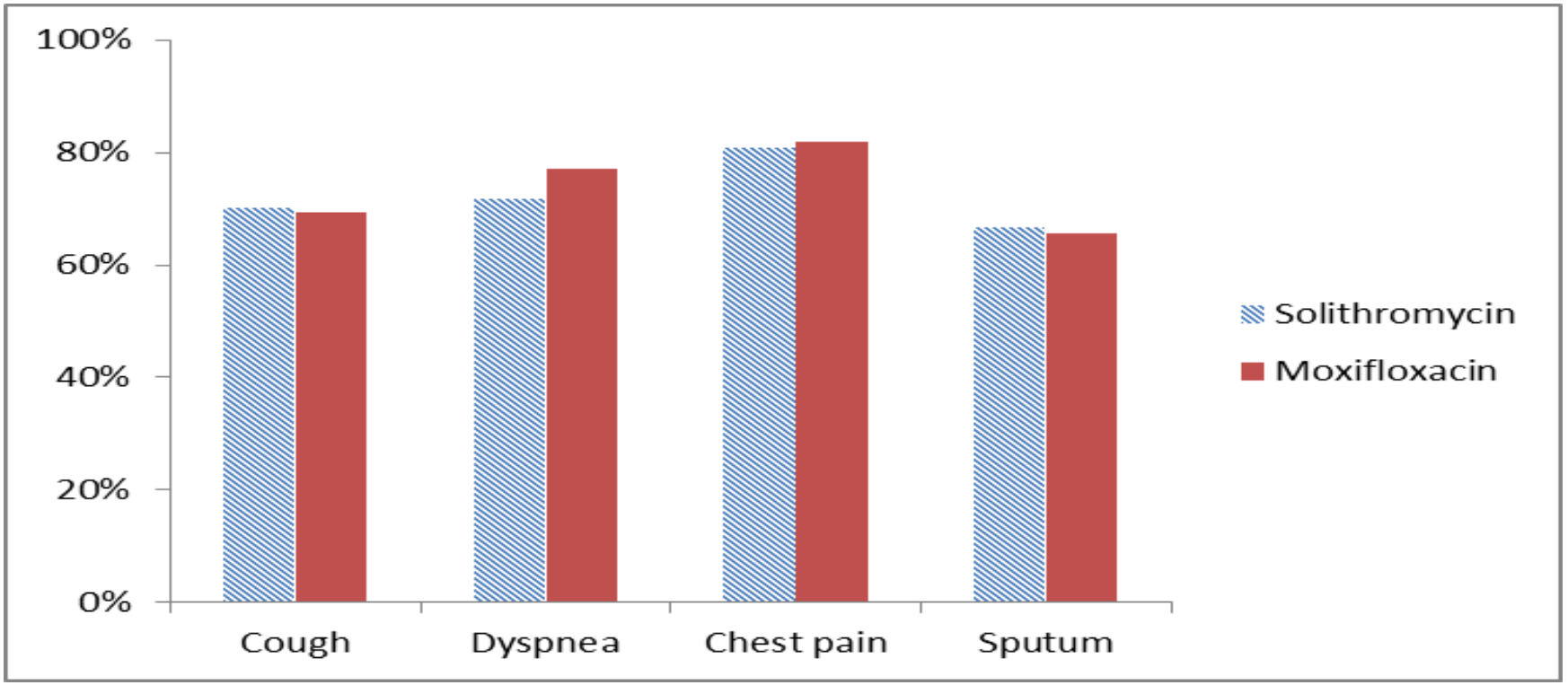


Primary efficacy analysis of Oral Study 300

- Early clinical response at 72 (-12/+36 hours)
- ITT population, 10% non-inferiority margin
- Solithromycin demonstrated non-inferiority

	Solithromycin (n = 426)	Moxifloxacin (n = 434)	Difference	95% confidence interval
Responder	333 (78.2%)	338 (77.9%)	0.3%	-5.5% to 6.1%
Nonresponder	81 (19.0%)	84 (19.4%)	-0.3%	
Indeterminate	12 (2.8%)	12 (2.8%)	0.1%	

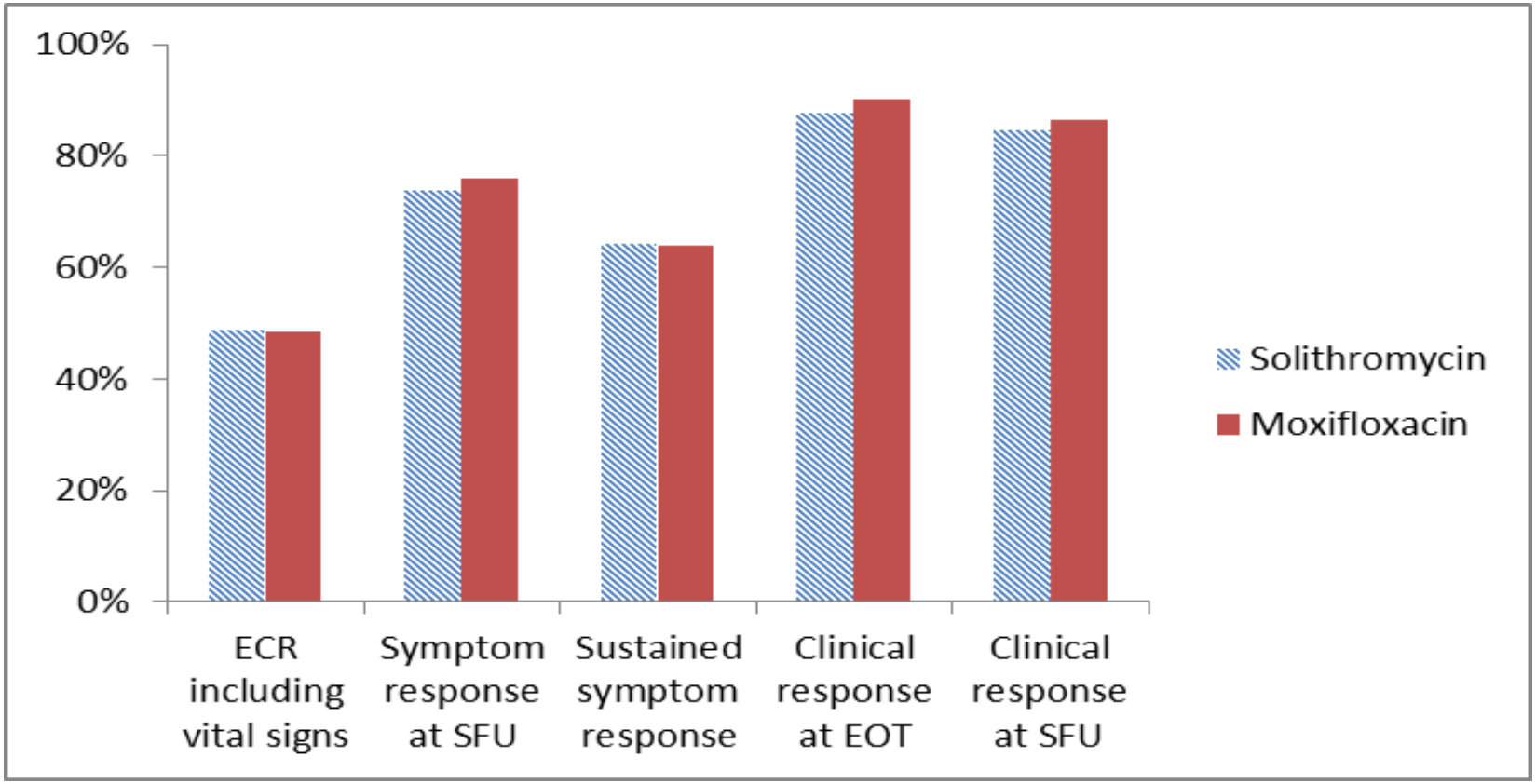
Symptoms absent or improved from baseline at the early clinical response visit at 72 (-12/+36) hours in the ITT Population of Oral Study 300



Subgroup analysis of early clinical response at 72 (-12/+36) hours in the ITT population of Oral Study 300

Subgroup	Solithromycin	Moxifloxacin	Difference	95% confidence interval
Prior therapy	42/53 (79.2%)	32/44 (72.7%)	6.5%	-12.7% to 25.7%
No prior therapy	291/373 (78.0%)	306/390 (78.5%)	-0.4%	-6.6% to 5.7%
Microbiological ITT	176/235 (74.9%)	178/226 (78.8%)	-3.9%	-12.0% to 4.3%
Not in mITT	157/191 (82.2%)	160/208 (76.9%)	5.3%	-3.1% to 13.7%
Clinically evaluable	307/388 (79.1%)	311/390 (79.7%)	-0.6%	-6.6% to 5.3%
Not clinical evaluable	26/38 (68.4%)	27/44 (61.4%)	7.1%	-16.0% to 30.1%
PORT Risk Class II	168/213 (78.9%)	175/217 (80.6%)	-1.8%	-9.8% to 6.3%
PORT Risk Class III	128/168 (76.2%)	130/177 (73.4%)	2.7%	-7.0% to 12.5%
PORT Risk Class IV	37/45 (82.2%)	33/40 (82.5%)	-0.3%	-16.8% to 16.2%

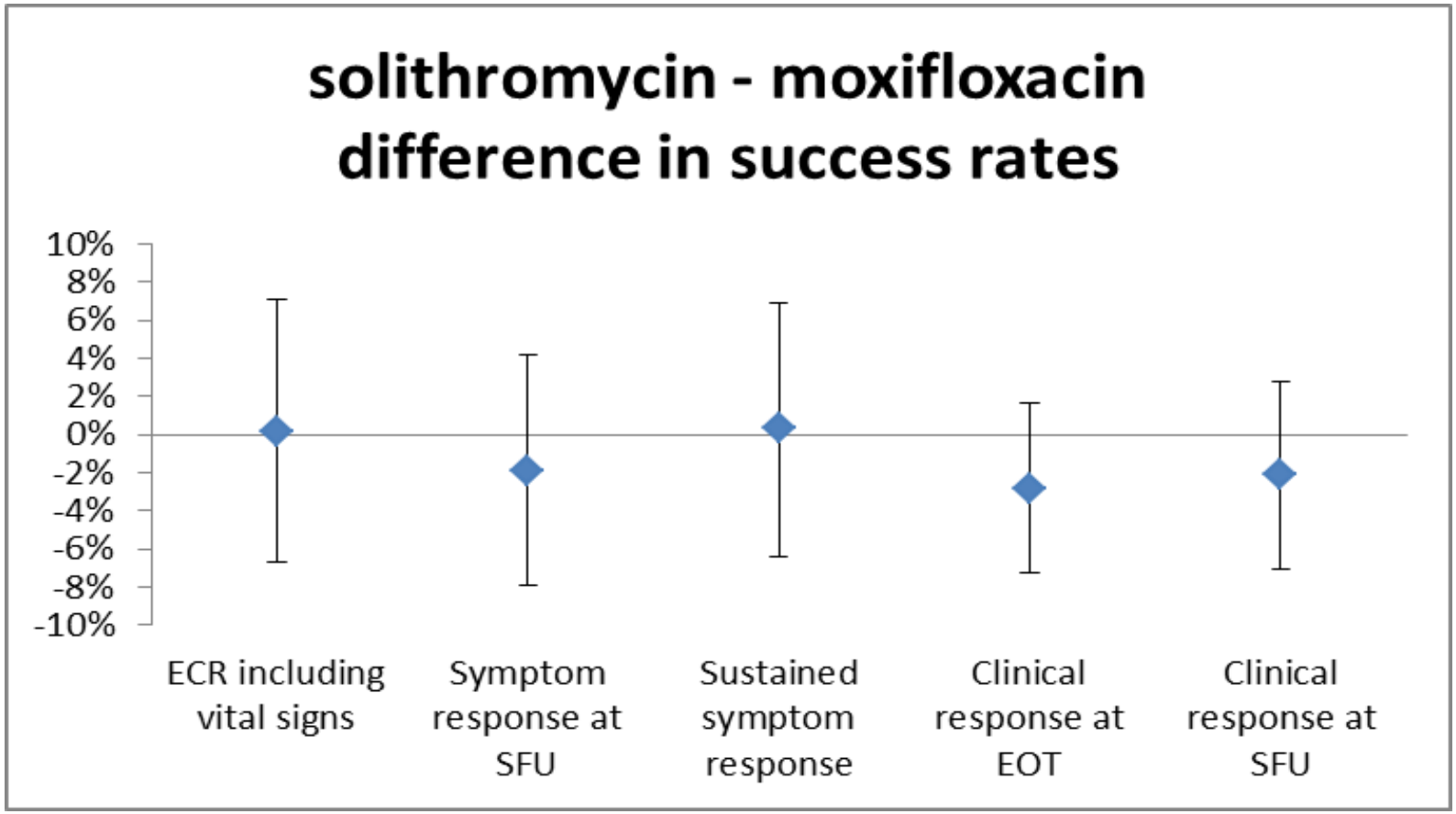
Analysis of Additional Endpoints in the ITT Population of Oral Study 300



Estimated treatment differences and confidence intervals for additional endpoints in the ITT Population of Oral Study 300

Favors solithromycin

Favors moxifloxacin



Subgroup analysis of investigator assessed clinical success at SFU (Day 12-17) in the ITT population of Oral Study 300

