IDWeek

Ceftobiprole Compared to Daptomycin With or Without Optional Aztreonam for the Treatment of Complicated *Staphylococcus aureus* Bacteremia (SAB): Results of a Phase 3, Randomized, Double-Blind Trial (ERADICATE)

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IDSA Infectious Diseases Society of America

hivma hiv medicine association

PIDS PEDIATRIC INFECTIOUS DISEASES SOCIETY

SHEA The Society for Healthcare Epidemiology of America

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

DISCLOSURES

- Advisor/Consultant: Aridis, Basilea Pharmaceutica, Karius, Lysovant

Staphylococcus aureus bacteremia (SAB): A leading cause of morbidity and mortality

- 120,000 SAB cases/yr in the USA with mortality ~20%
- FDA-approved treatments that cover MRSA are vancomycin and daptomycin
- >15 years since approval of a new antibiotic in the U.S. for SAB
  - Daptomycin Phase 3 SAB trial is the only randomized study resulting in an approval of a new antibiotic for SAB

Ceftobiprole provides bactericidal activity against MSSA and MRSA

- Ceftobiprole is an advanced-generation cephalosporin with bactericidal activity against MSSA and MRSA
  - Efficacy demonstrated in Phase 3 studies in ABSSSI and pneumonia
- ERADICATE is the largest Phase 3 study conducted for registration of a new antibiotic in SAB
  - Utilized a double-blind design
  - Protocol designed under FDA Special Protocol Assessment (SPA)

ERADICATE design and primary endpoint

- Randomized (1:1), double-blind, multicenter, non-inferiority trial
- Ceftobiprole vs daptomycin (± aztreonam) for up to 42 days of treatment
- Non-inferiority margin for difference in overall success rate: -15%

Primary efficacy endpoint:

Overall clinical success at 70 days post-randomization

- Success required: survival, symptom improvement, SAB clearance, no new SAB complications, no use of other potentially effective antibiotics
- Adjudication by a blinded independent Data Review Committee (DRC) consisting of 6 experienced US ID specialists
- Analyses adjusted for dialysis status and prior antibacterial treatment

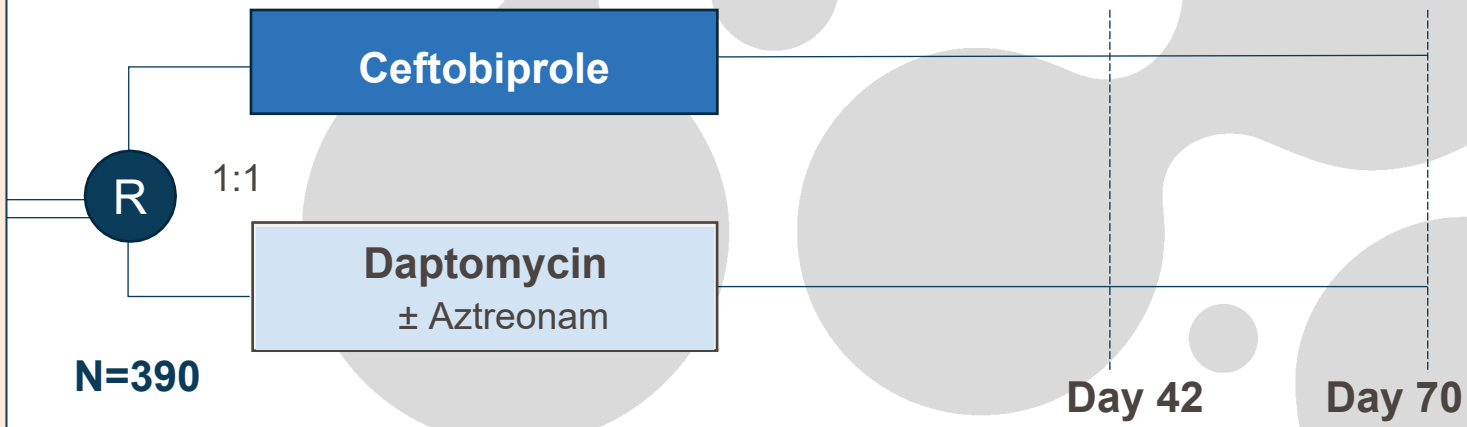
Study treatments and follow-up

Screening assessments (up to 72 hours prior to randomization)

