Plazomicin Is Associated With Improved Survival and Safety Compared With Colistin in the Treatment of Serious Infections Due to Carbapenem-resistant Enterobacteriaceae: Results of the CARE Study

Lynn E. Connolly[1], Adrian M. Jubb[1], Bridget O'Keeffe[1], Alisa W. Serio[1], Alex Smith[1], Jonathan Gall[1], Valerie Riddle[2], Kevin M. Krause[1], James A. McKinnell[3], Epaminondas Zakynthinos[4], and George L. Daikos[5]

[1]Achaogen, South San Francisco, CA, USA; [2]BioPharmAdvisors LLC, Parrish, FL, USA; [3]LA BioMed at Harbor-UCLA Medical Center, Los Angeles, CA, USA; [4]University Hospital, Larissa, Greece; [5]University of Athens, Athens, Greece

27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Vienna, Austria, April 22-25, 2017

Disclosures

- This presentation concerns a drug that is under clinical investigation and which has not yet been approved by any regulatory authority, including the US Food and Drug Administration (FDA)
- This drug is currently limited by law to investigational use, and no representation is made as to the safety or effectiveness for the purposes for which it is being investigated
- This presentation contains certain forward-looking statements reflecting Achaogen's current beliefs and expectations made pursuant to the safe harbor provisions of United States law, including, but not limited to, Achaogen's expectations relating to potential regulatory approval of plazomicin. Such forward-looking statements involve known and unknown risks, uncertainties and other important factors that may cause Achaogen's actual results, performance or achievements to be materially different from those implied by the forward-looking statements
- LE Connolly, AM Jubb, B O'Keeffe, AW Serio, A Smith, J Gall, and KM Krause are employees of and stockholders in Achaogen
- V Riddle is President/Owner of BioPharmAdvisors LLC, a paid contractor to Achaogen
- JA McKinnell, E Zakynthinos and GL Daikos have received honoraria and served on advisory boards for Achaogen

Combating Antibiotic-resistant Enterobacteriaceae (CARE)

COMBATING ANTIBIOTIC-RESISTANT ENTEROBACTERIACEAE

A Phase 3 Study Evaluating the Efficacy and Safety of Plazomicin in the Treatment of Patients With Serious Infections due to Carbapenem-resistant Enterobacteriaceae (CRE)

Primary Objective

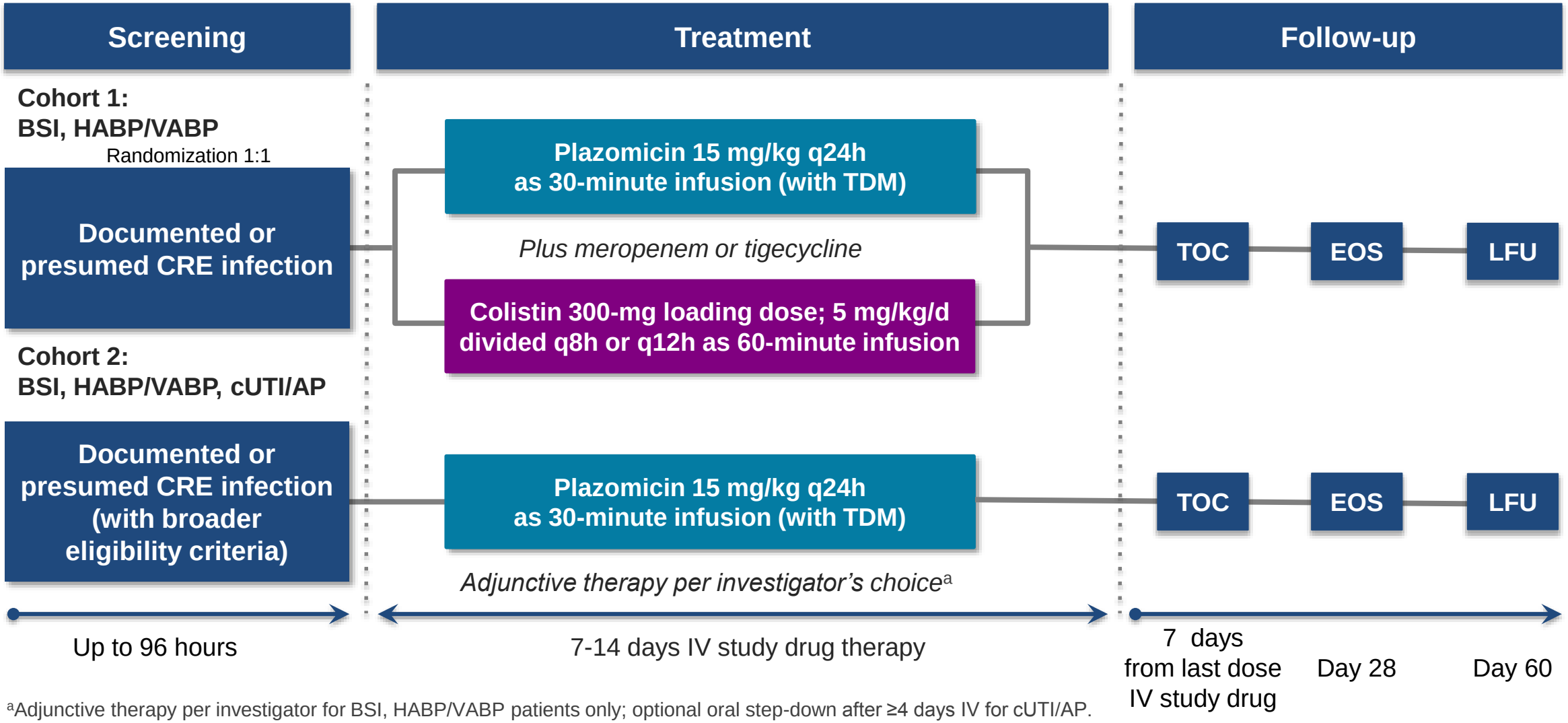
Evaluate the efficacy of plazomicin compared with colistin[a] in the treatment of BSI or HABP/VABP due to CRE based on primary endpoint:

- Day 28 all-cause mortality or significant disease-related complications[b]

[a]Plazomicin or colistin in combination with adjunctive therapy of meropenem or tigecycline.
[b]Within 7 days: New/worsening ARDS, new lung abscess or empyema, new-onset septic shock; persistence of bacteremia ≥5 days (BSI only); new-onset bacteremia (HABP/VABP only).

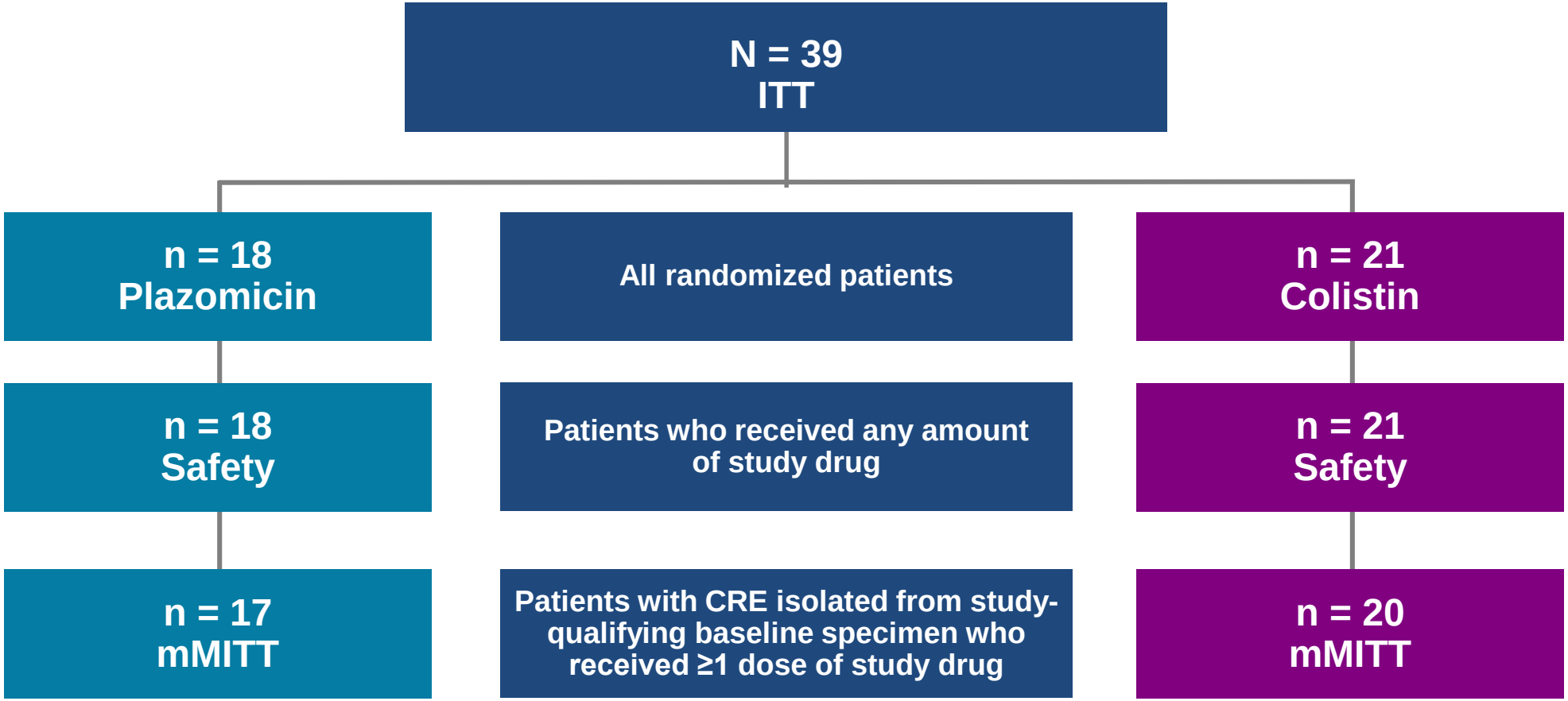
This trial is registered at ClinicalTrials.gov: NCT01970371.
ARDS, acute respiratory distress syndrome; BSI, bloodstream infection; CRE, carbapenem-resistant Enterobacteriaceae; HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia.