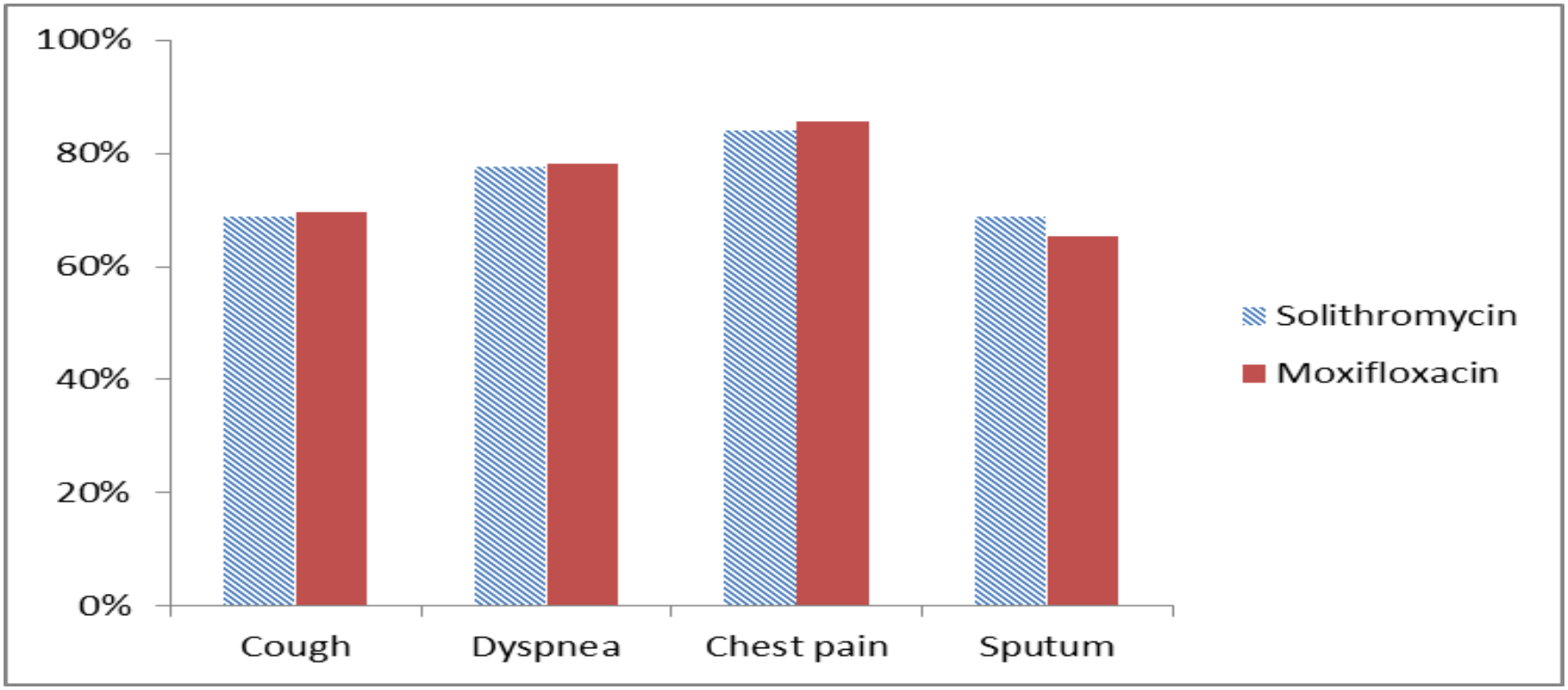
Subgroup	Solithromycin	Moxifloxacin	Difference	95% confidence interval
Prior therapy	42/53 (79.2%)	36/44 (81.8%)	-2.6%	-20.4% to 15.3%
No prior therapy	318/373 (85.3%)	340/390 (87.2%)	-1.9%	-7.1% to 3.2%
Microbiological ITT	197/235 (83.8%)	196/226 (86.7%)	-2.9%	-9.8% to 4.0%
Not in mITT	163/191 (85.3%)	180/208 (86.5%)	-1.2%	-8.5% to 6.1%
Clinically evaluable	342/388 (88.1%)	356/390 (91.3%)	-3.1%	-7.7% to 1.4%
Not clinical evaluable	18/38 (47.4%)	20/44 (45.5%)	1.9%	-21.6% to 25.5%
PORT Risk Class II	183/213 (85.9%)	193/217 (88.9%)	-3.0%	-9.8% to 3.7%
PORT Risk Class III	139/168 (82.7%)	151/177 (85.3%)	2.6%	-10.9% to 5.7%
PORT Risk Class IV	38/45 (84.4%)	32/40 (80.0%)	4.4%	-14.2% to 23.1%

Primary efficacy analysis of IV-to-oral Study 301

- Early clinical response at 72 (-12/+36 hours)
- ITT population, 10% non-inferiority margin
- Solithromycin demonstrated non-inferiority

	Solithromycin (n = 434)	Moxifloxacin (n = 429)	Difference	95% confidence interval
Responder	344 (79.3%)	342 (79.7%)	-0.5%	-6.1% to 5.2%
Nonresponder	76 (17.5%)	78 (18.2%)	-0.7%	
Indeterminate	14 (3.2%)	9 (2.1%)	1.1%	

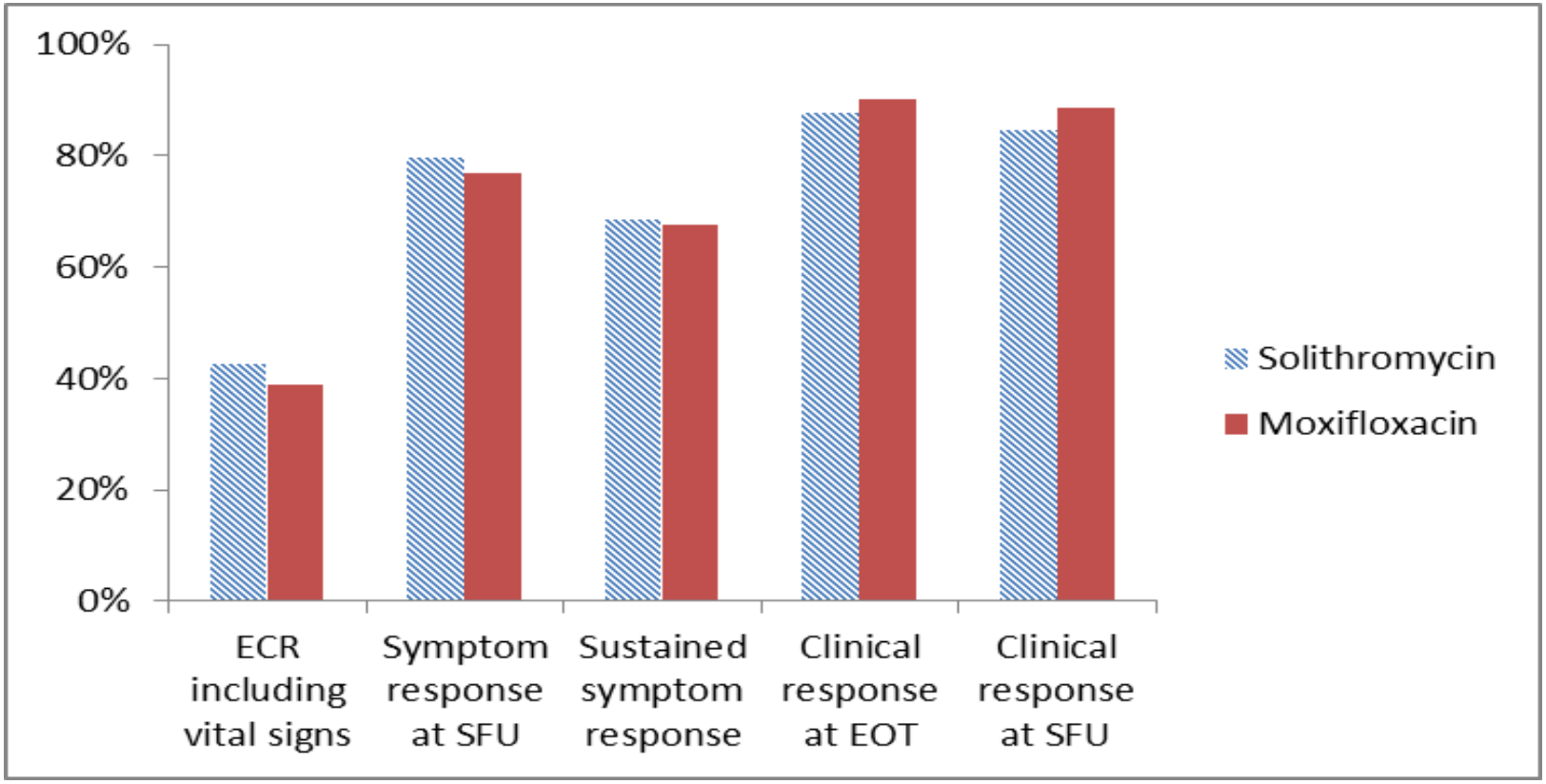
Symptoms absent or improved from baseline at the early clinical response visit at 72 (-12/+36) hours in the ITT Population of IV-to-oral Study 301



Subgroup analysis of early clinical response at 72 (-12/+36) hours in the ITT population of IV-to-oral Study 301

Subgroup	Solithromycin	Moxifloxacin	Difference	95% confidence interval
Prior therapy	82/102 (80.4%)	93/110 (84.5%)	-4.2%	-15.3% to 7.0%
No prior therapy	262/332 (78.9%)	249/319 (78.1%)	0.9%	-5.8% to 7.5%
Microbiological ITT	139/173 (80.3%)	121/153 (79.1%)	1.3%	-8.1% to 10.6%
Not in mITT	205/261 (78.5%)	221/276 (80.1%)	-1.5%	-8.8% to 5.7%
Clinically evaluable	314/391 (80.3%)	318/388 (82.0%)	-1.7%	-7.4% to 4.1%
Not clinical evaluable	30/43 (69.8%)	24/41 (58.5%)	11.2%	-11.5% to 34.0%
PORT Risk Class II	91/109 (83.5%)	82/107 (76.6%)	6.9%	-4.7% to 18.4%
PORT Risk Class III	174/215 (80.9%)	178/215 (82.8%)	-1.9%	-9.6% to 5.9%
PORT Risk Class IV	79/110 (71.8%)	82/107 (76.6%)	-4.8%	-17.4% to 7.7%

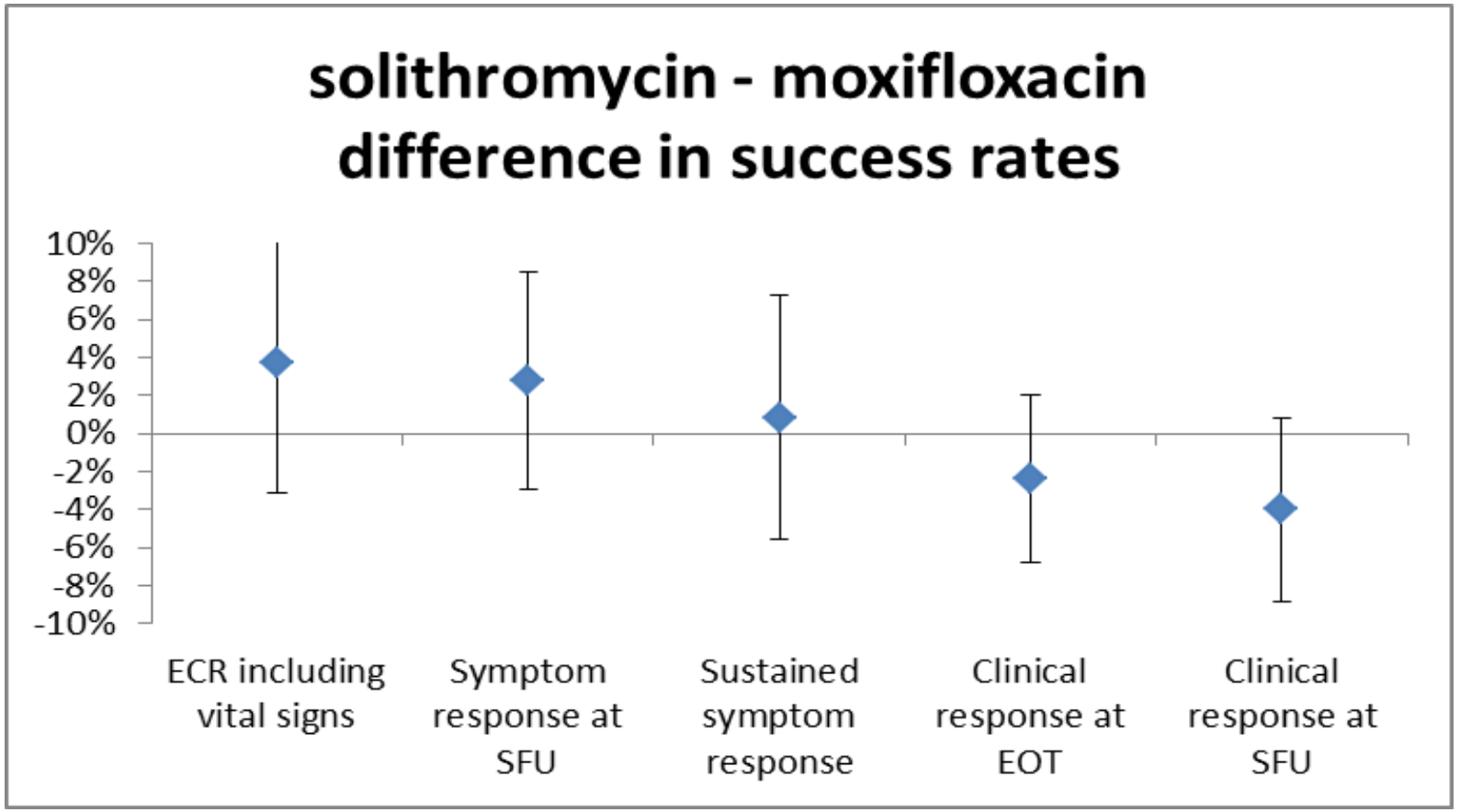
Analysis of Additional Endpoints in the ITT Population of IV-to-oral Study 301



Estimated treatment differences and confidence intervals for additional endpoints in the ITT Population of IV-to-oral Study 301

Favors solithromycin

Favors moxifloxacin



Subgroup analysis of investigator assessed clinical success at SFU (Day 12-17) in ITT population of IV-to-oral Study 301