- SAB based on ≥1 positive blood culture within 72h prior to randomization
- Confirmed or suspected complicated SAB or definitive right-sided infective endocarditis (RIE)

Active treatment (up to 42 days)

Primary endpoint assessment

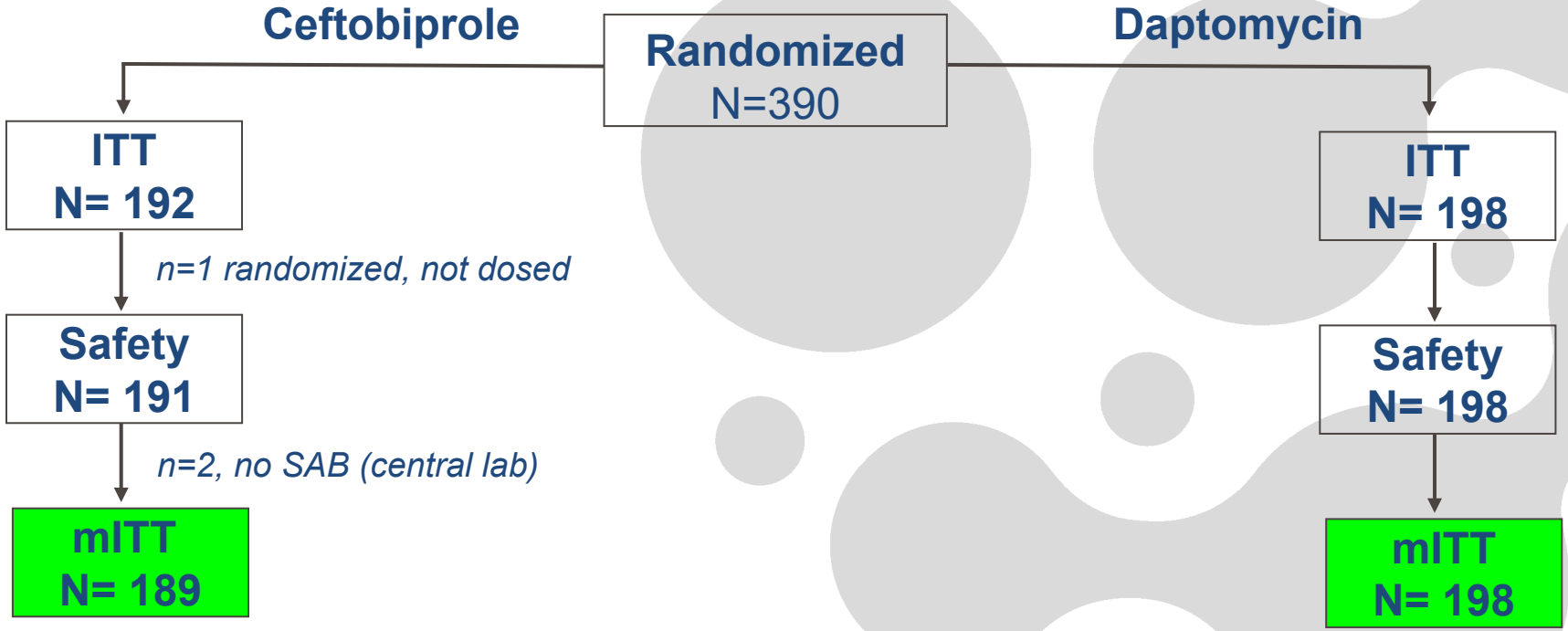


- Ceftobiprole: 500 mg q6h on Days 1-8 and 500 mg q8h from Day 9 onwards
- Daptomycin: 6-10 mg/kg q24h according to institutional standards
- Optional aztreonam: 1000 mg q12h

Dose adjustments according to renal function status

Patient disposition

60 sites in 17 countries:
USA, Eastern and Central Europe, Israel, Latin America, and South Africa
Study period: Aug-2018 to Mar-2022



ITT, intent-to-treat; mITT, microbiological intent-to-treat
mITT= Primary analysis population for efficacy, consisting of patients who received study medication and had a positive baseline blood culture for *S. aureus*