CARE Study Design



[a]Adjunctive therapy per investigator for BSI, HABP/VABP patients only; optional oral step-down after ≥4 days IV for cUTI/AP.
AP, acute pyelonephritis; cUTI, complicated urinary tract infection; EOS, end of study; IV, intravenous; LFU, late follow up; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours; TDM, therapeutic drug management; TOC, test of cure.

CARE Patient Disposition (Cohort 1)



Primary efficacy analysis population included patients with BSI or HABP/VABP due to CRE.
CRE = meropenem MIC of ≥4 µg/mL, or a meropenem MIC of 2 µg/mL and disk diffusion zone ≤19 mm on central laboratory testing.
ITT, intent-to-treat; MIC, minimum inhibitory concentration; mMITT, microbiological modified intent-to-treat.

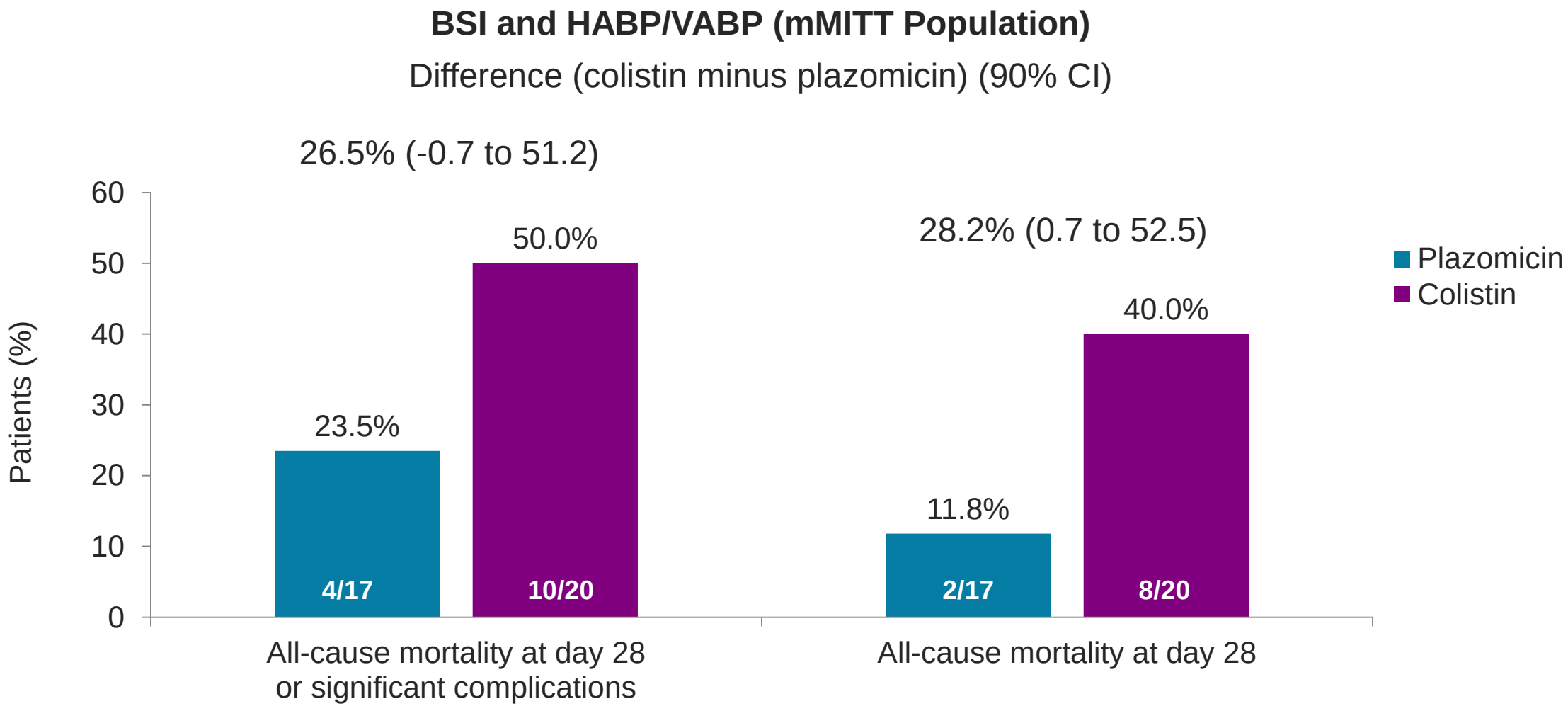
CARE Baseline Characteristics
Well Balanced Across Treatment Groups Overall