Subgroup	Solithromycin	Moxifloxacin	Difference	95% confidence interval
Overall ITT				
Clinical success	367/434 (84.6%)	380/429 (88.6%)	-4.0%	-8.8% to 0.8%
Clinical failure	54/434 (12.4%)	35/429 (8.2%)	4.3%	0.0% to 8.6%
Indeterminate	13/434 (3.0%)	14/429 (3.3%)		
Prior therapy	87/102 (85.3%)	97/110 (88.2%)	-2.9%	-13.0% to 7.2%
No prior therapy	280/332 (84.3%)	283/319 (88.7%)	-4.4%	-9.9% to 1.2%
Microbiological ITT	144/173 (83.2%)	135/153 (88.2%)	-5.0%	-13.2% to 3.2%
Not in mITT	223/261 (85.4%)	245/276 (88.8%)	-3.3%	-9.4% to 2.7%
Clinically evaluable	338/391 (86.4%)	359/388 (92.5%)	-6.1%	-10.6% to -1.5%
Not clinical evaluable	29/43 (67.4%)	21/41 (51.2%)	16.2%	-6.9% to 39.3%
PORT Risk Class II	90/109 (82.6%)	97/107 (90.7%)	-8.1%	-18.0% to 1.8%
PORT Risk Class III	189/215 (87.9%)	194/215 (90.2%)	-2.3%	-8.7% to 4.0%
PORT Risk Class IV	88/110 (80.0%)	89/107 (83.2%)	-3.2%	-14.4% to 8.0%

Reasons for clinical failure at the Day 12-17 visit in the ITT population of IV-to-oral Study 301

		Solithromycin	Moxifloxacin
Clinical failure		54/434 (12.4%)	35/429 (8.2%)
Classified as failure at end of therapy, and failure was carried forward to the SFU visit		42/434 (9.7%)	31/429 (7.2%)
Reason for end of therapy failure classification	Lack of resolution or worsening of baseline signs and symptoms and required additional antibacterial medication	17/434 (3.9%)	10/429 (2.3%)
	Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication	9/434 (2.1%)	9/429 (2.1%)
	Study drug discontinued due to an adverse event and required additional antibacterial medication	15/434 (3.5%)	10/429 (2.3%)
Classified as failure at the SFU visit	Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication	15/434 (3.5%)	8/429 (1.9%)
Classified as failure due to death from any cause		4/434 (0.9%)	6/429 (1.4%)

Subjects could be failures at both EOT and SFU, which is why numbers in separate categories do not add to the total number of clinical failures

Co-primary efficacy analysis with weighted pooling of the Phase 3 trials in the microbiological ITT

- Early clinical response at 72 (-12/+36 hours)
- mITT population, 15% non-inferiority margin
- Solithromycin demonstrated non-inferiority

	Solithromycin (n = 408)	Moxifloxacin (n = 379)	Difference	95% confidence interval
Responder	315 (77.2%)	299 (78.9%)	-1.7%	-7.4% to 4.2%
Nonresponder	81 (19.9%)	72 (19.0%)		
Indeterminate	12 (2.9%)	8 (2.1%)		

Results in baseline pathogen subgroups

– Pooled mITT populations from Studies 300 and 301

Pathogen subgroup	Early clinical response (72 hours)		Clinical response at SFU (Day 12-17)	
	Solithromycin	Moxifloxacin	Solithromycin	Moxifloxacin
S. pneumoniae	135/175 (77.1%)	149/178 (83.7%)	146/175 (83.4%)	155/178 (87.1%)
Macrolide resistant	17/24 (70.8%)	17/22 (77.3%)	22/24 (91.7%)	19/22 (86.4%)
S. aureus	31/43 (72.1%)	22/30 (73.3%)	32/43 (74.4%)	27/30 (90.0%)
Macrolide resistant	3/7 (42.9%)	3/3 (100%)	5/7 (71.4%)	3/3 (100%)
H. influenzae	78/98 (79.6%)	61/75 (81.3%)	79/98 (80.6%)	68/75 (90.7%)
M. catarrhalis	26/32 (81.2%)	20/26 (76.9%)	27/32 (84.4%)	23/26 (88.5%)
L. pneumophila	61/79 (77.2%)	64/80 (80.0%)	71/79 (89.9%)	75/80 (93.8%)
M. pneumoniae	65/76 (85.5%)	56/72 (77.8%)	65/76 (85.5%)	65/72 (90.3%)
Macrolide resistant	1/1 (100%)	2/2 (100%)	1/1 (100%)	2/2 (100%)

Macrolide resistant *S. pneumoniae*: azithromycin MIC ≥2 mcg/mL or erythromycin MIC ≥1 mcg/mL

Efficacy Conclusions

- The Phase 3 Studies 300 and 301 provided evidence that solithromycin is effective for the treatment of CABP
  - Study designs were appropriate for assessing non-inferiority
  - Overall efficacy results were similar to moxifloxacin

Presentation of Clinical Safety

Antimicrobial Drugs Advisory Committee Meeting
November 4, 2016

Ramya Gopinath, M.D.
Medical Officer
Division of Anti-Infective Products
Center for Drug Evaluation and Research, FDA

Outline

- Overview of Clinical Development Program
- Safety Overview
- Discussion of Hepatotoxicity

Solithromycin Clinical Development Program

Trials	Solithromycin	Moxifloxacin/ Levofloxacin	Phase 1 Control	Total
Phase 1 Trials				
24 Trials	**554**	0	176	671*
Phase 2 and 3 Trials – Safety Populations				
CE01-200	**64**	68	N/A	132
CE01-300	**424**	432	N/A	856
CE01-301	**432**	426	N/A	858
Phase 2/3 Subtotal	**920**	926		
TOTAL	**1474**	926	176	2517

*Some subjects received both study drugs in some studies; only healthy subjects from the renal and hepatic impairment studies are included.

Safety Overview - Phase 3 Trials

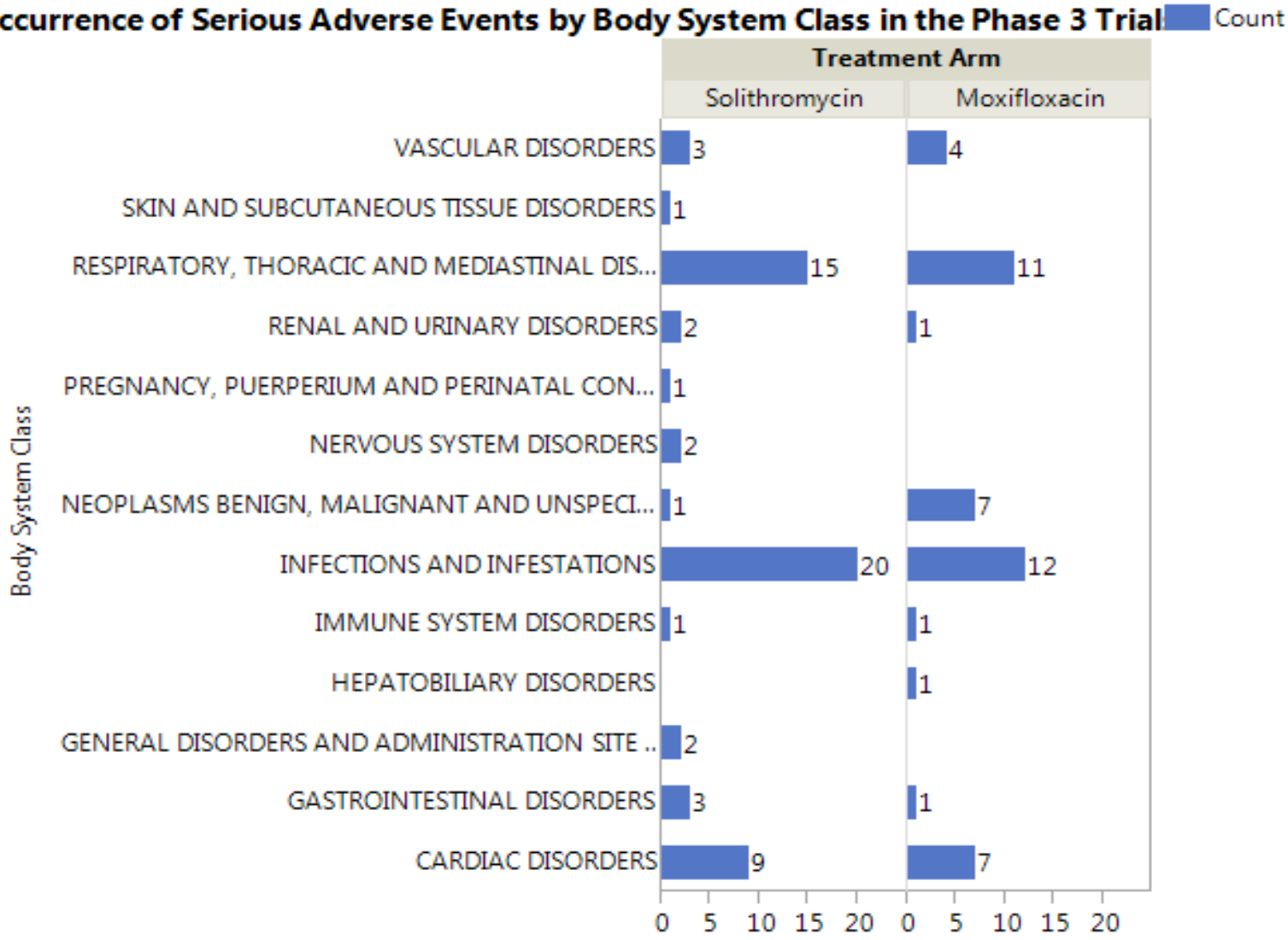
	Oral Study 300		IV to Oral Study 301	
	Soli N=424	Moxi N=432	Soli N=432	Moxi N=426
Premature Withdrawal from the Study	18 (4.2)	19 (4.4)	26 (6.0)	17 (4.0)
Premature Discontinuation of Study Drug	28 (6.6)	24 (5.6)	44 (10.2)	35 (8.2)
Adverse Event	16 (3.8)	13 (3.0)	21 (4.9)	17 (3.7)
Clinical Failure	6 (1.4)	5 (1.2)	14 (3.2)	8 (1.9)
Deaths	6 (1.4)	6 (1.4)	5 (1.2)	7* (1.6)
Serious Adverse Events	28 (6.6)	27 (6.3)	30 (6.9)	23 (5.4)

*2 patients died several months after the end of the study period and are not included here

Deaths in the Solithromycin Arm of Phase 3 Trials

- All deaths (n=11) were characterized as Clinical Failures
- All deaths were in patients with PORT III or IV class pneumonia; 7 were in patients >65 years
- 3 deaths appeared unrelated to solithromycin
- 81 yo woman – possible solithromycin-rivaroxaban interaction; death on Day 8
- 67 yo man – underlying hepatic/cardiac disease/abnormal ECG at baseline; possible ventricular arrhythmia resulting in sudden cardiac death on Day 3
- 6 patients – potential therapeutic failures

Occurrence of Serious Adverse Events in the Pooled Phase 3 Safety Population



Treatment-Emergent Adverse Events

	Study 300		Study 301	
	Soli N=424 n (%)	Moxi N=432 n (%)	Soli N=432 n (%)	Moxi N=426 n (%)
Subjects with TEAEs	155 (36.6)	154 (35.6)	223 (51.6)	148 (34.7)
TEAEs excluding IV infusion site reactions	155 (36.6)	154 (35.6)	149 (34.5)	140 (32.9)
TEAEs leading to premature drug discontinuation	16 (3.8)	13 (3.0)	25 (5.8)	17 (3.8)

Selected Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects in the Phase 3 Safety Populations

Preferred Term	CE01-300		CE01-301	
	Soli N=424 n (%)	Moxi N=432 n (%)	Soli N=432 n (%)	Moxi N=426 n (%)
Diarrhea	18 (4.2)	28 (6.5)	19 (4.4)	25 (5.9)
Nausea	15 (3.5)	17 (3.9)	14 (3.2)	7 (1.6)
Vomiting	10 (2.4)	10 (2.3)	4 (0.9)	3 (0.7)
Hypokalemia	2 (0.5)	3 (0.7)	11 (2.5)	9 (2.1)
Headache	19 (4.5)	11 (2.5)	15 (3.5)	18 (4.2)
Dizziness	9 (2.1)	7 (1.6)	11 (2.5)	5 (1.2)
Abdominal pain	9 (2.1)	10 (2.3)	3 (0.7)	4 (0.9)

Infusion Site Reactions in Study 301

Infusion-site reactions occurred in 31.3% of patients in the solithromycin arm vs. 5.2% of patients in the moxifloxacin arm

Preferred Term	Soli N=432 n (%)	Moxi N=426 n (%)
Infusion site erythema	19 (4.4)	2 (0.5)
Infusion site pain	45 (10.4)	6 (1.4)
Infusion site phlebitis	43 (10)	4 (0.9)
Infusion site thrombosis	9 (2.1)	7 (1.6)
Infusion related reaction	35 (8.1)	1 (0.2)

Ketolide-specific AEs

- **Exacerbation of Myasthenia Gravis (MG) -** Patients with MG were excluded from clinical trials
- **QT prolongation**
  - Patients on drugs known to prolong the QT interval were excluded from clinical trials
  - A thorough QT study was negative for QT prolongation but solithromycin-induced tachycardia was observed
- **Visual Disorders**
  - In Phase 1, there were two patients with blurry vision, and one with asthenopia ("tired eyes")
  - In the Phase 3 trials, 1 solithromycin patient saw "black spots"
- **Syncope** – 1 patient had syncope in Phase 3; 2 in the Phase 2 study
- **Hepatotoxicity**

Hepatotoxicity

FDA Guidance and Premarketing Evaluation of DILI

Hy's Law

Overview of Hepatotoxicity with Solithromycin

Structure-Activity Relationship

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Conclusions and Questions

FDA guidance for Premarketing Clinical Evaluation of Drug-Induced Liver Injury (DILI)*

- Drug-induced hepatocellular injury (excluding other causes) accompanied by jaundice can have a poor prognosis, with a roughly 10% rate of mortality or liver transplantation due to acute liver failure

- DILI has been one of the most frequent causes of safety-related drug marketing withdrawals for the past 50 years

- Only the most overt hepatotoxins are expected to show cases of severe DILI in 1,000-3,000 subjects

- Most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at frequencies ≤1 in 10,000

*http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

Premarketing Evaluation of DILI

Challenge: To distinguish drugs likely to cause severe DILI from drugs unlikely to do so

- The type of liver injury that leads to severe DILI is predominantly hepatocellular injury (ALT/AST elevation), especially when this injury is extensive enough to reduce the liver's functional ability to clear bilirubin or impact its synthetic function
- The finding of a higher rate of ALT elevations in drug-treated subjects than in a control group is a sensitive, though not specific, signal of potential to cause severe DILI
- A higher rate of more marked ALT elevations (10-15x Upper Limit of Normal [ULN] is more specific for severe DILI, though still limited
- The single most specific predictor for the potential of severe hepatotoxicity is…

Hy's Law

- ALT/AST elevation ≥3x ULN + total bilirubin (TBL) elevation >2x ULN, without:
  - Evidence of cholestasis
  - Any other cause of hepatic injury

- On the background of: higher incidence of hepatocellular injury caused by the drug (AST/ALT ≥3x ULN) compared with the control drug

- Such a drug is likely to cause severe DILI [resulting in liver failure or death] at a rate roughly 1/10th the rate of Hy's Law cases

Hy's Law

- If the true incidence of severe injury is 1/10,000, and the rate of Hy's Law cases is 1/1,000, about 3,000 exposed subjects (Rule of 3) would be needed to have a 95 percent probability of observing at least one Hy's Law case in the treated population*

- No known occurrences of "false positive" Hy's Law findings for a drug that was subsequently found NOT to cause severe DILI in a larger population

- Failure to find a Hy's Law case does NOT imply that a drug with aminotransferase elevations is free of a risk of severe DILI (depends on the size of the exposed population, time of exposure, discontinuation rules use in protocols, true incidence rate of severe DILI).