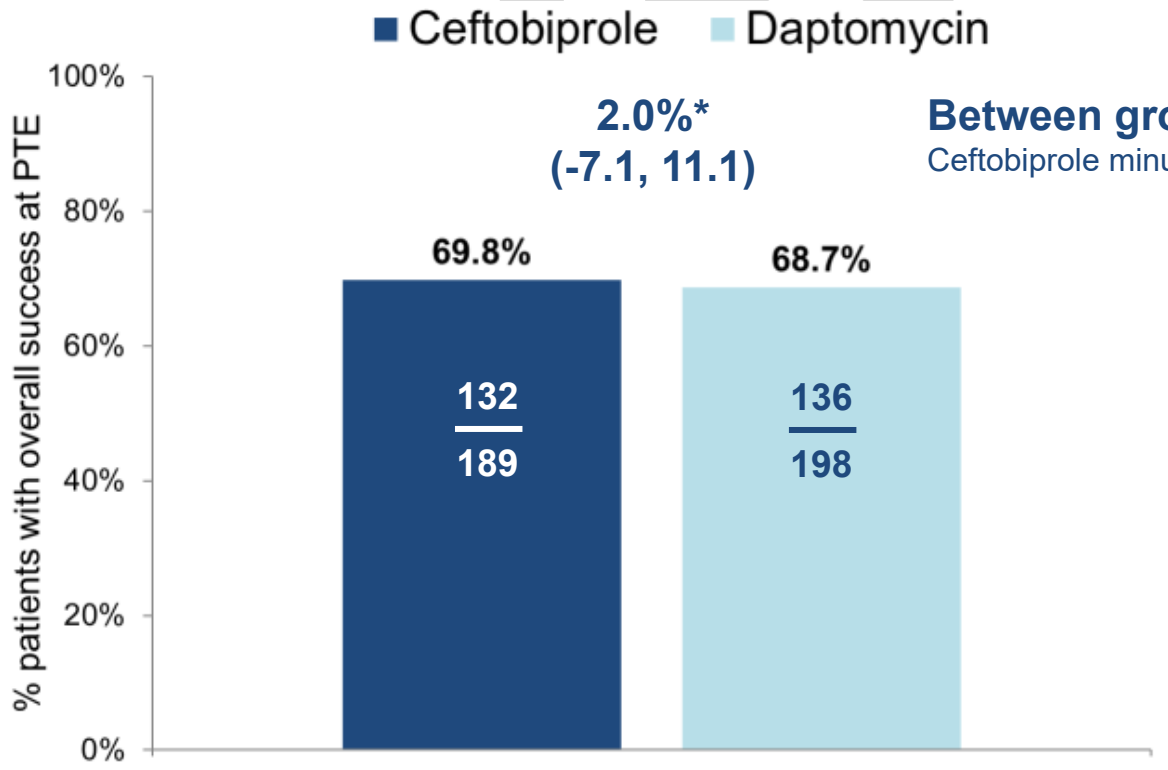
Patient characteristics were balanced

Demographic variables	Ceftobiprole N=189	Daptomycin N=198	Total N=387
Age, mean (min-max) (years)	55.5 (20-89)	56.5 (19-91)	56.0 (19-91)
Gender, male	67.7%	70.7%	69.3%
Race, White	94.7%	97.0%	95.9%
North America	2.6%	2.5%	2.6%
Europe	92.6%	93.4%	93.0%
Latin America/South Africa	4.8%	4.0%	4.4%
Aztreonam treatment at baseline	-	31.3%	
Most frequent baseline categories of complicated SAB (Investigator-assessed)			
Skin and skin structure infection	61.4%	61.1%	61.2%
Intra-abdominal abscess	13.8%	14.6%	14.2%
Chronic dialysis	12.7%	12.6%	12.7%
Septic arthritis	11.6%	9.6%	10.6%
Persistent SAB*	8.5%	8.1%	8.3%
Osteomyelitis	6.9%	8.6%	7.8%
Definite right-sided endocarditis	7.9%	5.1%	6.5%

