

CONTEPO™ (fosfomycin for injection)
ICD-10 Coordination and
Maintenance Committee Update
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Matthew Helgeson, PharmD, BCPS
Senior Medical Science Liaison, Medical Affairs
Nabriva Therapeutics

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Nabriva
THERAPEUTICS

NABRIVA DISCLAIMER

CONTEPO™ IS A DRUG CANDIDATE THAT IS NOT CURRENTLY APPROVED BY THE FDA. NABRIVA THERAPEUTICS FILED AN NDA WITH THE FDA ON OCTOBER 31, 2018.

THIS CLINICAL PRESENTATION IS BASED ON THE RESULTS OF THE ZEUS CLINICAL TRIAL, AS WELL AS ADDITIONAL PUBLICLY-AVAILABLE DATA AND INFORMATION. THE MATERIAL CONTAINED HEREIN IS STRICTLY LIMITED TO SCIENTIFIC AND NON-PROMOTIONAL USE FOR THE ICD-10 COORDINATION AND MAINTENANCE COMMITTEE MEETING ON MARCH 5-6, 2019 IN SUPPORT OF A NEW ICD-10-PCS ADMINISTRATION CODE CONTEPO FOR FY 2020.

CONTEPO™: The First-in-Class IV Epoxide Antibiotic in the US

Proven Activity Against Clinically Relevant MDR Pathogens, Providing a Critically Needed Alternative for the Treatment of cUTI, Including Pyelonephritis

Key Attributes of CONTEPO

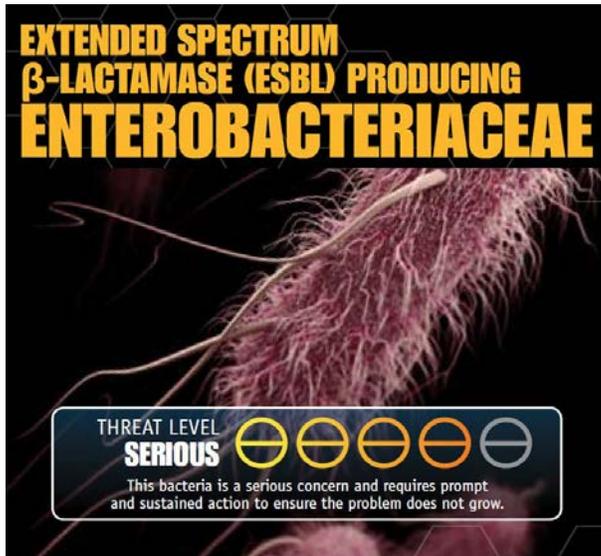
- New antibiotic in US with unique mechanism of action
- IV formulation and sole member of the epoxide antibiotic class
- Broad spectrum of *in vitro* activity against a variety of clinically relevant MDR pathogens
 - Extended-spectrum beta-lactamase [ESBL]-producing Enterobacteriaceae
 - Carbapenem-resistant Enterobacteriaceae [CRE]
 - Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci
- *In vitro* additivity or synergy in combination with other antibiotic classes
- Small molecular size enabling high tissue concentrations and renal elimination, important for treatment of cUTI
- Designated by FDA as a Qualified Infectious Disease Product (QIDP) with Fast Track review
- NDA filed October 31, 2018 with PDUFA date prior to July 1, 2019
 - NDA based on pivotal clinical trial (ZEUS) in cUTI, which met the primary endpoint by demonstrating non-inferiority to piperacillin-tazobactam

Coding Issue Overview

- There are currently no ICD-10-PCS codes that uniquely describe CONTEPO administration
 - A unique ICD-10-PCS Section X code is needed:
 - To identify CONTEPO in order to facilitate billing and reporting purposes
 - To identify and track the use of CONTEPO for the treatment of cUTI or AP and related outcomes data
 - If NTAP is granted, for claims processing and payment adjustments for qualifying cases of CONTEPO
- Nabriva submitted an NTAP application for CONTEPO for fiscal year 2020
- Information on the administration of CONTEPO could be found in the patient's medical record or pharmacy ordering forms in order to code and bill appropriately

ESBL producing and Carbapenem Resistant Enterobacteriaceae are “Priority Pathogens”

High morbidity and mortality due to lack of effective therapy



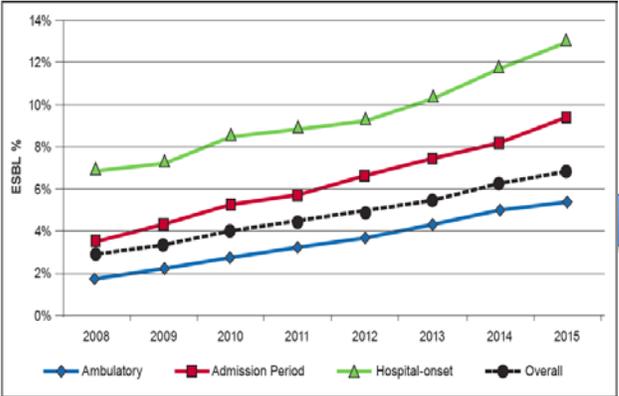
- Antibiotic resistant infections increasing rapidly¹
- Limited *or no effective* treatment options²
- High morbidity and mortality³
- Serious threat for hospitalized patients
- Significant burden to healthcare system and society⁴