*Rosner 1995, The Binomial Distribution, Fundamentals of Biostatistics, Duxbury Press, Belmont CA

Challenges in Predicting DILI Risk In a 'Real World' Post-Marketing Population

- In clinical trial databases, DILI signals may be mild-moderate & show reversible toxicity
- Drug-specific DILI clinical signatures, as well as histopathologic & liver test profiles may differ among individuals
- Risk for severe DILI caused by a drug may be more concentrated in certain patient populations; this may be detected only when the drug is used in a heterogenous real-world population
- Drug-drug interactions in the setting of wide postmarketing use of a drug in combination with possibly less monitoring may lead to increased risk of severe DILI
- The manner in which a DILI signal of mild-moderate acute hepatocellular injury detected in a small clinical study population will 'play out' can only be determined in adequately powered clinical studies

Hepatotoxicity

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Hepatotoxicity - Solithromycin

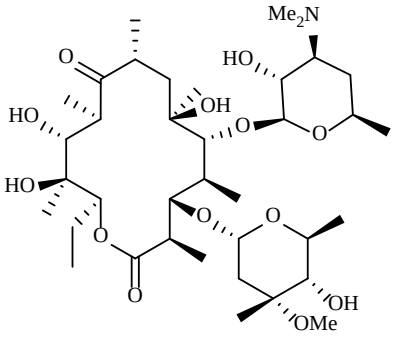
- Despite a limited safety database in the Phase 2 and 3 trials (n=920) and the non-CABP studies (n=10), a pronounced hepatic injury signal was seen

- A range of hepatic injury patterns - hepatocellular, cholestatic, and hypersensitivity was observed

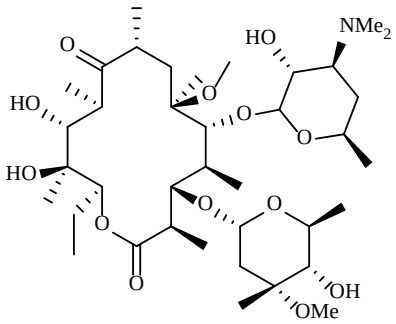
- There were no Hy's Law cases

- In 2 subjects in the Phase 3 trials, drug was stopped due to hepatic enzyme elevation

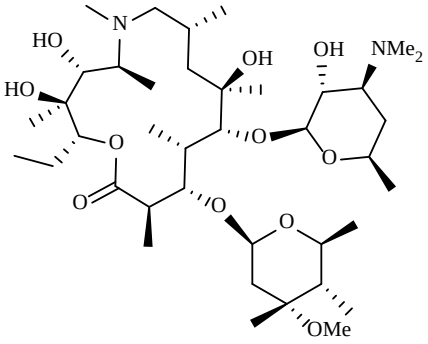
The Structure of Solithromycin in Comparison with Telithromycin and Older Macrolides



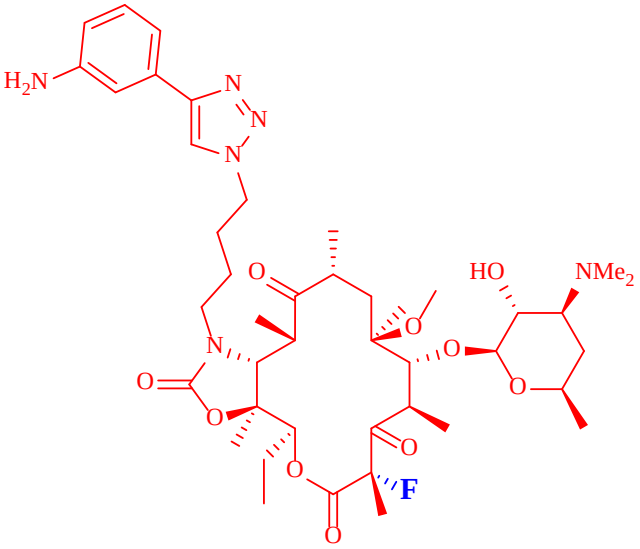
Erythromycin



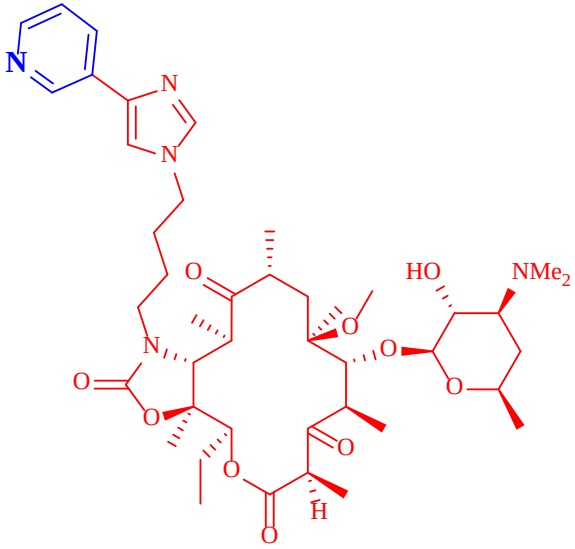
Clarithromycin



Azithromycin



Solithromycin



Telithromycin

Structure-Activity Relationship

- Quantitative structure-activity relationship (QSAR) of solithromycin was evaluated by the Division of Applied Regulatory Science at FDA; it was determined that solithromycin is 85% similar in structure to telithromycin and that hepatotoxicity would be expected with the use of solithromycin

- Computational modeling commissioned by Cempra using DILIsym® suggested that solithromycin may have a different mechanism of hepatic injury compared with erythromycin…but other possible mechanisms of injury, such as hypersensitivity, were not evaluated in the model

- A comparison of solithromycin with telithromycin using DILIsym® is ongoing

Hepatotoxicity

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Hy's Law

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Hepatotoxicity: Nonclinical Studies

- In rats and monkeys, solithromycin is widely distributed to tissues, and with repeated dosing, accumulates in the liver at much higher concentrations than in plasma (liver concentration was 1168x plasma concentration in monkeys after 13 weeks)
- The active metabolites N-acetyl-CEM-101 and CEM-214 account for significant levels of exposure in these animals; in humans, they account for <6% exposure following oral solithromycin administration
- Repeat-dose toxicity studies identified the liver as the primary target organ of toxicity with:
  - Biliary inflammation, centrilobular necrosis/degeneration and death observed in a 4-week oral rat study
  - Weight loss, centrilobular hepatocellular vacuolation, Kupffer cell hyperplasia and moderate increases in AST, ALT and GGT observed in a 13-week oral monkey study
  - Accumulation in lysosomes and phospholipidosis
- Determination of the human equivalent dose (HED) and threshold for toxicity is difficult due to accumulation of solithromycin in the liver and macrophages

Hepatotoxicity – Phase 1

- 41 of 550* (7.5%) healthy subjects exposed to solithromycin had ALT elevation > ULN in comparison to 2.3% of controls

- 2 (0.4%) of these healthy human volunteers discontinued solithromycin due to ALT elevation > 5x ULN
  1) 46 yo male received one dose of solithromycin 400 mg on Day 1

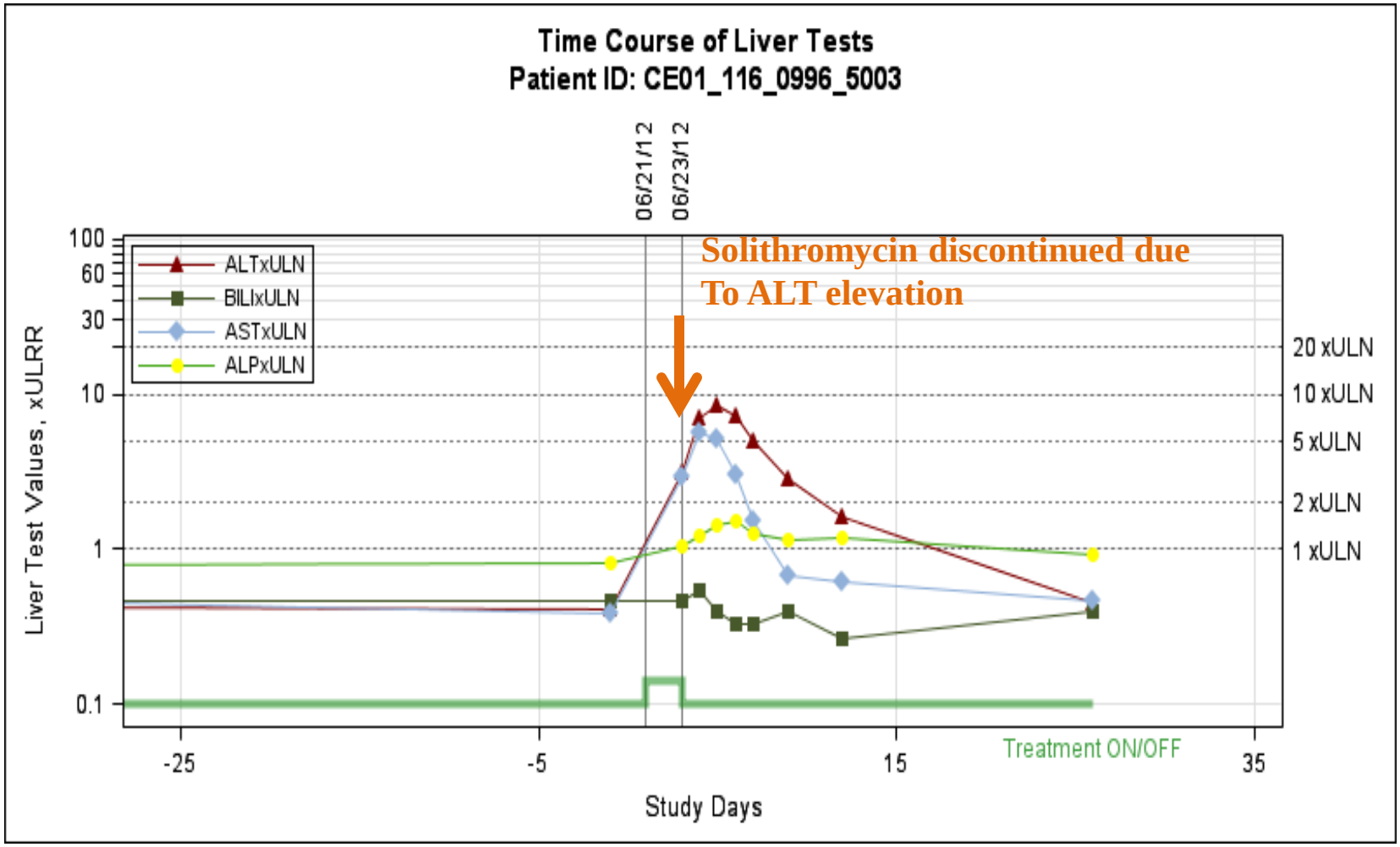
     Baseline: Normal ALT/AST

     Day 8: Max ALT 106 U/L (1.7x ULN) and max AST 240 U/L (5.1x ULN). Bilirubin/ALP were normal throughout. The subject was asymptomatic and AST/ALT returned to normal

*554 subjects were exposed to solithromycin in the Phase 1 studies; 550 subjects were used here per the Applicant's analysis

Hepatotoxicity – Phase 1

2) 36 yo healthy male volunteer received three 800 mg IV doses of solithromycin on Days 1-3.