*DRC-assessed

Ceftobiprole met primary endpoint

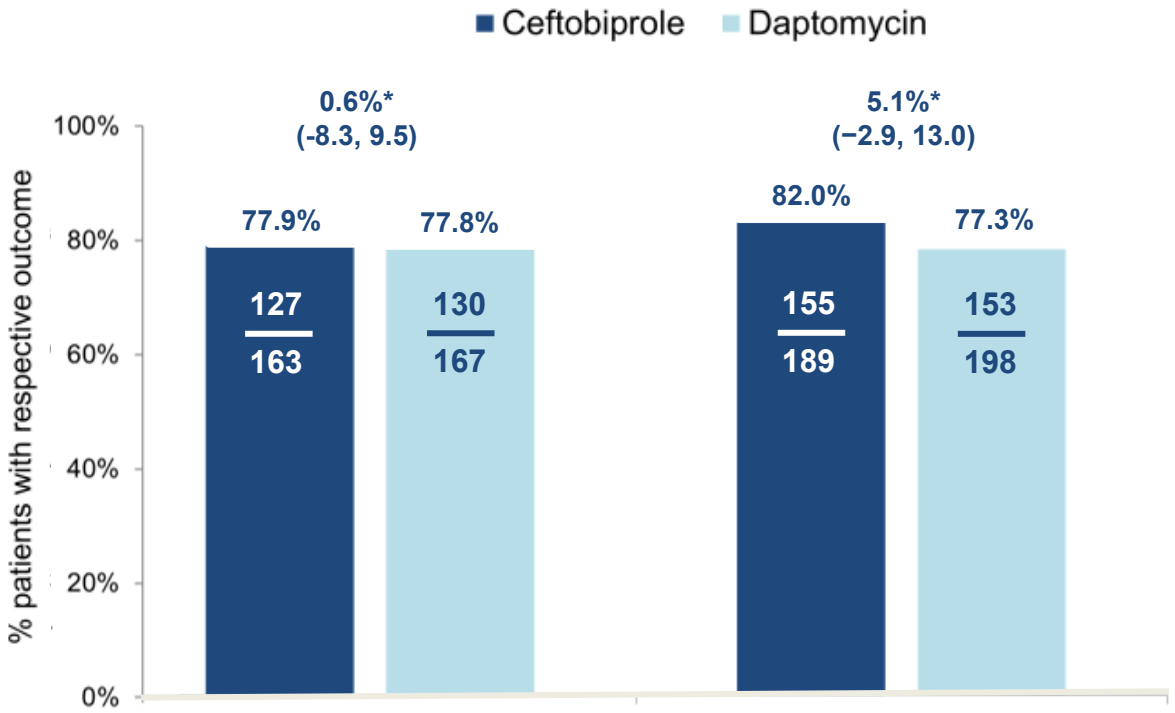
DRC assessed overall success at PTE in mITT population



Between group difference (95% CI)
Ceftobiprole minus daptomycin (± aztreonam)

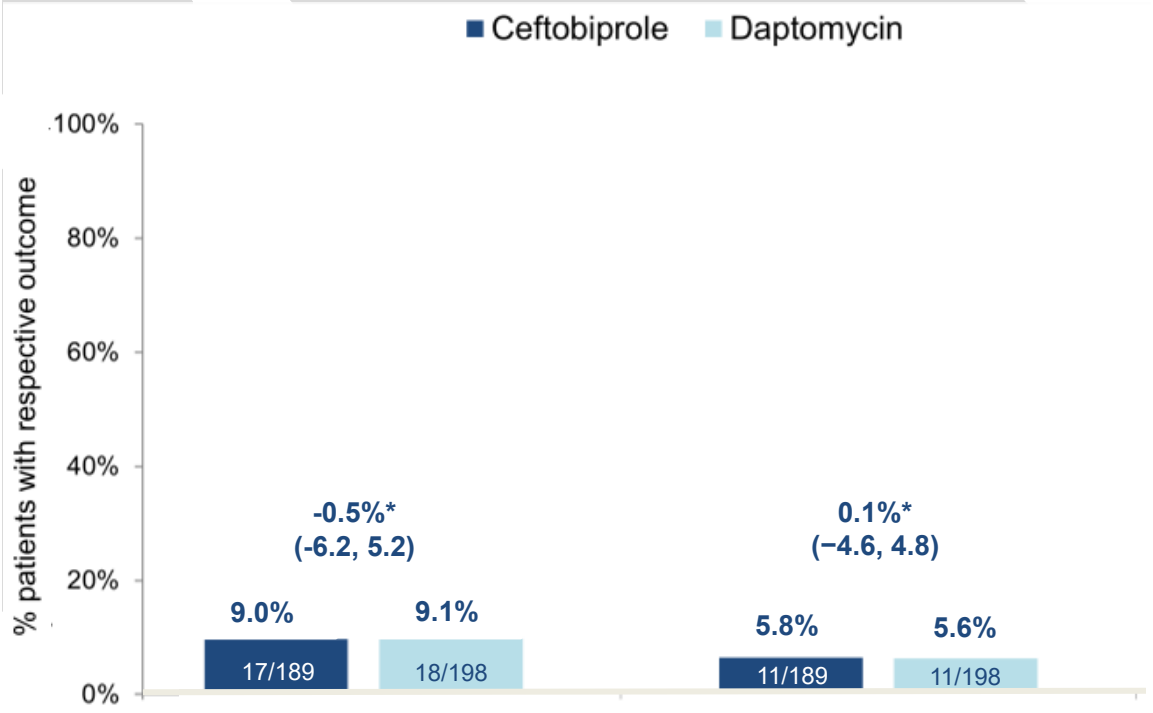
*Cochran-Mantel-Haenszel weights method adjusted for actual stratum (dialysis status and prior antibacterial treatment use)
PTE: post-treatment evaluation visit at 70 days post-randomization