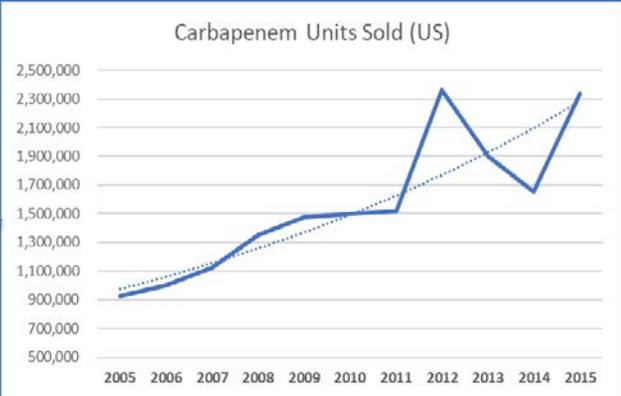
1. The Surveillance Network database CDDEP.org Resistance Map; Braykov et al 2013
2. CDC Antibiotic Resistance Threats in the United States 2013
3. Tzouveleki et al., Clin Microbiol Rev. 2012 Oct;25(4):682-707
4. Bartsch et al. Clin Microbiol Infect 2016; Sept 15

Resistance is a Growing Concern in the Treatment of Gram Negative Infections Leading to Increased Use of Carbapenem Antibiotics

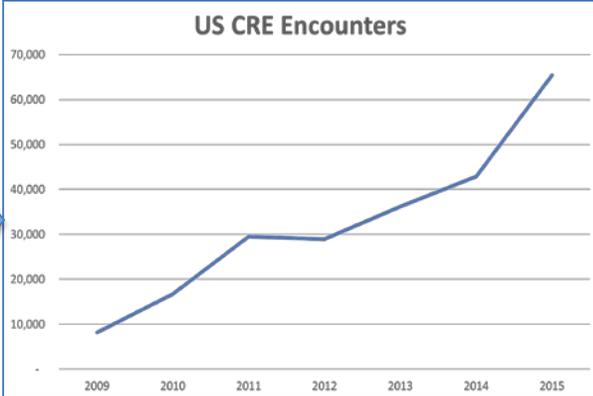
- Increased ESBLs have led to an increased reliance on carbapenem therapy



ESBL resistance rates increased steadily from 2008 through 2015 in ambulatory, admission, and hospital settings in the U.S. with E coli accounting for 71% of all ESBLs⁽¹⁾



Carbapenem use has more than doubled in the US between 2005 and 2015⁽²⁾



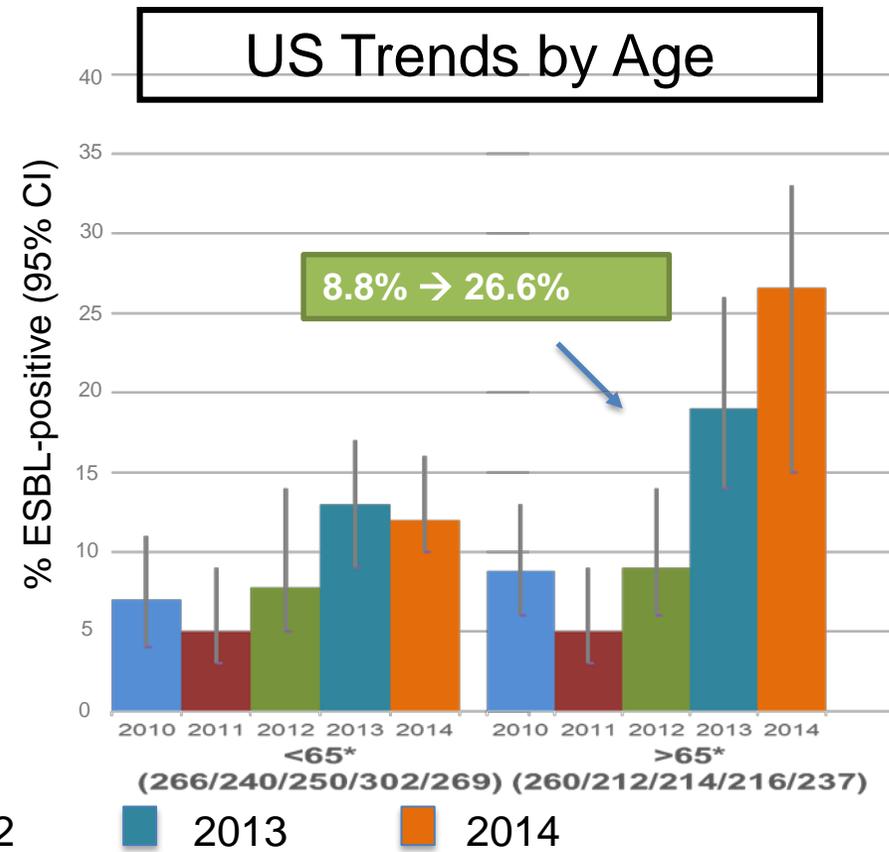
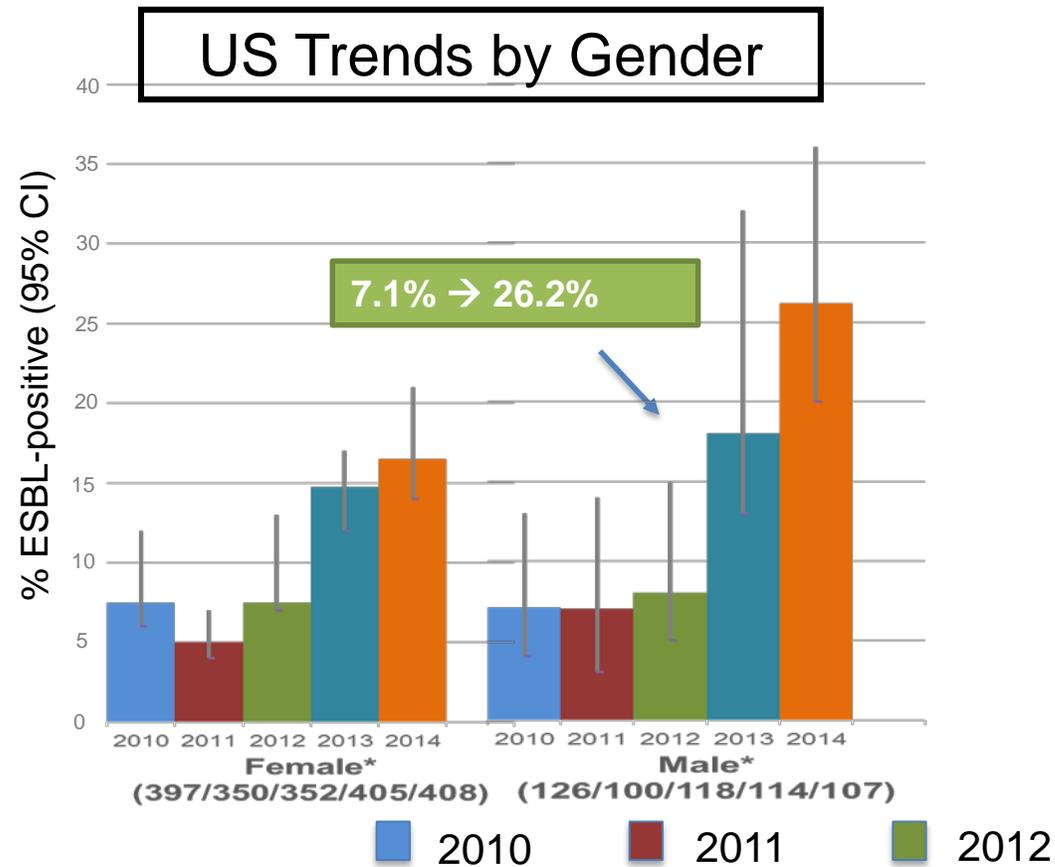
CRE (Carbapenem Resistant Enterobacteriaceae) trend in the US poses a real concern⁽²⁾