Hepatotoxicity – Phase 2

- ALT elevation > 3x ULN:
  - 1 of 59 (1.7%) patients with a post-baseline value treated with solithromycin vs. 2 of 65 (3.1%) patients treated with levofloxacin. The solithromycin patient was hepatitis C antibody positive

- AST elevation > 3x ULN:
  - 2 of 59 (3.4%) solithromycin recipients vs. 1 of 65 (1.5%) moxifloxacin recipients

- Bilirubin elevation >2x<3x ULN in 1 (1.6%) patient (Gilbert's)

Hepatotoxicity – Phase 3 Trials

Hepatic enzyme	Degree of Elevation	CE01-300		CE01-301		Pooled Phase 3 Trials	
		Soli N=412 n (%)	**Moxi N=423 n(%)**	**Soli N=418 n(%)**	**Moxi N=415 n(%)**	**Soli N=830 n(%)**	**Moxi N=838 n(%)**
ALT	>ULN	**172 (41.7)**	**141 (33.3)**	**198 (47.4)**	**122 (29.4)**	**370 (44.6)**	**263 (31.5)**
	>3x ULN	**22 (5.3)**	**15 (3.5)**	**38 (9.1)**	**15 (3.6)**	**60 (7.2)**	**30 (3.6)**
	>5x ULN	**7 (1.7)**	**5 (1.2)**	**13 (3.1)**	**3 (0.7)**	**20 (2.4)**	**8 (0.9)**
	>10x ULN	1 (0.2)	2 (0.5)	0	0	1(0.1)	2 (0.2)
	>20x ULN	1 (0.2)	1 (0.2)	0	0	1(0.1)	1 (0.1)
AST		**Soli N=406 n(%)**	**Moxi N=416 n(%)**	**Soli N=416 n(%)**	**Moxi N=409 n(%)**	**Soli N=822 n(%)**	**Moxi N=825 n(%)**
	>ULN	130 (32)	112 (26.9)	154 (37)	97 (23.7)	**284 (34.5)**	**209 (25.3)**
	>3x ULN	**10 (2.5)**	**8 (1.9)**	**20 (4.8)**	**10 (2.4)**	**30 (3.6)**	**18 (2.2)**
	>5x ULN	**4 (1)**	**4 (1)**	**9 (2.2)**	**2 (0.5)**	**13 (1.6)**	**6 (0.7)**
	>10x ULN	2 (0.5)	2 (0.5)	2 (0.5)	0	4 (0.5)	2 (0.2)
	>20x ULN	0	1 (0.2)	0	0	0	1 (0.1)

Hepatotoxicity – Phase 3 Trials

Hepatic enzyme	Degree of Elevation	CE01-300		CE01-301		Pooled Phase 3 Trials	
Bilirubin		**Soli N=412 n(%)**	**Moxi N=422 n(%)**	**Soli N=416 n(%)**	**Moxi N=413 n(%)**	**Soli N=828 n(%)**	**Moxi N=835 n(%)**
	>ULN	15 (3.6)	16 (3.8)	21 (5.0)	17 (4.1)	36 (4.3)	33 (4)
	>2xULN	**2 (0.5)**	**0**	**2 (0.5)**	**2 (0.5)**	**4/828 (0.5)**	**2/835 (0.2)**
ALP		**Soli N=411 n(%)**	**Moxi N=423 n(%)**	**Soli N=417 n(%)**	**Moxi N=415 n(%)**	**Soli N=828 n(%)**	**Moxi N=838 n(%)**
	>1.5xULN	22 (5.4)	17 (4)	21 (5)	7 (1.7)	**43 (5.2)**	**24 (2.9)**
	>3.0xULN	4 (0.9)	1 (0.2)	0	1 (0.2)	**8 (1.0)**	**3 (0.4)**
	>5.0xULN	3 (0.7)	1 (0.2)	0	0	3 (0.4)	1 (0.1)
	>10xULN	0	0	1(0.2)	0	1 (0.1)	0

Time to ALT and AST Elevation

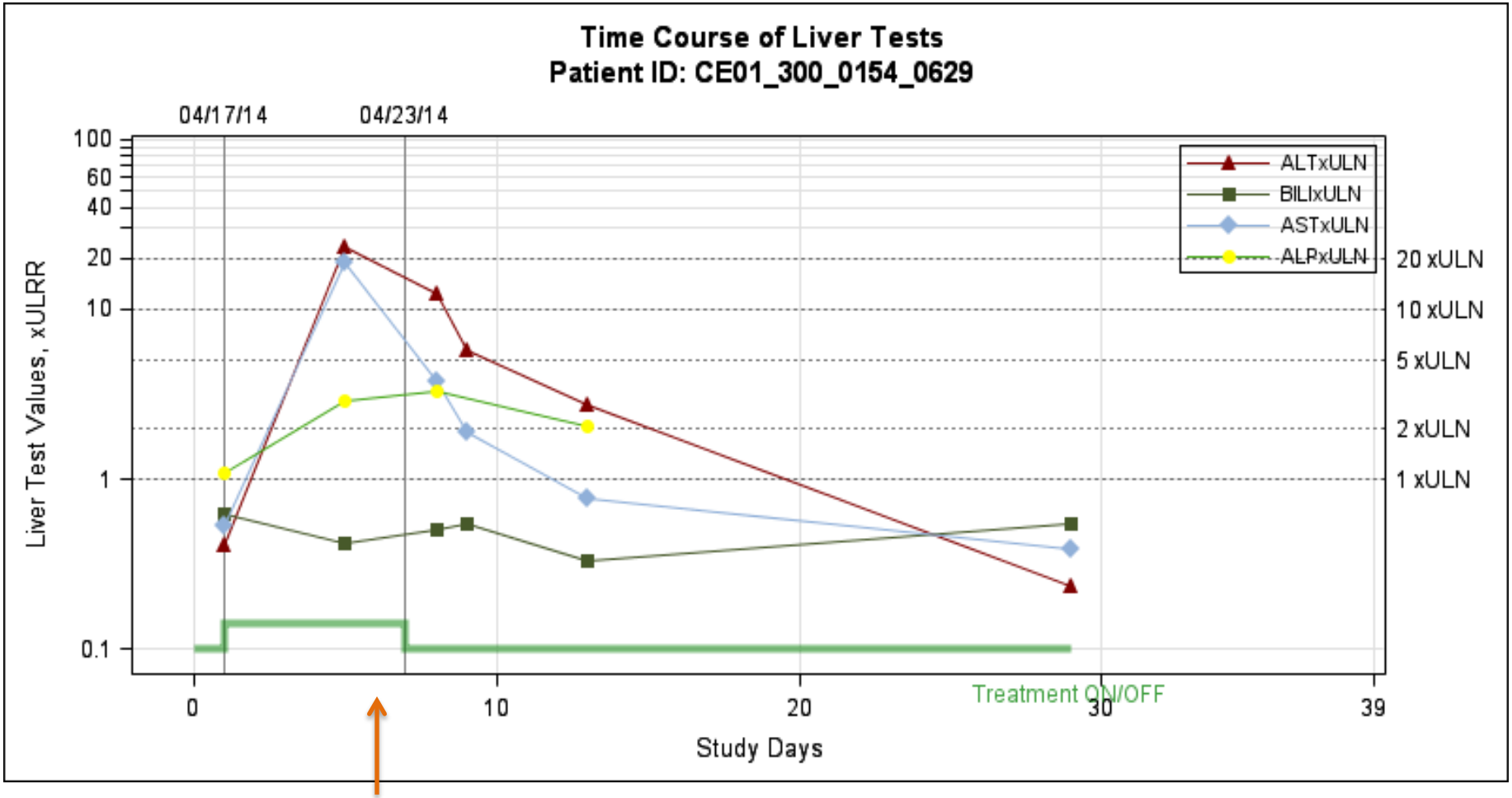
- In Study 300, 73% (16/22) of patients with ALT >3x ULN experienced the maximum ALT level (MAL) between Days 1 and 5 (NB: blood was drawn on Days 1 and 4), but 27% experienced the MAL between Days 6 and 15

- In Study 301, 50% (19/38) of patients with ALT >3x ULN experienced the MAL between Days 1 and 5, but 50% experienced it between Days 6 and 15

- 80% of maximum AST levels in patients with AST > 3x ULN occurred between Days 1 and 5

- Possible implications for monitoring hepatic enzymes in patients receiving treatment

Patient CE01-300-154-0629 – 65 year old woman



Solithromycin discontinued due to ALT/AST elevation

Hepatotoxicity - non-CABP Trials

Study	Solithromycin Dose	Treatment Duration	Patients with ALT elevation >3x ULN, n(%)
CE01-204: COPD N=4	400 mg PO daily	28 days	**3 (75)**
CE01-205: NASH N=6	Originally 400 mg PO daily. Protocol amended to 200 mg PO daily, with the option of 200 mg 3x/week, then amended again to 200 mg PO daily for 1 week, then 200 mg 3x/week	13 weeks	**1 (16.7)**

COPD Study/Subject 001: 69 yo Male with Cholestatic Hepatitis with Jaundice and Eosinophilia

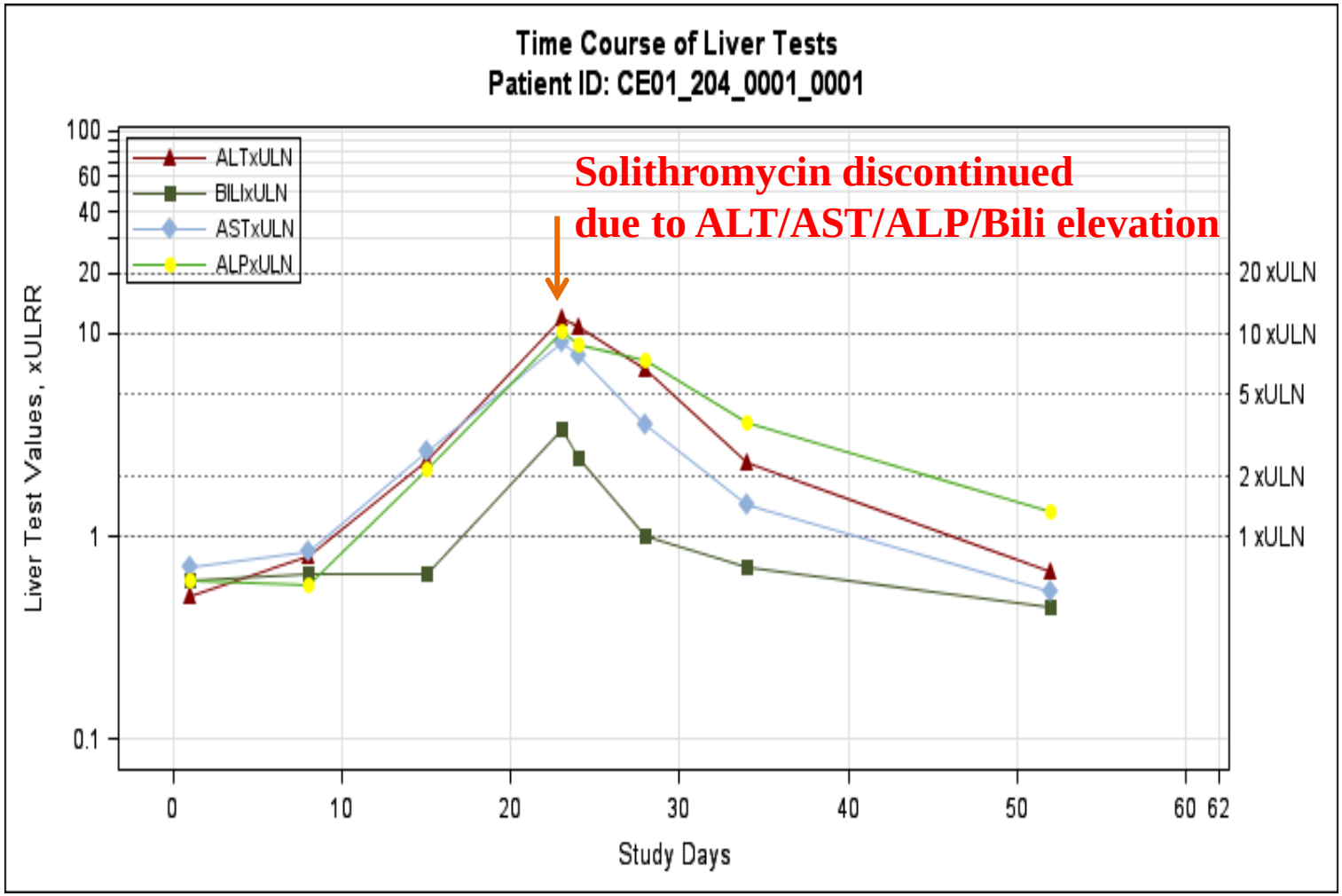
PMH: COPD and BPH; Medications: fluticasone-salmeterol/salbutamol inhalers and finasteride 5mg PO daily. Planned study treatment: Solithromycin 400 mg once a day for a 28-day course.

Liver Enzyme Measurements, Eosinophil Count and INR Over Time

Study Day	ALT		AST		Bilirubin		ALP		EOS	INR
	U/L	×ULN	U/L	×ULN	Total ULN:1.2 mg/dL	Direct ULN:0.4 mg/dL	U/L	×ULN	×10^3/µL	
1	20	0.5	29	0.7	0.7	0.2	78	0.6	0.3	
8	32	0.8	34	0.8	0.8	0.2	74	0.6	0.2	
15	95	1.4	106	2.6	0.8	0.3	277	2.1	0.4	0.9
23	**476**	11.9	**368**	9.0	**4**	2.2	**1316**	10.1	**1.6**	0.9
24	427	10.7	322	7.9	2.9	1.5	1155	8.9	**1.8**	1
28	269	6.7	144	3.5	1.2	0.5	969	7.5	1.2	
34	92	2.3	59	1.4	0.8		471	3.6	0.7	0.9
52	27	0.7	22	0.5	0.5	0.2	170	1.3	0.4	

Other investigations: Liver ultrasound normal, viral hepatitis screen negative

COPD Study/Subject 001 – Hepatic Enzyme Changes



Hepatotoxicity

Premarketing Evaluation of DILI

Hy's Law

Solithromycin Development Program

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A Few Words About Telithromycin