Secondary efficacy outcomes are similar



Overall success at PTE (CE)

Microbiological eradication at PTE (mITT)



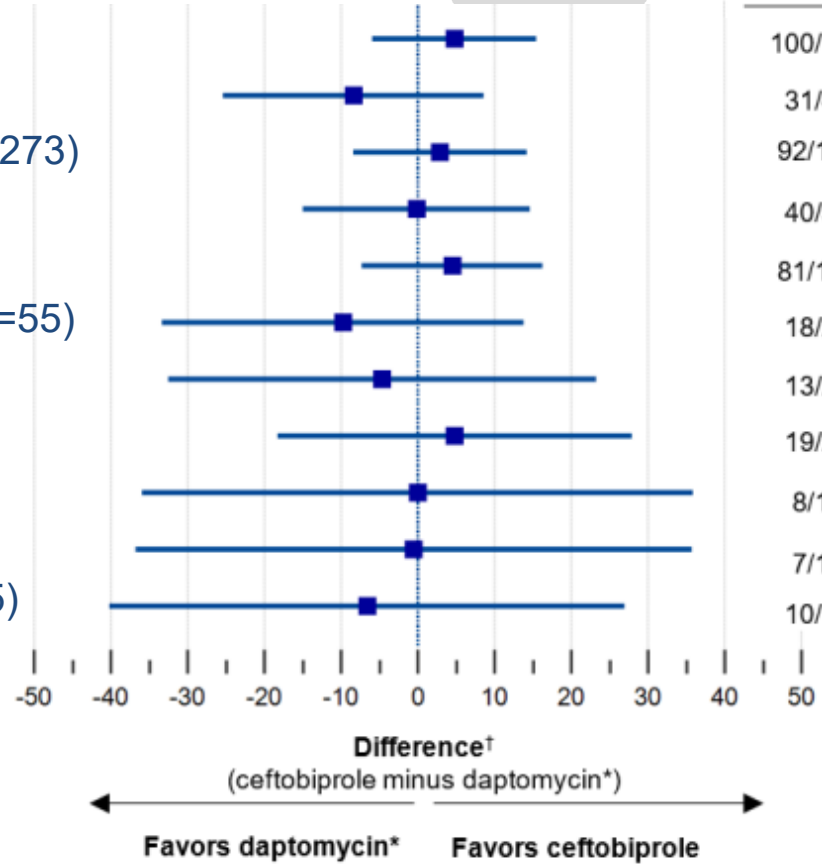
All-cause mortality through PTE (mITT)

New SAB complications (mITT)

*Between-group difference (95%CI) of ceftobiprole minus daptomycin (± aztreonam), adjusted for actual stratum (dialysis status and prior antibacterial treatment use) using Cochran-Mantel-Haenszel weights method. CE: Clinically evaluable population, PTE: post-treatment evaluation visit at 70 days post-randomization

Primary outcome subgroup analyses

- **MSSA** (n=287)
- **MRSA** (n=94)
- **Prior antibiotic use, yes** (n=273)
- **Prior antibiotic, no** (n=114)
- **ABSSSI** (n=237)
- **Intra-abdominal abscess** (n=55)
- **Chronic dialysis** (n=49)
- **Septic arthritis** (n=41)
- **Persistent SAB** (n=32)
- **Osteomyelitis** (n=30)
- **Definite right-sided IE** (n=25)