Infections resistant to carbapenems, other β -lactams, fluoroquinolones and other antibiotic classes (i.e., MDR) are associated with high mortality (>30%), almost double the rate of infections with non-MDR pathogens^(3,4)

(1) DeRyke et al, Poster # 332, ASM Microbe 2016
 (2) IQVIA NSP Sales Database, 2005-2015
 (3) Patolia et al, Ther Adv Infectious Dis 2018, Vol. 5(1) 11-18
 (4) Nelson et al, Infect Control Hosp Epidemiol 2017;38:848-856

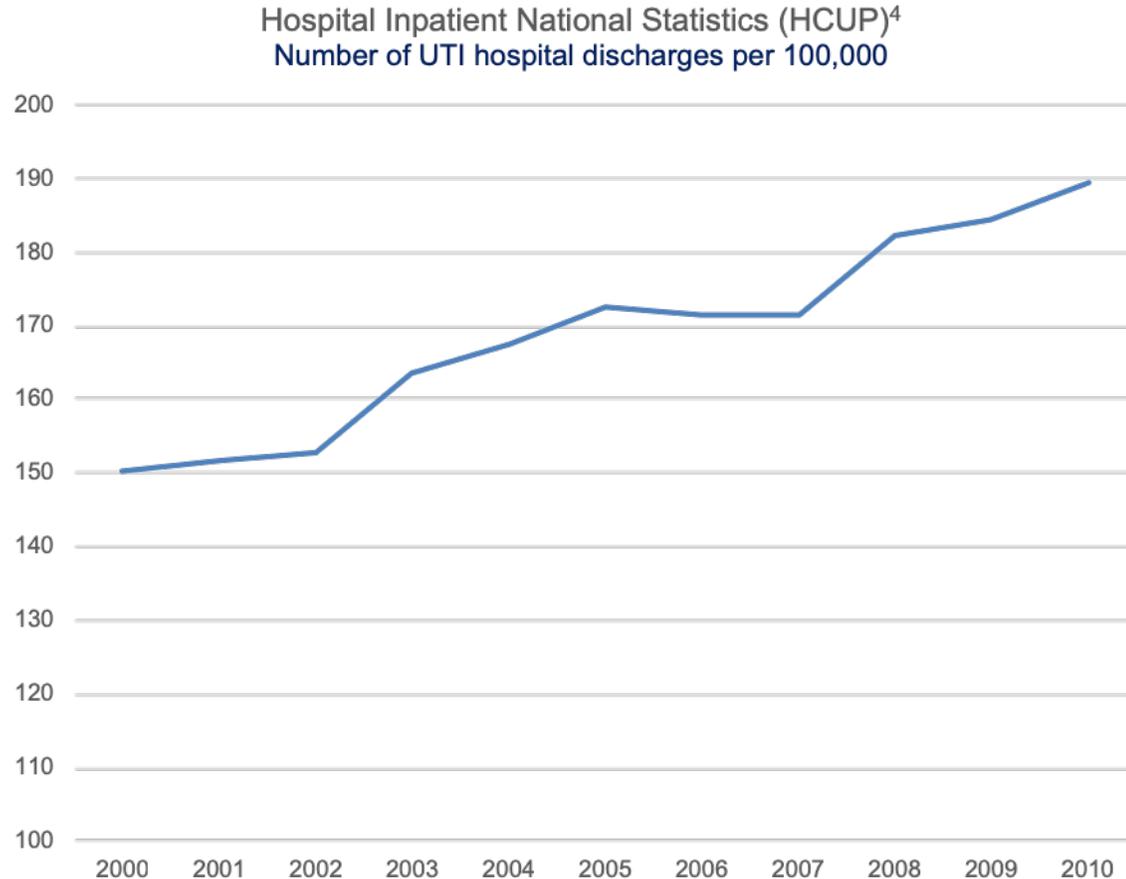
Infections Caused by ESBL(+) Pathogens Have Increased Most Significantly Among *Males* and *>65 Years of Age*