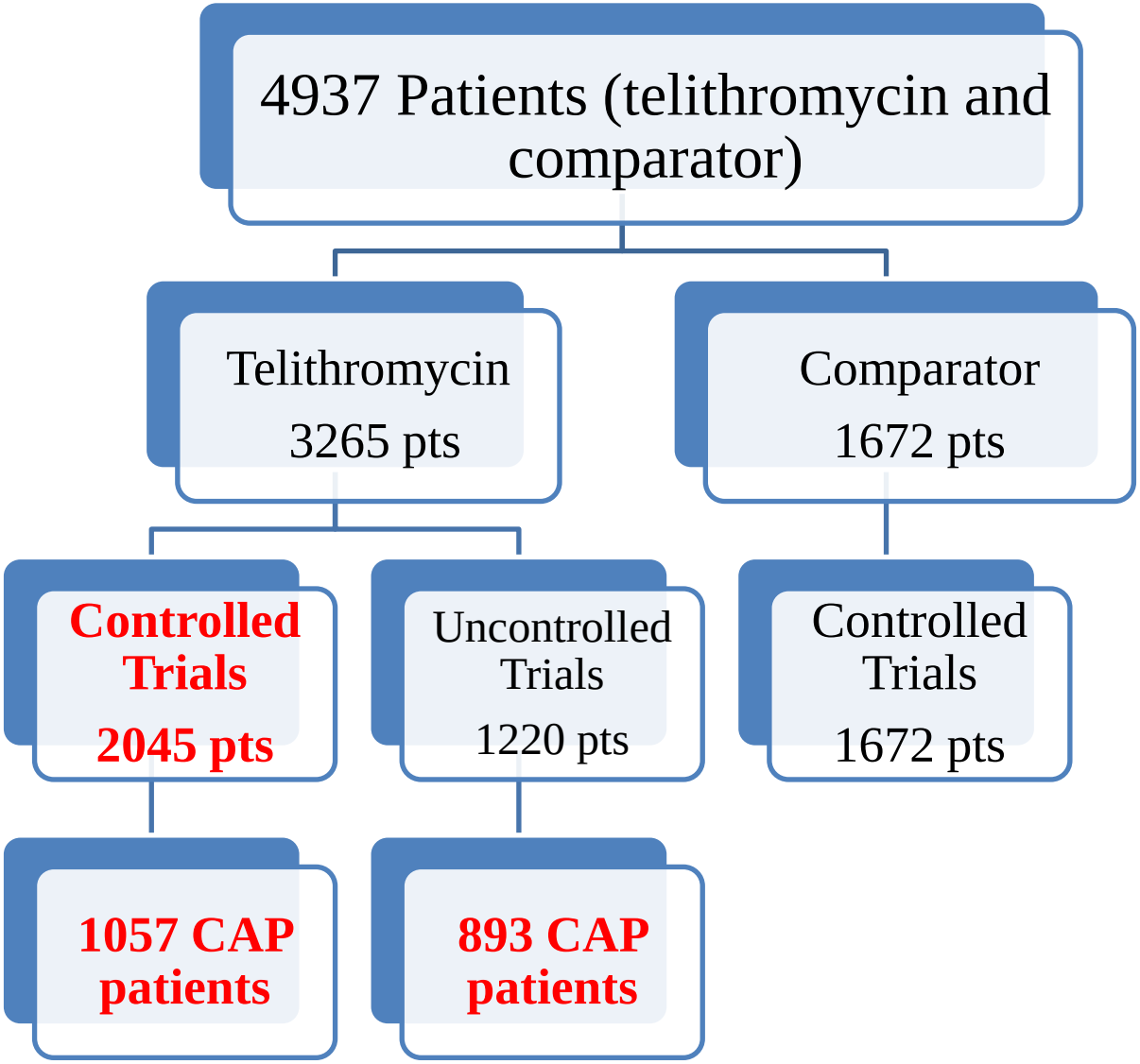
Conclusions and Questions

Telithromycin

- First-in-class ketolide
- Approved by FDA in 2004 for community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB) and acute bacterial sinusitis (ABS)
- Severe hepatotoxicity leading to hospitalization, death (n=4) and liver transplant (n=1) started to manifest soon after approval*
- 2006 – approved indications limited to CAP only
- Currently discontinued

* http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

Telithromycin – Phase 3 Safety Populations



Telithromycin - Hepatic Data

- Nonclinical
  - Hepatotoxicity in dogs, rats, monkeys

    (Increased AST & ALT; liver necrosis in 4-week rat study; hepatocellular hypertrophy, multinucleated hepatocytes)
- Phase I
  - Clustering of hepatic AEs in elderly at 2000 mg x1 (3 of 8 subjects)
  - No clear dose-response for hepatic AEs
- Phase III Controlled CAP Trials
  - Low ALT elevation rates were observed and were similar in the telithromycin and comparator arms
  - No telithromycin-induced hepatic deaths

ALT Elevation from Normal Baseline in the Pooled Phase 3 CAP Studies of Telithromycin*

Extent of Elevation	Teli N=395, n (%)	All Comp N=388, n (%)
≤ULN	309 (78.2)	317 (81.7)
>ULN ≤2x ULN	72 (18.2)	64 (16.5)
>2x to ≤3x ULN	10 (2.5)	4 (1.0)
>3x to ≤5x ULN	**3 (0.8)**	**2 (0.5)**
>5x to ≤10xULN	**1 (0.3)**	**1 (0.3)**
>15x to ≤20 x ULN	**-**	**-**
>20x ULN	**-**	**-**

*http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-144_Ketek_Medr_P7.pdf

Hepatotoxicity with Telithromycin*

- 42 cases of severe liver injury between 2004-2006
- Typical latency to onset of liver injury was rapid – median 10 days (range 2-43 days)
- Typical symptoms included abdominal pain, fatigue, weakness, jaundice, fever
- Primarily hepatocellular pattern of injury
- Abdominal pain was seen in 45% of cases; ascites in 17% of cases
- Recurrence of injury with re-exposure (n=4), suggesting hypersensitivity

*Brinker AD, Wassel RT, Lyndly J et al. Telithromycin-associated hepatotoxicity: Clinical Spectrum and causality assessment of 42 cases. Hepatology 2008; 49(1): 250-7

Hepatotoxicity of Other Antibacterials*

- Cholestatic hepatitis/mixed cholestatic and hepatocellular injury are seen across all macrolides
- The NIH LiverTox website provides estimated incidences of these AEs per 100,000 prescriptions
  - Erythromycin: 3.6/100,000
  - Clarithromycin: 3.8/100,000
- Often occurs 1-3 weeks after starting treatment; recovery within 4-8 weeks of stopping treatment
- Asymptomatic and transient aminotransferase elevation occurs at a low rate (1-2%)
- Hypersensitivity seems less common

*https://livertox.nih.gov/

Hepatotoxicity

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Conclusions – Solithromycin-related Hepatotoxicity

A pronounced hepatic injury signal is observed in a safety database of 920 patients who received a full therapeutic dose of solithromycin for 5-7 days for treatment of CABP

- Clear solithromycin exposure-ALT elevation relationship which appears to be dose- and duration-dependent

- Multiple toxicity patterns – hepatocellular, cholestatic, possible hypersensitivity

Conclusions – Solithromycin-related Hepatotoxicity

- No cases fulfilled Hy's Law criteria, but…

- Using the "Rule of 3's" in this limited database, the risk of serious DILI can only be capped at roughly 1:333. The likelihood of severe DILI is known to be much less than that; thus, this database is not large enough to accurately evaluate this risk

- The additional risk of increased exposure to solithromycin through factors such as increased duration of treatment, drug-drug interactions, concomitant illnesses, and unadjusted use in renal failure needs to be considered given the robust signal observed

- The risk of hypersensitivity – to older macrolides or solithromycin itself – and its role in severe solithromycin-related drug-induced liver injury (DILI) is unknown

Conclusions – Solithromycin-related Hepatotoxicity

- Aminotransferase signal for hepatotoxicity seen with solithromycin in the Phase 3 trials is greater than was seen with telithromycin in Phase 3 trials; telithromycin was associated with severe hepatic injury post-marketing

- Although exploratory computational modeling in DILIsym® may suggest that solithromycin does not have the same mechanism of hepatotoxicity as erythromycin and possibly telithromycin, the high observed incidence of hepatic injury in the relatively small Phase 3 safety database suggests the potential that solithromycin may trigger additional pathways associated with DILI, raising great concern for safety

Presentation of Clinical Pharmacology

Antimicrobial Drugs Advisory Committee Meeting
November 4, 2016

Yongheng Zhang, PhD
Clinical Pharmacology Reviewer
Office of Clinical Pharmacology
OTS, CDER, FDA

Outline

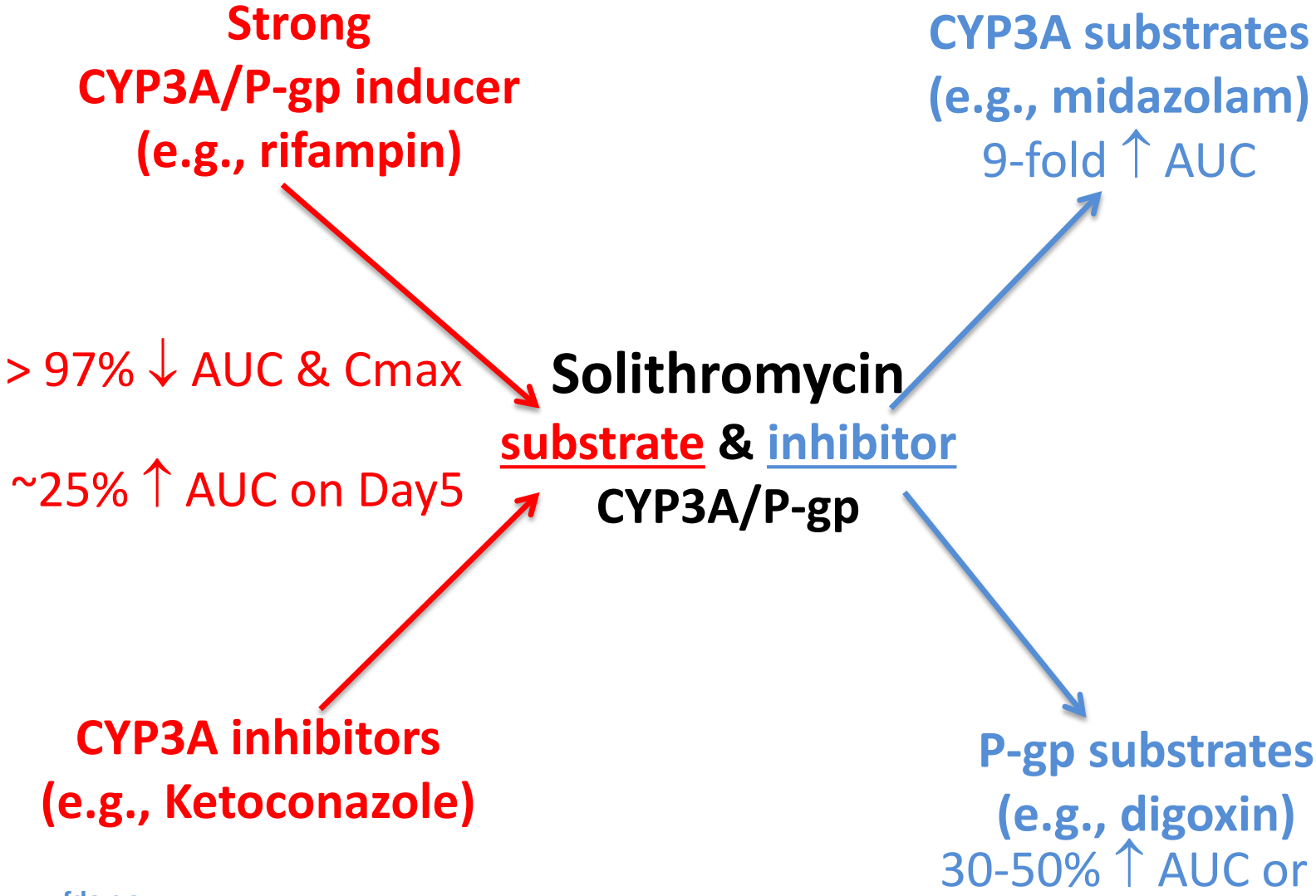
- Pharmacokinetics highlights
- Drug interactions
- Exposure-response (E-R) relationships for efficacy and safety
- Dosing considerations

Pharmacokinetics Highlights

ABSORPTION	DISTRIBUTION
• Absolute BA~ 62% (400 mg oral/IV) • No food effect • T_{max}: 2-4 hr	• Plasma protein binding (~81%) • Volume of distribution : ~400 L • Higher concentration in epithelial lining fluid (ELF) than in plasma
METABOLISM	**EXCRETION**
• CYP3A & P-gp substrate & inhibitor • Inhibits its own metabolism • In plasma: parent (major) & two metabolites (< 6 % of parent AUC)	• Terminal $T_{1/2}$~ 8.5 hr • Fecal ~77 % (mostly metabolites) • urinary ~14 % (10% parent)

- ✓ **PK nonlinear due to time-dependent inhibition of CYP3A & saturation of intestinal P-gp**
- ✓ **PK highly variable**
- ✓ **Higher exposure in CABP patients than in healthy subjects**

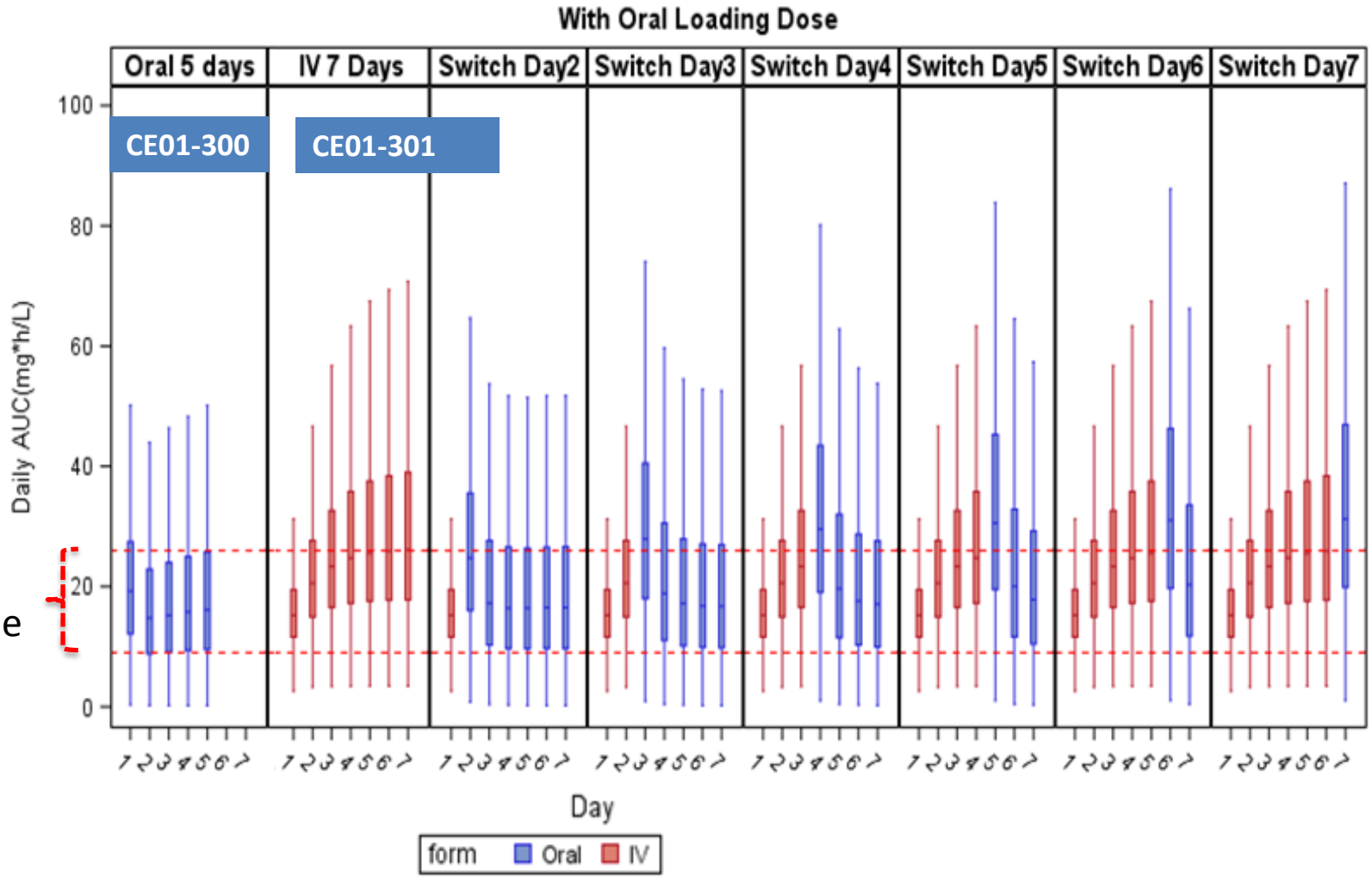
Drug Interactions



Outline

- Pharmacokinetics highlights
- Drug interactions
- Exposure-response (E-R) relationships for efficacy and safety
- Dosing considerations