Baseline Characteristic (mMITT Population)		Plazomicin (N = 17)	Colistin (N = 20)
Age, years, mean ± SD		66.7 ± 12	63.1 ± 19
Male, n (%)		12 (70.6)	10 (50.0)
APACHE II score, n (%)	15 to 20 21 to 30 >30	10 (58.8) 6 (35.3) 1 (5.9)	11 (55.0) 9 (45.0) 0 (0.0)
Infection type, n (%)	BSI HABP/VABP	14 (82.4) 3 (17.6)	15 (75.0) 5 (25.0)
Baseline pathogens, n (%)	Monomicrobial Polymicrobial	14 (82.4) 3 (17.6)	17 (85.0) 3 (15.0)
Creatinine clearance, n (%)[a]	>90 mL/min ≤90 mL/min CRRT	4 (23.5) 7 (41.2) 4 (23.5)	10 (50.0) 6 (30.0) 2 (10.0)
Adjunctive therapy, n (%)	Meropenem Tigecycline	6 (35.3) 11 (64.7)	9 (45.0) 11 (55.0)

[a]Cockcroft-Gault estimation; baseline central laboratory data not available for subset of patients in each arm.

APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, continuous renal replacement therapy.

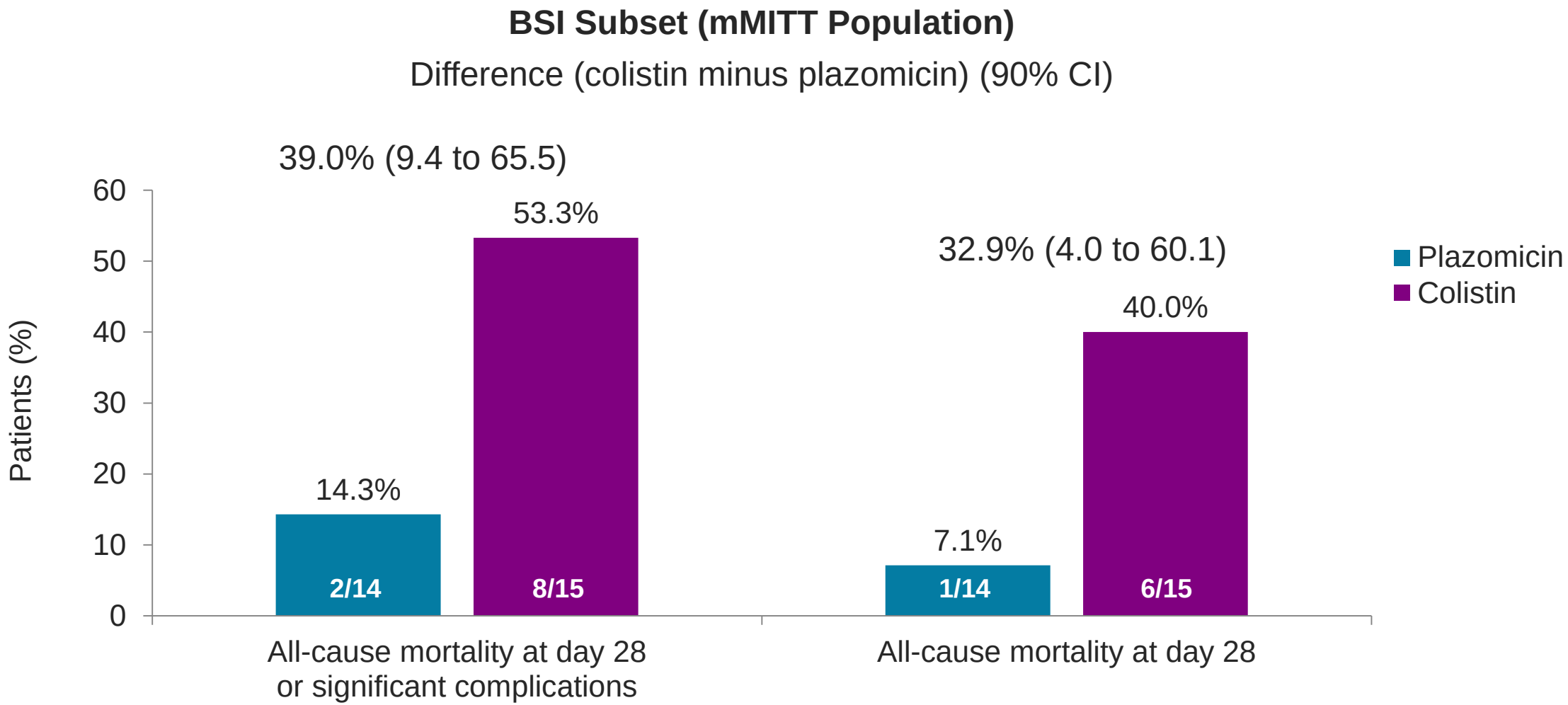
CARE Efficacy Results
Reduced Mortality at Day 28 for Plazomicin versus Colistin



Two-sided 90% confidence interval (CI) calculated based on the unconditional exact method.

CARE Efficacy Results

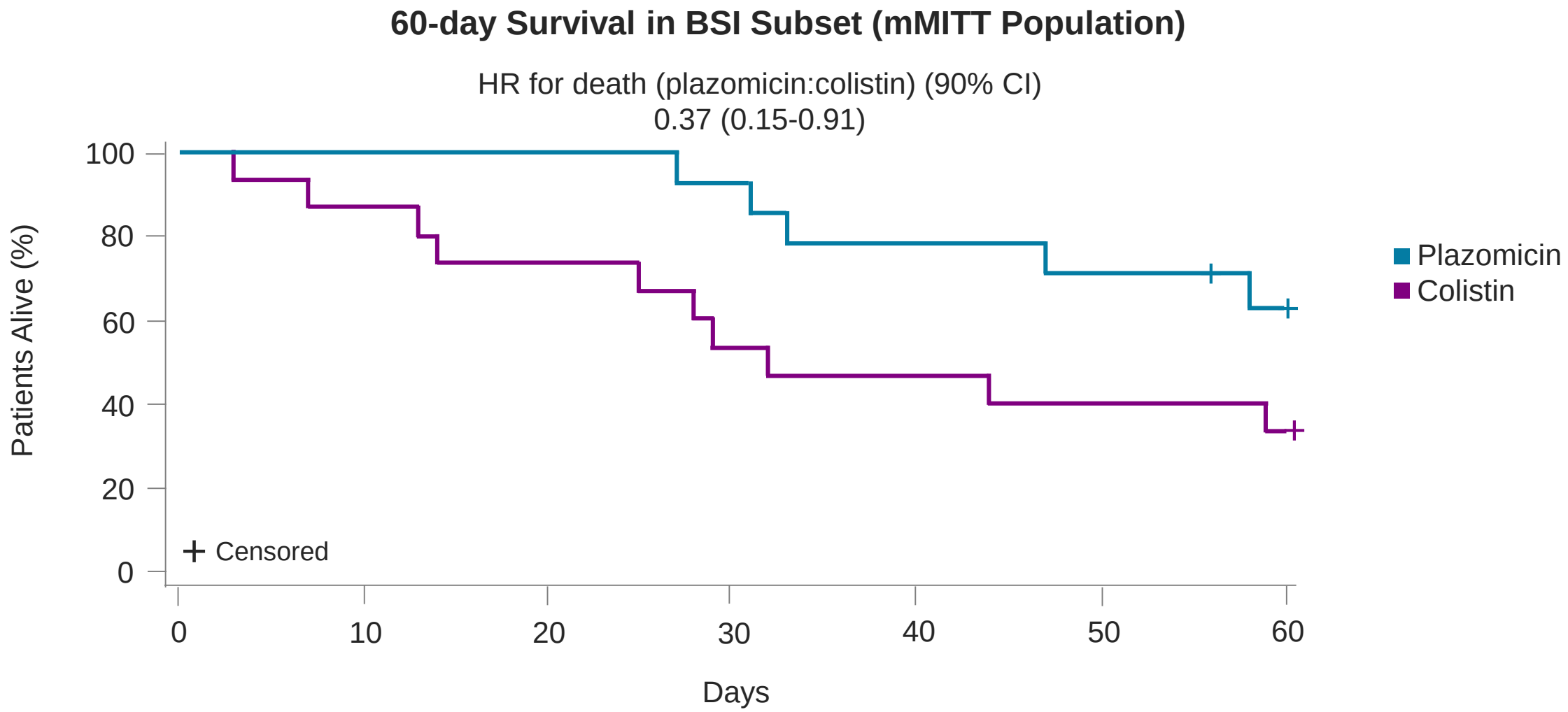
Reduced Mortality at Day 28 for Plazomicin versus Colistin in BSI