- 3,498 *E.coli* isolates were collected from 2010 to 2014 in the Study for Monitoring Antimicrobial Resistance Trends (SMART) in the United States (and Canada)
- Steepest increase in ESBL rates over a 5 year study period were found among US males and older patients.



Number of Hospitalizations for UTI Continues to Increase

Majority of patients admitted to hospitals for UTI are Medicare beneficiaries⁴



- UTI is one of the most commonly diagnosed infections in **older adults**¹
- **Second only to respiratory infections** in hospitalized patients and community-dwelling adults over the **age of 65 years**^{2,3}
- Among hospital admissions for UTI, the **majority of patients (66%) are Medicare beneficiaries (>65 years of age)**⁴

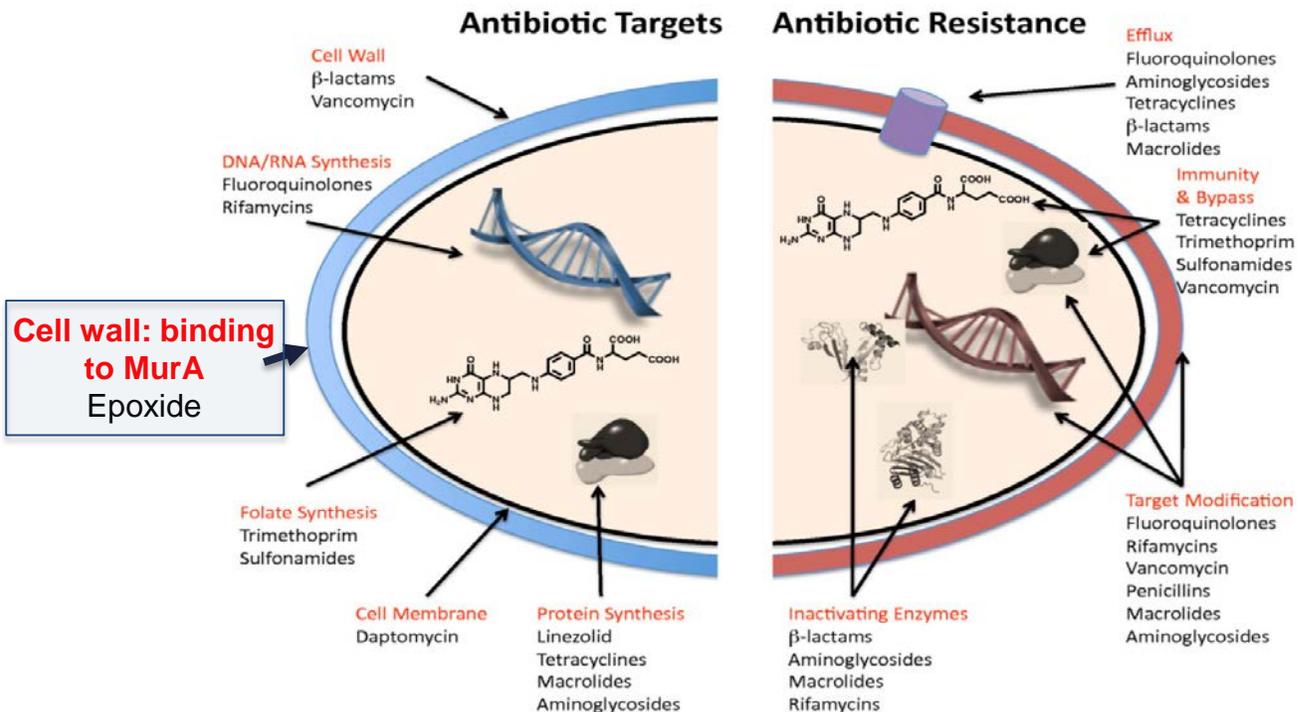
1. Rowe TA, Juthani-Mehta M. Urinary tract infection in older adults. Aging Health 2013;9(5):1-14.

2. Curns AT, Holman RC, Sejvar JJ, Owings MF, Schonberger LB. Infectious disease hospitalizations among older adults in the United States from 1990 through 2002. Arch Intern Med. 2005;165(21):2514-2520.

3. Ruben FL, Dearwater SR, Norden CW, et al. Clinical infections in the noninstitutionalized geriatric age group: methods utilized and incidence of infections The Pittsburgh Good Health Study. Am J Epidemiol. 1995;141(2):145-157.