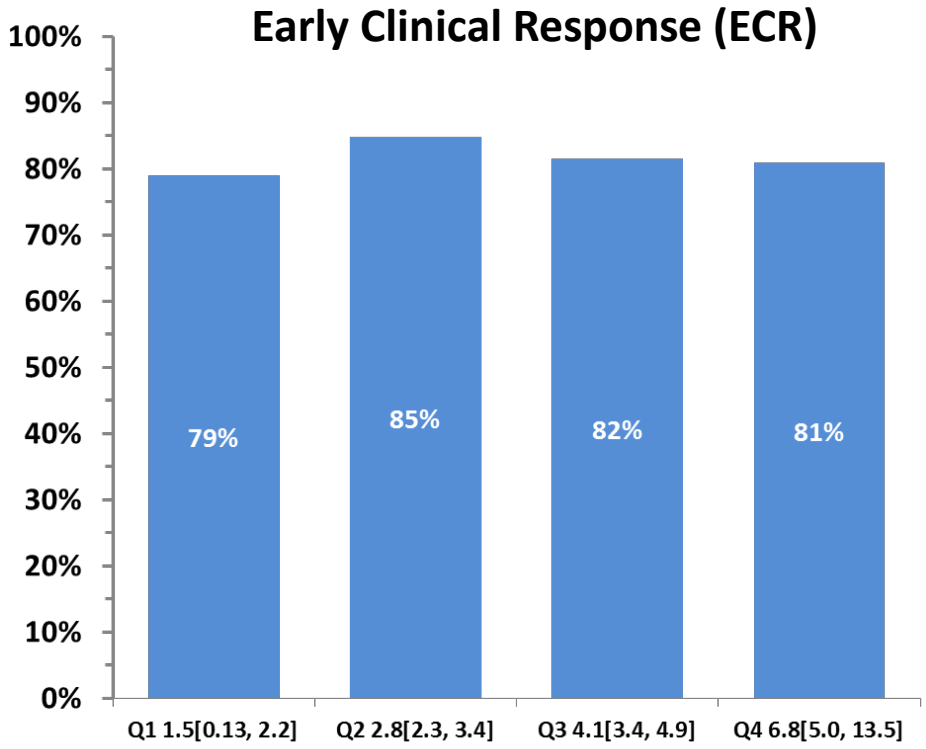
Daily Exposure Comparison by Dosing Regimens of Two Phase 3 Trials (CE01-300 & -301)



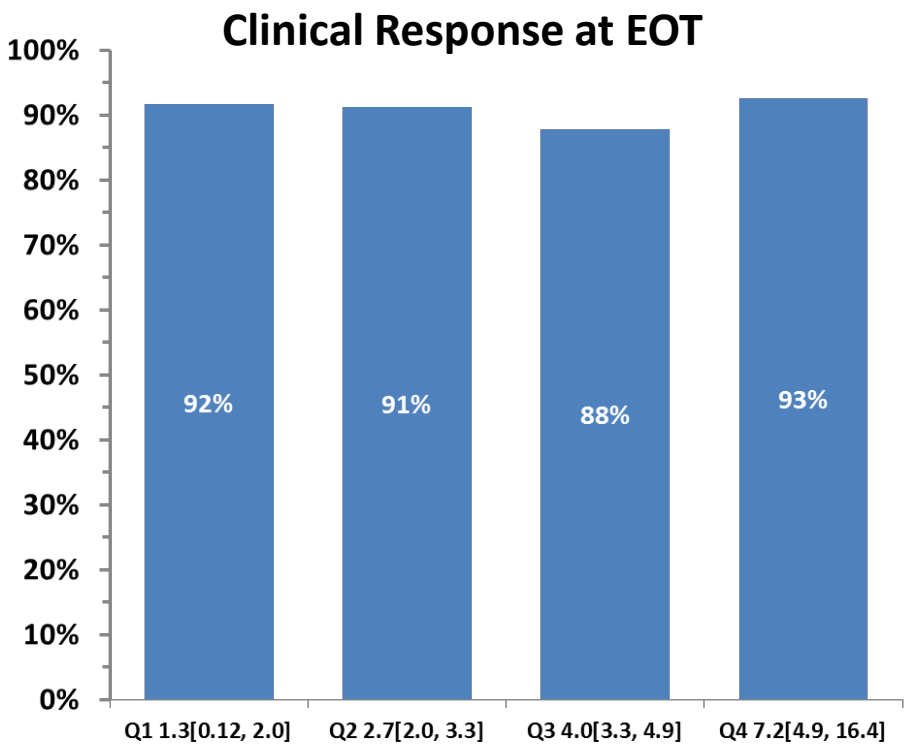
Day 5 AUC interquartile range

- ✓ **Longer treatment & higher daily exposure in CE01-301 (IV only & IV-to-oral) vs CE01-300 (Oral only)**

Exposure (AUC)-Response Relationship for Efficacy
(ITT population with PK info; n=817)



Average daily $AUC_{0\text{-}72h,\ free}$
Mean [min, max]

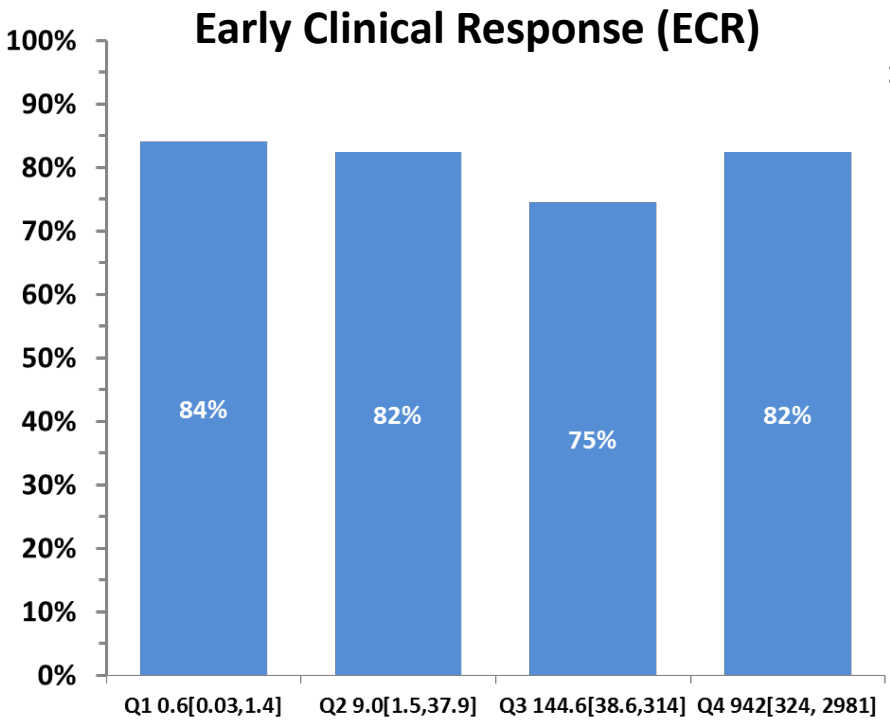


Average daily AUC_{free}
Mean [min, max]

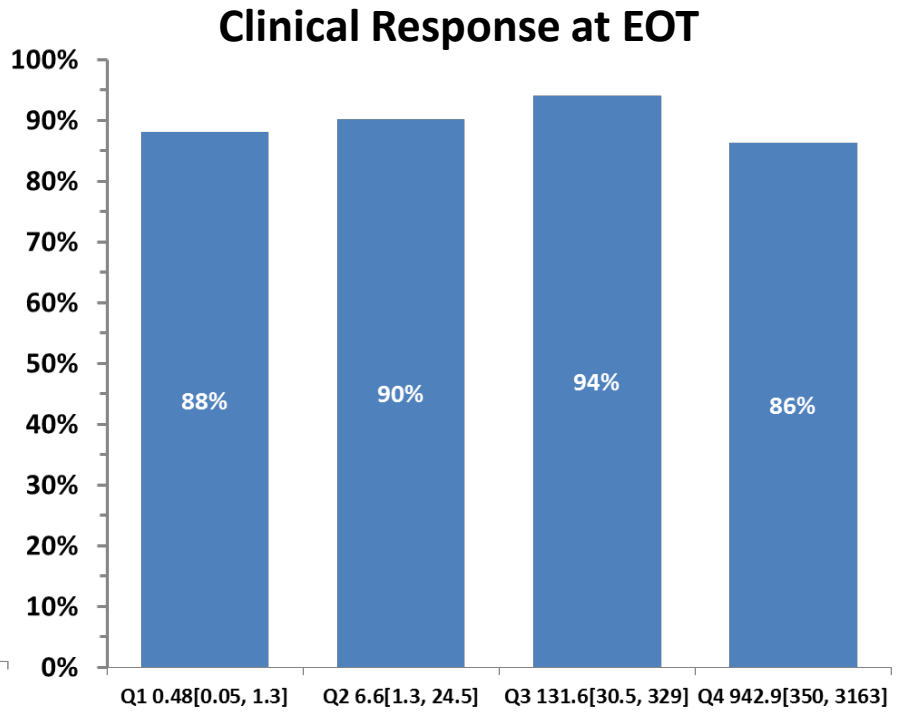
- ✓ Flat exposure-response relationship identified over the exposure range observed in Phase 3 trials

AUC:MIC-Response Relationship for Efficacy

(mITT population with both MIC and PK info, n=203)



Average daily $AUC_{0\text{-}72h,\ free}$: MIC mean[min, max]



Average daily AUC_{free}: MIC mean[min, max]

- ✓ **Flat AUC:MIC-response relationship identified over the AUC:MIC range observed in Phase 3 trials**

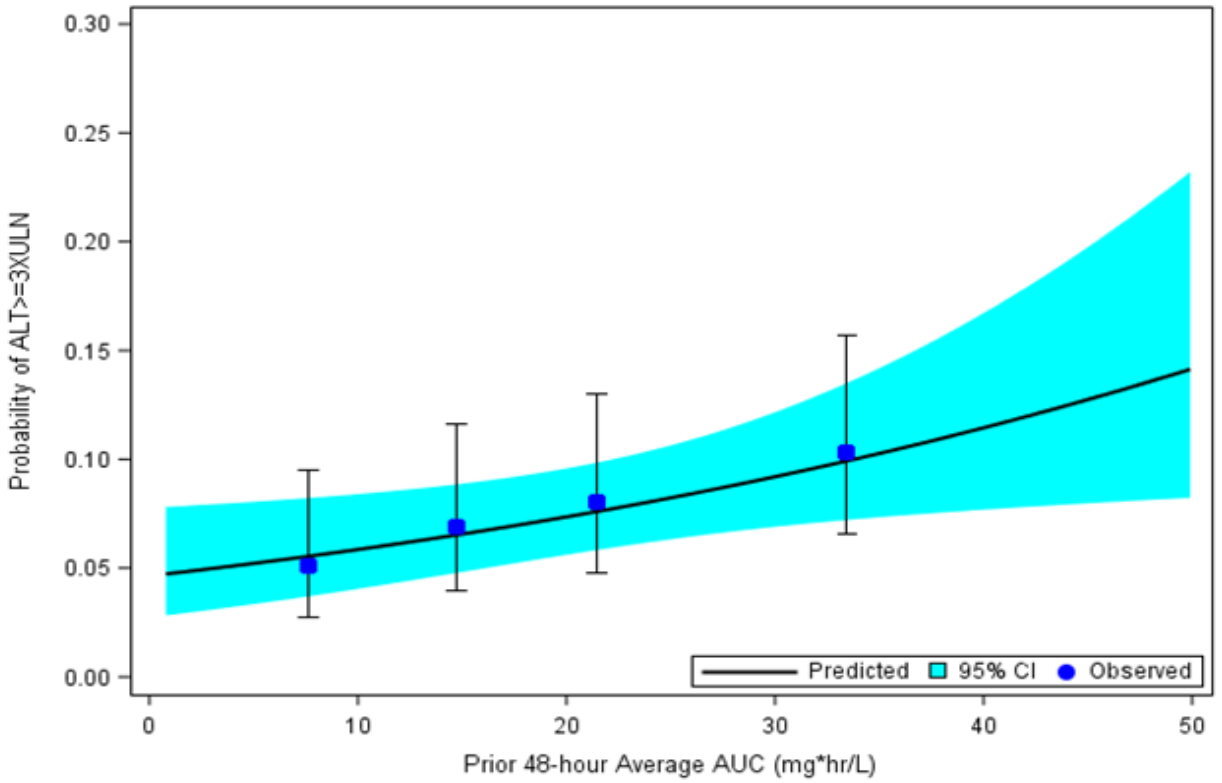
Safety: Incidence of ALT Elevation

	Study CE01-300		Study CE01-301	
ALT elevation*	Solithromycin Oral n/N (%)	Moxifloxacin Oral n/N (%)	Solithromycin IV to Oral n/N (%)	Moxifloxacin IV to Oral n/N (%)
≥ 3×ULN	22/412 (5.3%)	15/423 (3.5%)	38/418 (9.1%)	15/415 (3.6%)
≥ 5×ULN	7/412 (1.7%)	5/423 (1.2%)	13/418 (3.1%)	3/415 (0.7%)

* ALT measured at baseline (Day -1 or 1), Days 4, 7 and 12-17.