Two-sided 90% CI calculated based on the unconditional exact method.

CARE Kaplan-Meier Survival Curve

Sustained Survival Benefit in Plazomicin-treated Patients With BSI



Estimate of hazard ratio (HR) calculated as plazomicin:colistin based on Cox proportional hazards regression model.

CARE Overall Summary of AEs and SAEs
Favorable Safety Profile for Plazomicin Versus Colistin

Adverse Event (Safety Population)	Plazomicin (N = 18) n (%)	Colistin (N = 21) n (%)
AE	16 (88.9)	21 (100.0)
Study drug-related	5 (27.8)	9 (42.9)
Led to discontinuation of study drug	2 (11.1)	1 (4.8)
Related to renal function	6 (33.3)	11 (52.4)
SAE	9 (50.0)	17 (81.0)
Study drug-related	1 (5.6)	4 (19.0)
Led to death (up to day 60)	8 (44.4)	13 (61.9)
Related to renal function	2 (11.1)	6 (28.6)

- Reduced drug-related AEs, SAEs, and AEs related to renal function in plazomicin arm
- No study drug-related deaths or events of ototoxicity reported

AE, adverse event; SAE, serious adverse event.

CARE Laboratory Parameters Associated With Renal Function

Notable Reduction in Serum Creatinine Elevations in Plazomicin Arm

Serum Creatinine (Safety Population)[a]	Plazomicin (N = 18) n/N1 (%)	Colistin (N = 21) n/N1 (%)
≥0.5 mg/dL increase any time on study (including on or post IV therapy)	2/12 (16.7)	8/16 (50.0)
≥0.5 mg/dL increase while on IV therapy	1/12 (8.3)	6/16 (37.5)
Full recovery or improvement[b]	1/1	3/6

[a]Patients starting CRRT prior to baseline were excluded from the analysis, as were all post-baseline serum creatinine measurements collected after start of CRRT.
[b]Full recovery defined as last post-baseline serum creatinine value <0.5 mg/dL above the baseline value. Improvement defined as last post-baseline serum creatinine value ≥0.3 mg/dL less than the peak serum creatinine but not <0.5 mg/dL above the baseline value.

CARE Conclusions

- Patients with serious CRE infections had significant mortality and disease-related complications
- Plazomicin treatment was associated with reduced all-cause mortality at day 28
- Survival benefit in plazomicin-treated BSI patients was sustained through day 60
- Favorable safety profile for plazomicin-treated patients compared with colistin when used as part of a combination regimen for the treatment of life-threatening infections due to CRE
- Data from the CARE study suggest that plazomicin could offer an important new treatment option for patients with serious infections due to CRE

Acknowledgments

- The authors thank the investigators, patients, and families involved in this clinical trial program
- This project has been funded, in whole or in part, with federal funds from the US Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201000046C
- Medical writing support was provided by Jean Turner, of PAREXEL, and funded by Achaogen