4. Data on file. Source: Healthcare Utilization Project (HCUP): <https://www.hcup-us.ahrq.gov/>

Fosfomycin: An IV Epoxide Formulation Provides a Differentiated Mechanism of Action



- Fosfomycin works at the first commitment step in cell wall synthesis, different than all other cell wall active IV antibiotics
- Its unique mechanism of action results in:
 - Broad spectrum microbiologic activity, including MDR pathogens with limited available treatment options
 - No cross-resistance with other antibiotic classes
 - Demonstrated *in vitro* synergy or additive effect in combination with other antimicrobial classes

Figure adapted from: Wright GD. Q&A: Antibiotic resistance: where does it come from and what can we do about it? BMC Biology. 2010;8:123. doi:10.1186/1741-7007-8-123

CONTEPO Administration

- CONTEPO is to be administered as follows:
 - 6 g every 8 hours by IV infusion over 1 hour for up to 14 days, in patients 18 years of age or older patients with an estimated creatinine clearance (CrCl) greater than or equal to 50 mL/min
- Dosage adjustment is required for patients whose CrCl is 50 mL/min or less

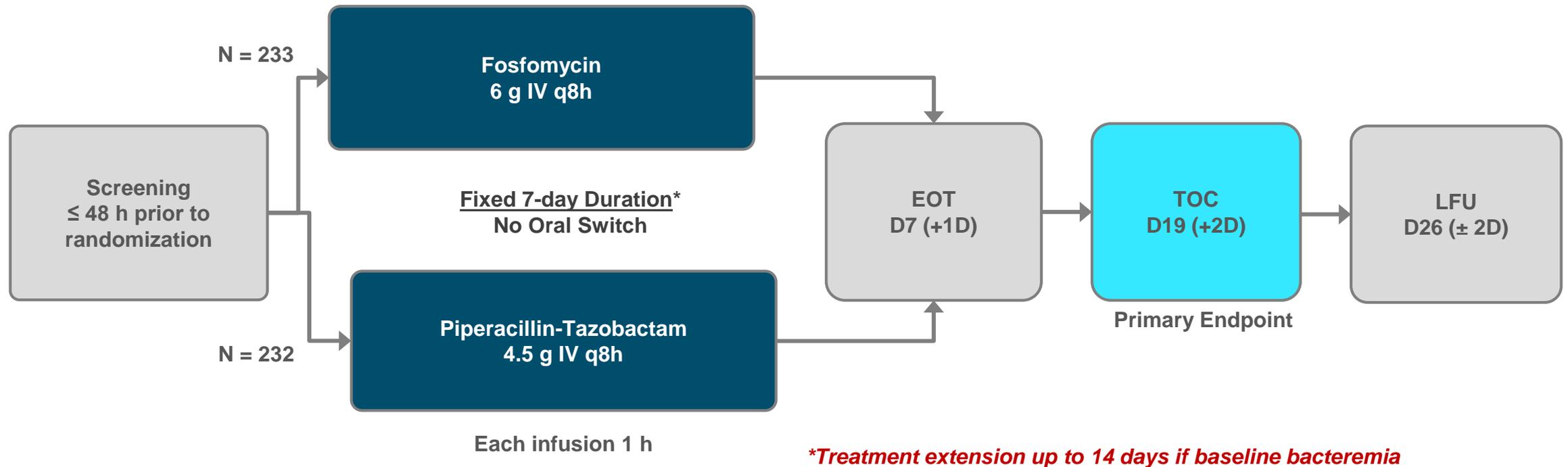
Estimated CrCL (mL/min) ^a	Treatment Regimen ^b
Greater than 50	6 g every 8 hours (no adjustment)
Greater than 40 to less than or equal to 50	4 g every 8 hours
Greater than 30 to less than or equal to 40	6 g loading dose, then 3 g every 8 hours
Greater than or equal to 20 to less than or equal to 30	6g loading dose, then 5 g every 24 hours

^aCrCl estimated using Cockcroft-Gault formula.

^bAll doses of CONTEPO are administered over 1 hour.

ZEUS: Pivotal Study in cUTI or Acute Pyelonephritis (AP)

Study Design Elements



- Stratification by region (US [1], ex-US [464]), diagnosis (cUTI [54%], AP [46%]), prior antibiotic use (~7%)

Abbreviations: IV = intravenous; EOT = End of Treatment; TOC = Test of Cure; LFU = Late Follow-up