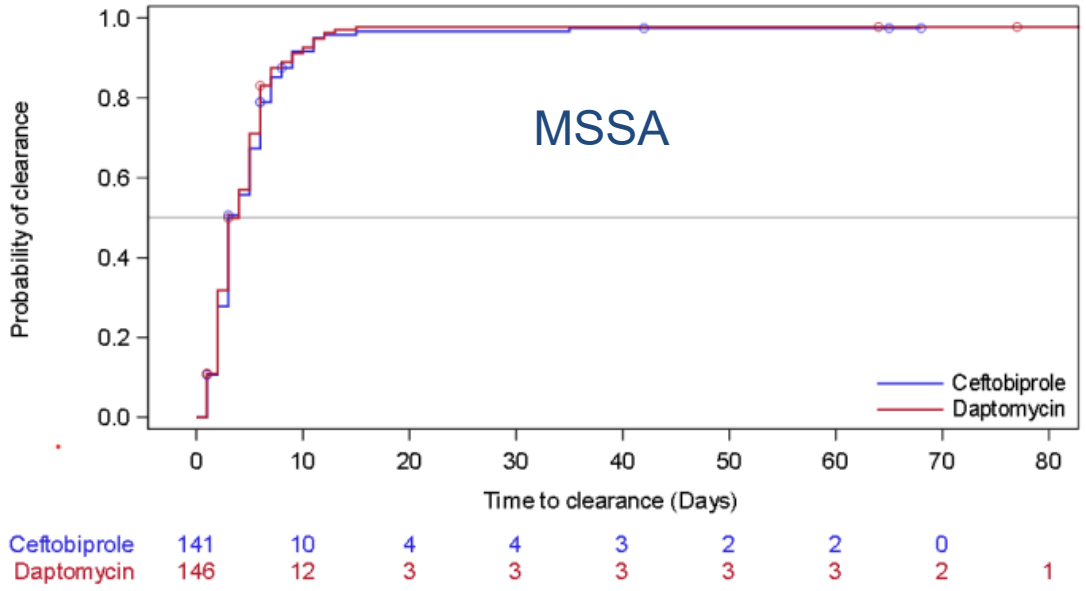


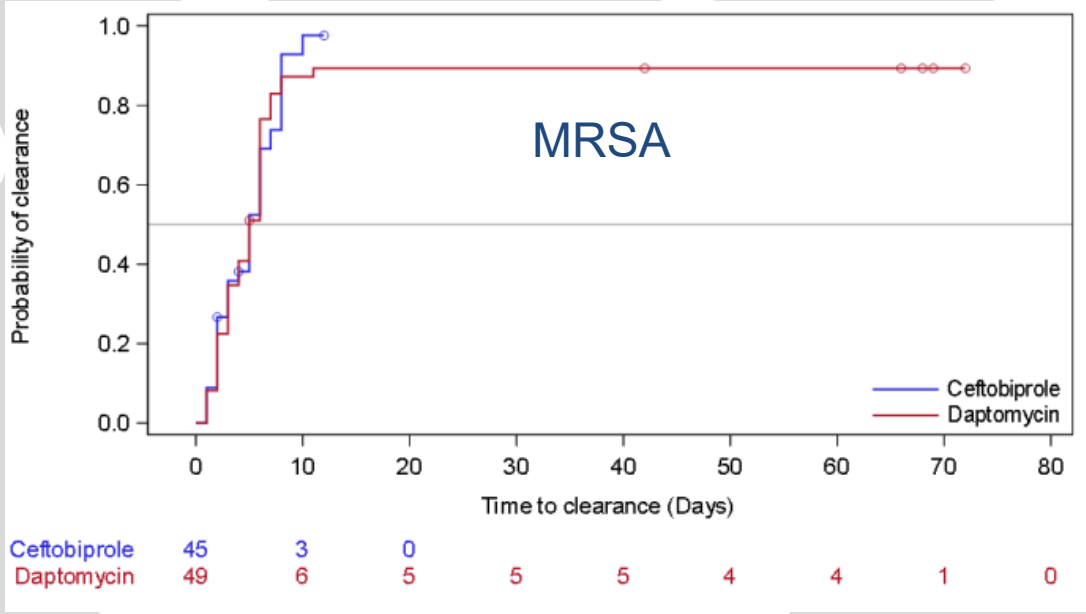
Ceftobiprole n/N (%)	Daptomycin* n/N (%)	Difference† (95%CI)
100/141 (70.9)	97/146 (66.4)	4.8% (-5.9, 15.5)
31/45 (68.9)	38/49 (77.6)	-8.3% (-25.3, 8.6)
92/139 (66.2)	85/134 (63.4)	2.9% (-8.4, 14.2)
40/50 (80.0)	51/64 (79.7)	-0.2% (-15.0, 14.6)
81/116 (69.8)	80/121 (66.1)	4.5% (-7.3, 16.3)
18/26 (69.2)	22/29 (75.9)	-9.7% (-33.3, 13.9)
13/24 (54.2)	15/25 (60.0)	-4.6% (-32.5, 23.3)
19/22 (86.4)	16/19 (84.2)	4.8% (-18.2, 27.9)
8/16 (50.0)	8/16 (50.0)	-0.0% (-35.9, 35.9)
7/13 (53.8)	9/17 (52.9)	-0.5% (-36.7, 35.8)
10/15 (66.7)	7/10 (70.0)	-6.6% (-40.1, 27.0)