- Phase 1: Dose escalation studies in phase 1 identified ALT elevation as a dose limiting factor
- Phase 3: Overall higher daily exposure and longer treatment in CE01-301 vs CE01-300

E-R Relationship for Probability of ALT ≥3×ULN

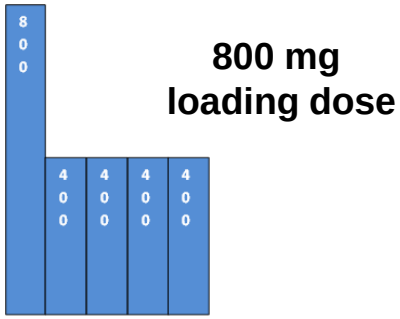
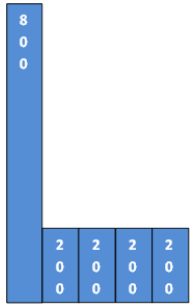
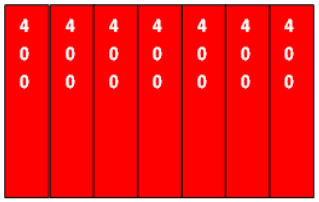
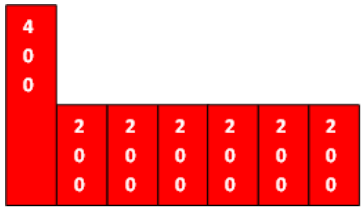
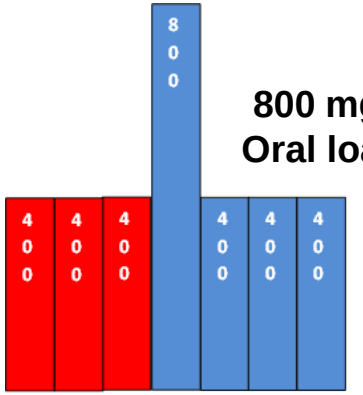
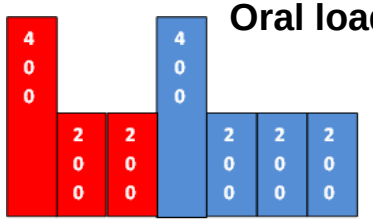


- ✓ **The increase in the incidence of ALT elevation was associated with the increase in solithromycin exposure (i.e., AUC)**

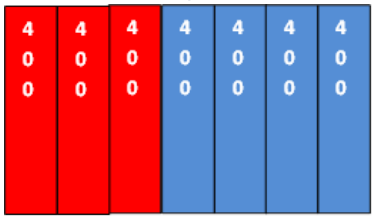
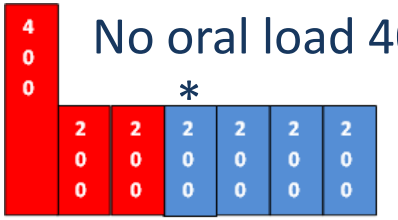
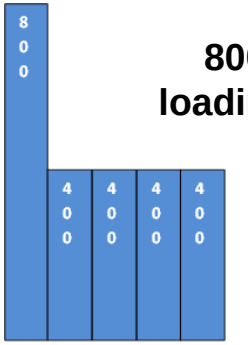
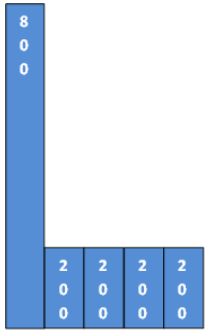
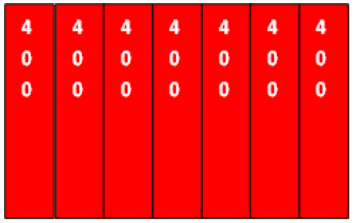
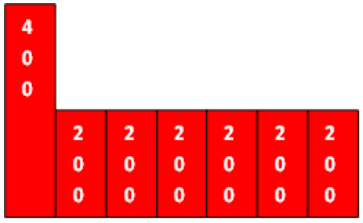
Outline

- Pharmacokinetics highlights
- Drug interactions
- E-R relationships on efficacy and safety
- Dosing considerations

Dosing Regimens Proposed by the Applicant

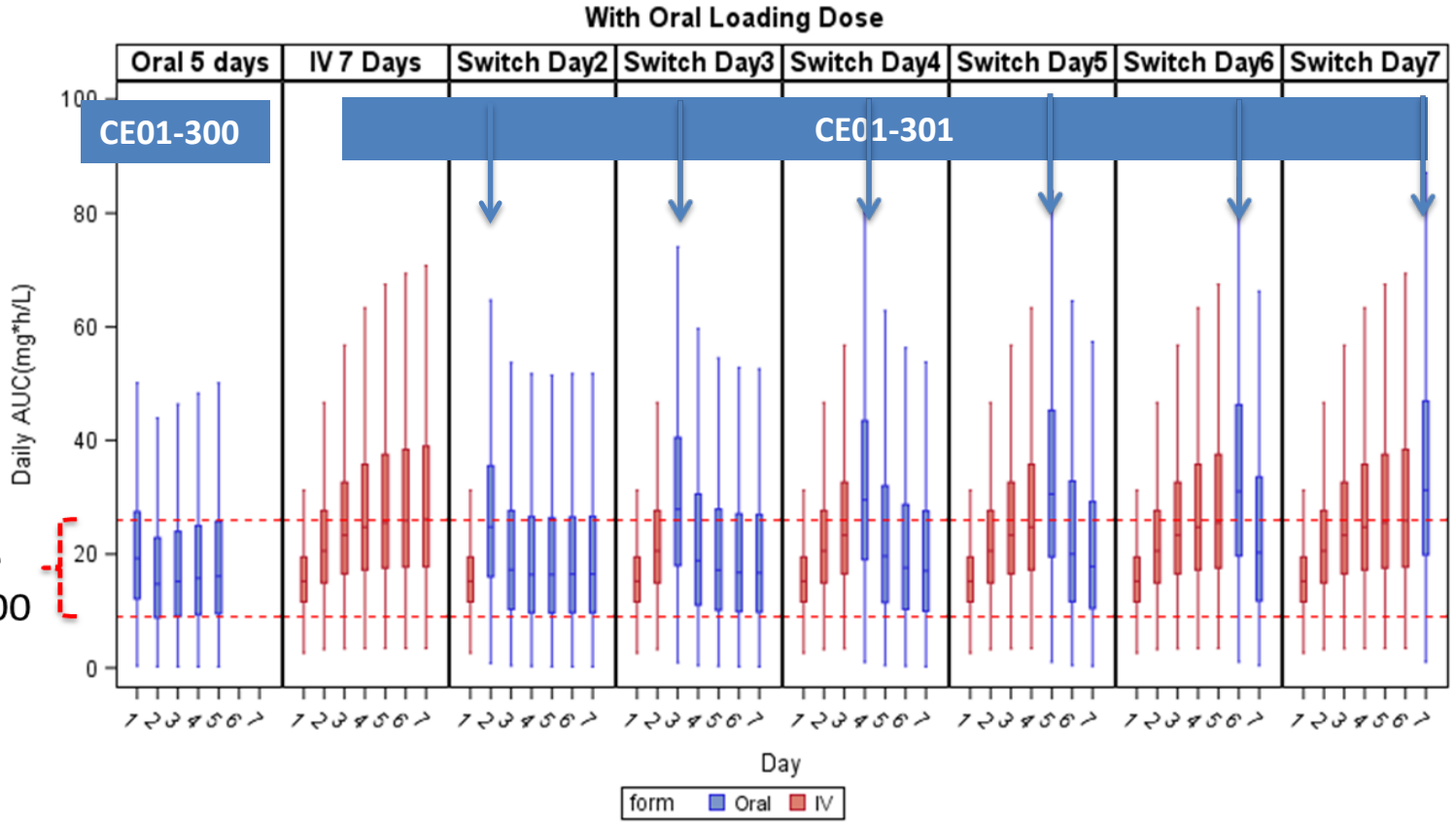
	Clcr ≥ 30 mL/min	Clcr < 30 mL/min
Oral-only 5 days	 **800 mg loading dose**	
IV-only 7 days		
IV-to-Oral 7 days	 **800 mg Oral load**	 **400 mg Oral load**
	Dosing regimens studied in phase 2 & 3 trials	Based on dedicated renal impairment PK study, Pop PK & PBPK model predictions

Dosing Considerations
(Remove oral load in IV-to-oral dosing regimen)

	Clcr ≥ 30 mL/min	Clcr < 30 mL/min
IV-to-Oral 7 days Alternative	No oral load 800 mg * 	 No oral load 400 mg *
Oral-only 5 days	 **800 mg loading dose**	
IV-only 7 days		

Dosing Considerations

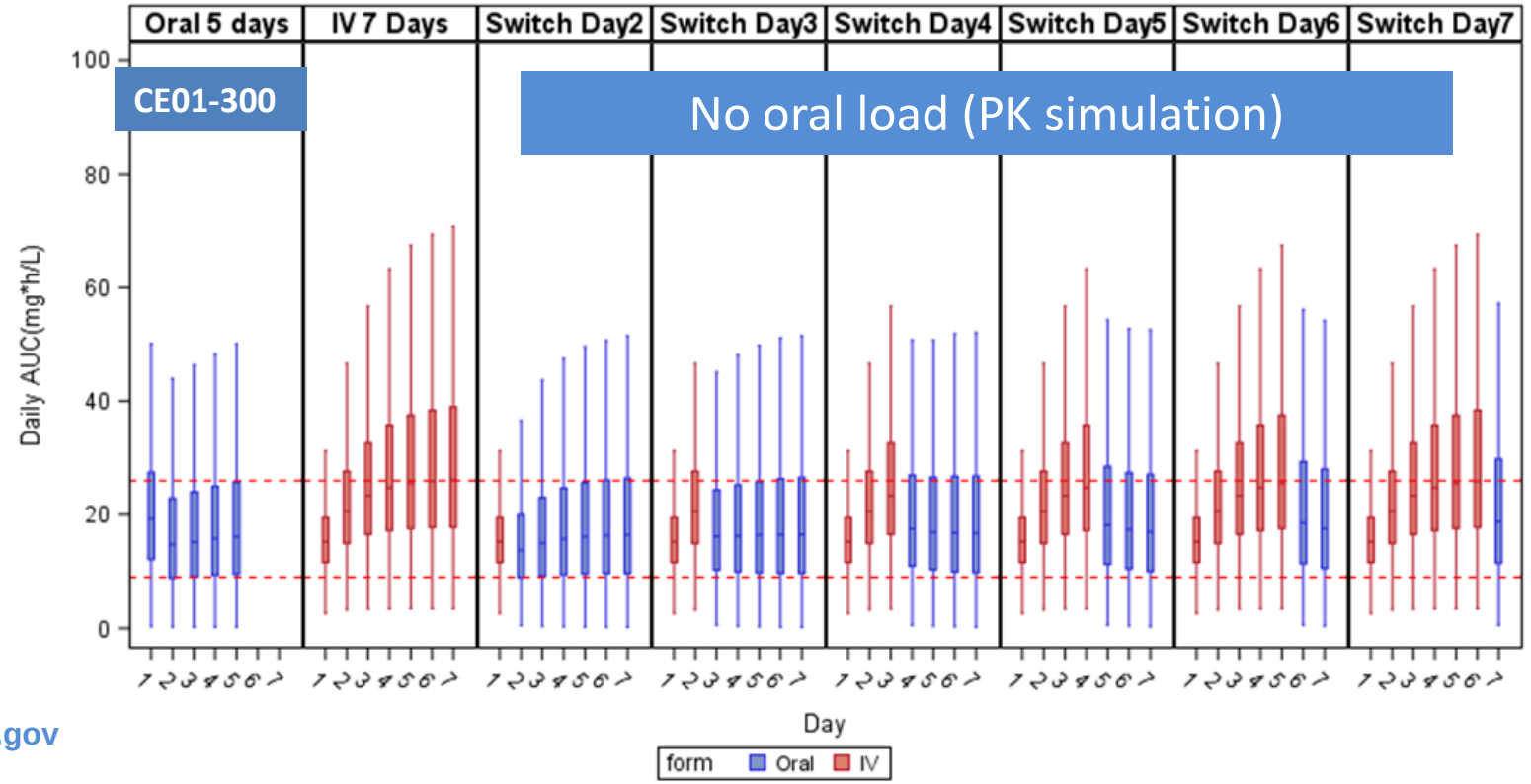
- **Remove oral load in IV-to-oral may potentially reduce the increased risk of ALT elevation in Study CE01-301**
  - ✓The oral load resulted in the highest daily AUC on the day of switch
  - ✓This oral load, along with the IV dose and longer treatment, may have contributed to the increased incidence of ALT elevation observed in CE01-301 (Exposure –ALT elevation relationship)



Day 5 interquartile AUC in 01-300

Dosing Considerations
(Remove oral load in IV-to-oral dosing regimen)

- **Efficacy not expected to be compromised**
  - ✓ Patients can transition with 400 mg instead of 800 mg oral load and still maintain daily AUC at or exceeding Day 5 AUC observed in CE01-300, which was shown to be efficacious



Dosing Considerations
(Remove oral load in IV-to-oral dosing regimen)

- Potentially mitigate the risk of ALT elevation in IV-to-oral
- Efficacy not expected to be compromised
- **The alternative IV-to-oral dosing regimen is simpler than the original proposal, therefore, may help reduce the potential for dosing errors**

Summary

- ADME & PK highlights
  - ➢ no food effect, higher ELF exposure, nonlinear PK, and high PK variability
- Drug interactions
  - ➢CYP 3A & P-gp substrate/inhibitor
- E-R relationships for efficacy and safety
  - ➢ Exposure –ALT elevation
- Dosing considerations
  - ➢ Remove oral load in IV-to-oral dosing regimen

Thank You!