ZEUS: Patient Demographics

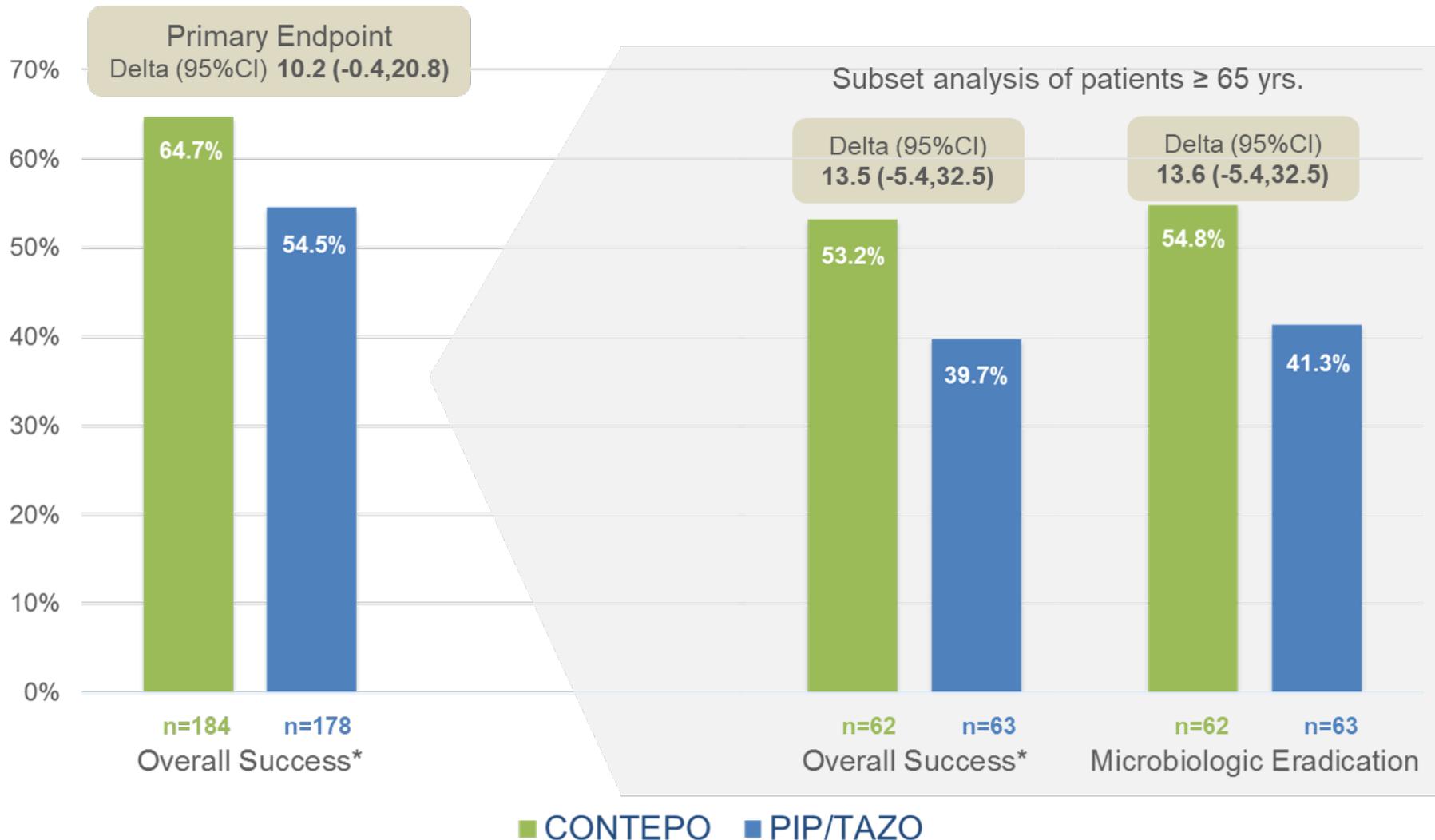
Microbiologic-modified ITT (m-MITT) population

Characteristic; n (%)	CONTEPO N = 184	PIP-TAZ N = 178	TOTAL N = 362
Mean age (years) (SD)	49.9 (20.92)	51.3 (20.71)	50.6 (20.80)
≥65	62 (33.7%)	63 (35.4%)	125 (34.5%)
Female	119 (64.7%)	111 (62.4%)	230 (63.5%)
Creatinine Clearance > 50 mL/min	158 (85.9%)	158 (88.8%)	316 (87.3%)
Infection Type			
Acute Pyelonephritis	100 (54.3%)	96 (53.9%)	196 (54.1%)
Complicated UTI	84 (45.7%)	82 (46.1%)	166 (45.9%)
Risk Factor for cUTI			
Functional/anatomical abnormality of the urogenital tract	35 (41.2%)	42 (50.0%)	77 (21.3%)
Complete or partial obstructive uropathy	36 (42.4%)	30 (35.7%)	66 (18.2%)
Estimated Charlson Comorbidity Index ≥3	69 (37.5%)	71 (39.9%)	140 (38.7%)
SIRS criteria met^a	62 (33.7%)	52 (29.2%)	114 (31.5%)
Baseline bacteremia	19 (10.3%)	13 (7.3%)	32 (8.8%)

a. SIRS criteria are met if patient had ≥2 of the following: temperature <36°C or >38°C, heart rate >90 bpm, respiratory rate >20 breaths/min, white blood cell Count >12,000 or <4000 cells/mm³. Source: ZTI-01-200 CSR Table(s): 14.1.2.3 and 14.1.2.6