* Daptomycin (± aztreonam)

† Between-group difference of ceftobiprole minus daptomycin ± aztreonam, adjusted for actual stratum (dialysis status and prior antibacterial treatment use) using Cochran-Mantel-Haenszel weights method.

Time to *S. aureus* bloodstream clearance





Ongoing, not eradicated									
Ceftobiprole	141	10	4	4	3	2	2	0	
Daptomycin	146	12	3	3	3	3	3	2	1

Ongoing, not eradicated									
Ceftobiprole	45	3	0						
Daptomycin	49	6	5	5	5	4	4	1	0

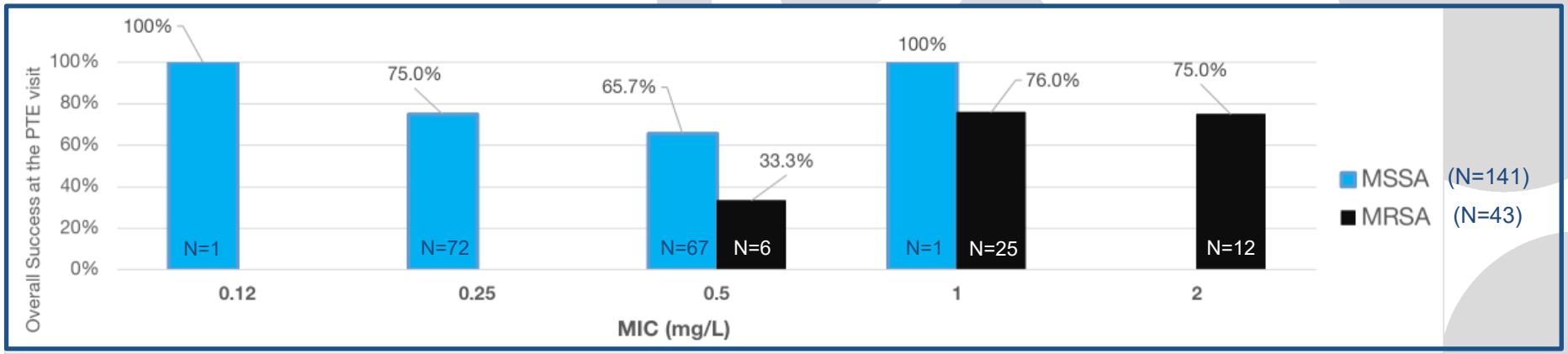
Endpoint (mITT)	MSSA		MRSA		*S. aureus* (overall)	
	Ceftobiprole N=141	Daptomycin N=146	Ceftobiprole N=45	Daptomycin N=49	Ceftobiprole N=189	Daptomycin N=198
Patients with clearance achieved	**94.3%**	**95.2%**	**93.3%**	**87.8%**	**94.2%**	**92.9%**
Median time (days) to clearance (95%CI)	**3** (3, 5)	**4** (3, 5)	**5** (3, 6)	**5** (4, 6)	**4** (3, 5)	**4** (3, 5)

Two sets of peripheral blood cultures (aerobic and anaerobic) were to be obtained at baseline; and post-baseline on Days 1, 2 and 3; thereafter approximately every 48–72 h until negative blood culture results for *S. aureus* at two time points taken ≥24 h apart. At least one blood culture was to be obtained at the PTE visit, or in the period between 7 days after end of treatment and the PTE visit.