ZEUS: Pivotal Clinical Trial Achieved Primary Endpoint

Overall Success at Test of Cure in the m-MITT Population

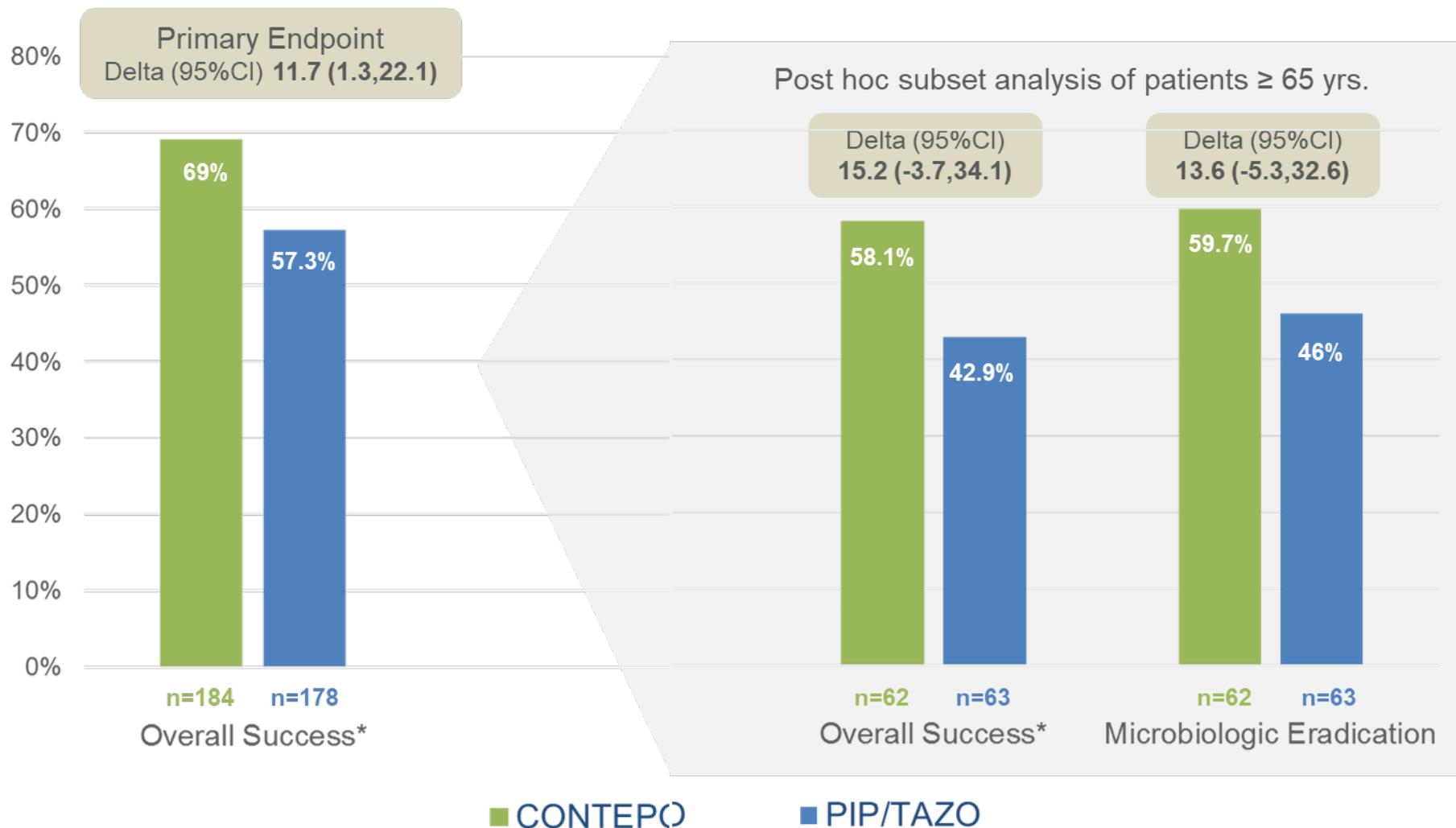


- N=465 patients (ITT); 362 in micro-MITT
- 34% of patients in m-MITT population were ≥ 65 years

*Overall Success: composite endpoint consisting of clinical cure plus microbiologic eradication

ZEUS: Reanalysis[^] of Primary Endpoint Using Pulse-Field Gel Electrophoresis (PFGE)

20 unique pathogens identified at follow-up compared to baseline phenotypes



- Improved specificity of PFGE testing demonstrated higher overall success rates in both arms, significantly favoring CONTEPO over standard of care (PIP/TAZO)

Overall success: composite endpoint consisting of clinical cure plus microbiologic eradication

ZEUS: Overview of Adverse Events

(ITT, Safety Population)

	ZTI-01 N=233 (%)	PIP-TAZ N=231 (%)
Any Adverse Event (AE)	99 (42.5)	74 (32.0)
Any Treatment-Emergent TEAE	98 (42.1)	74 (32.0)
Mild	84 (36.1)	49 (21.2)
Moderate	35 (15.0)	38 (16.5)
Severe	5 (2.1)	4 (1.7)
TEAEs Leading to Discontinuation of Study Drug	7 (3.0)	6 (2.6)
Any Serious AE (SAE)	5 (2.1)	6 (2.6)
Drug-Related	1 (0.4)	1 (0.4)
Death	0 (0)	0 (0)
Led to Discontinuation of Study Drug	0 (0)	1 (0.4)
Common TEAEs by System Organ Class (≥ 5%)		
GI Disorders	25 (10.7)	17 (7.4)
Investigations (lab abnormalities)	20 (8.6)	8 (3.5)
Infections/Infestations	17 (7.3)	20 (8.7)
Metabolism/Nutrition Disorders	17 (7.3)	4 (1.7)
General/Administration Site Disorders	14 (6.0)	14 (6.1)

Most Treatment-Emergent AEs (TEAEs) were mild to moderate

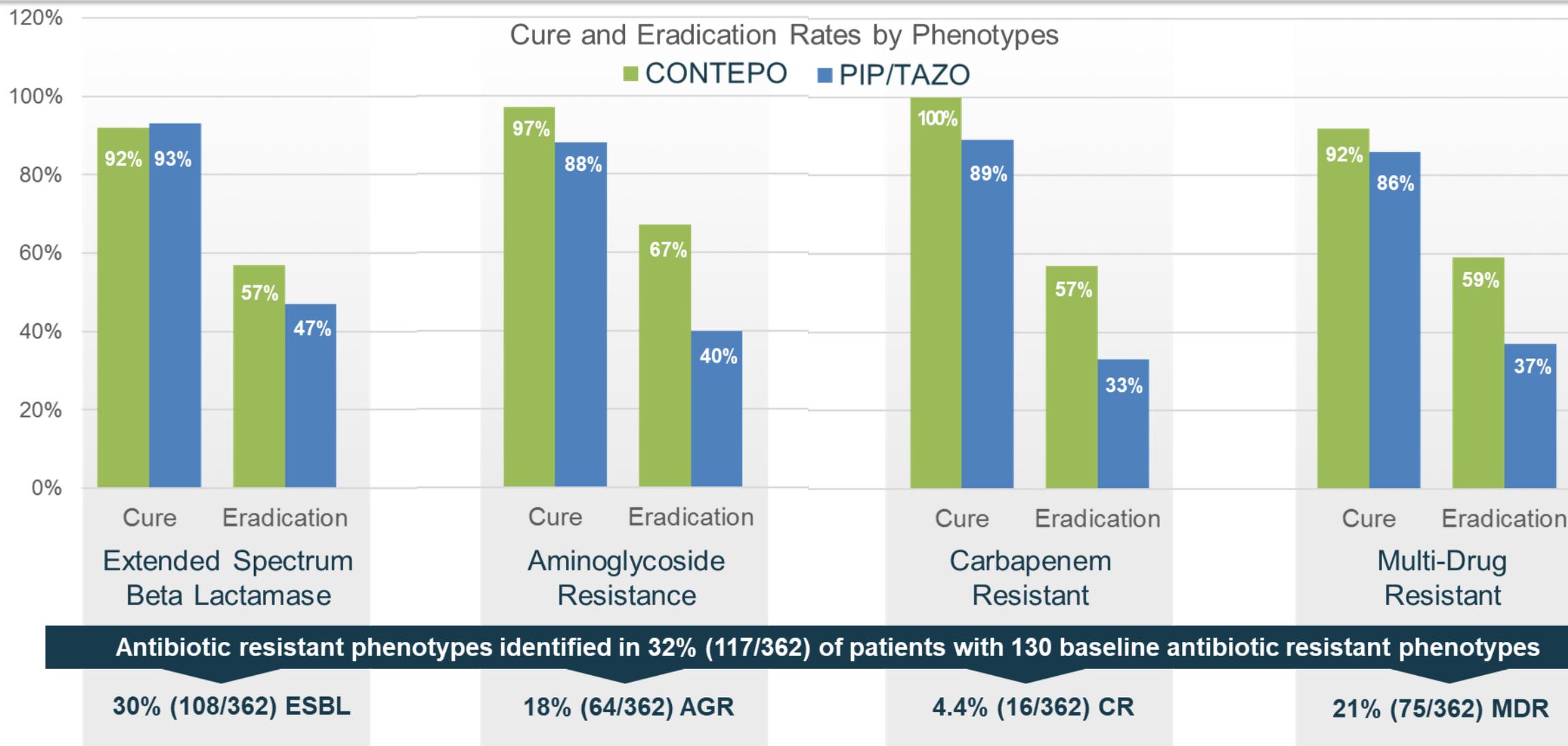
Severe AEs, SAEs, and discontinuations uncommon and similar between treatment groups

CONTEPO was generally well tolerated in population ≥ 65 years

TEAEs reported in 12.4% patients ≥ 65 years compared to 29.6% < 65 years of age

ZEUS: Clinical and Microbiological Outcomes in Antibiotic Resistant Phenotypes

Consistently High Cure and Eradication Rate Seen with CONTEPO Regardless of Resistance Phenotype



CONTEPO™: The First-in-Class IV Epoxide Antibiotic in the US

Proven Activity Against Clinically Relevant MDR Pathogens, Providing a Critically Needed Alternative for the Treatment of cUTI, Including Pyelonephritis

CONTEPO is a new IV antibiotic with a differentiated mechanism of action from currently available IV antibiotics. Because it addresses pathogens through a different site of action from currently available treatment options, it has the potential to treat cUTI, including infections caused by MDR pathogens -- a substantial clinical improvement. If approved, CONTEPO will add a much needed treatment option for cUTI patients in the battle against antibiotic resistant infections

CONTEPO is a first-in-class epoxide IV antibiotic

- New mechanism of action.
- Bactericidal, broad spectrum of activity.
- No existing evidence of cross-resistance.
- Effective against MDR pathogens.

CONTEPO offers a treatment option for a patient population unresponsive to, or ineligible for, currently available treatments

- For infections in seriously ill patients with suspected or confirmed MDR pathogens.
- Potential to preserve carbapenems and other last-line agents.

CONTEPO improved outcomes for patients compared to a currently available treatment in ZEUS*

- Potential to decrease length of hospitalization and patient mortality due to improved outcomes associated with early appropriate therapy in patients with suspected or confirmed MDR pathogens.

A unique ICD-10-PCS Section X code will help identify and track the use of CONTEPO for the treatment of cUTI or AP and related outcomes data and is need to identify qualifying cases if granted NTAP

*In Phase 2/3 study, non-inferior to PIP-TAZ (~10% higher overall success with CONTEPO); post hoc blinded analysis using PFGE favored CONTEPO (lower 95% CI >0)