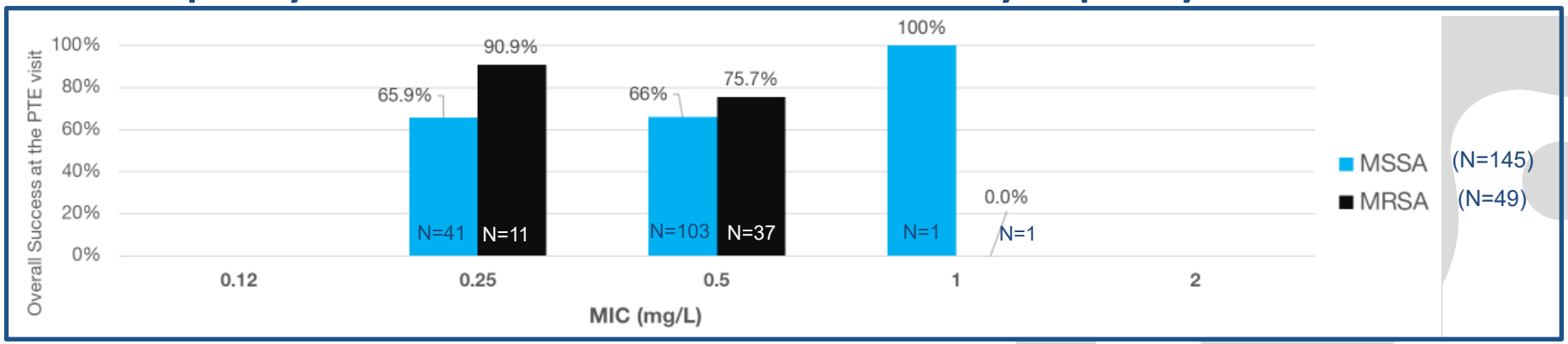
Bloodstream clearance was defined as two consecutive study days with blood-culture-negative assessments for *S. aureus*, without any subsequent *S. aureus* relapse or reinfection per DRC assessment. The first day with negative blood culture was used for calculating the time from randomization to bloodstream clearance. Patients without clearance were censored at the last study visit.

No relationship between success and *S. aureus* MIC

Ceftobiprole - Overall Success at the PTE visit by Ceftobiprole MIC



Daptomycin - Overall Success at the PTE visit by Daptomycin MIC



Relapse and resistance development

- SAB relapse in 4 daptomycin patients (3.0%, 2 MSSA, 2 MRSA) and 2 ceftobiprole patients (1.1%, both MSSA)
- On-treatment MIC increases ≥4 fold observed in 3 patients on daptomycin (1.5%, 2 MSSA, 1 MRSA) but none on ceftobiprole
- 16 patients had vancomycin MICs of 2-8 mg/L (8 MRSA, 8 MSSA); in these patients overall success rates were 87.5% (7/8) with ceftobiprole and 50.0% (4/8) with daptomycin

Overview of adverse events

Patient with at least one event in the respective category	Ceftobiprole N= 191	Daptomycin N=198
Adverse events (AEs)	63.4%	59.1%
Study drug-related AEs*	13.1%	5.6%
- Gastrointestinal disorders	9.4%	1.5%
Severe AEs	15.2%	19.2%
Study drug-related severe AEs*	0.5%	1.0%
Serious AEs (SAEs)	18.8%	22.7%
Study-drug-related SAEs	1.0%	2.0%
AEs leading to treatment discontinuation	9.4%	9.1%
Study drug-related AEs leading to treatment discontinuation	4.7%	1.5%
AEs leading to death	8.9%	9.1%
Study drug-related AEs leading to death	0	0

*Relationship to study medication as assessed by the investigator

Tolerability of ceftobiprole and daptomycin

- More ceftobiprole-related GI AEs (9.4%) compared to daptomycin (1.5%), mainly driven by mild to moderate nausea
  - consistent with known safety profile of ceftobiprole
- Ceftobiprole-related treatment discontinuations (4.7%) mainly due to GI and allergy-type events
- Daptomycin-related treatment discontinuations (1.5%) due to eosinophilic pneumonia and myopathy
- No events related to *C. difficile* in either group

GI: gastrointestinal

Summary

- In the first double-blind registrational trial for *S. aureus* bacteremia, ceftobiprole was non-inferior to daptomycin
- Success did not vary by *S. aureus* MIC and development of ceftobiprole resistance was not observed
- Mortality, microbiological eradication, and new SAB complications were similar between treatment groups
- Both treatments well tolerated; nausea more common with ceftobiprole
- Ceftobiprole could become a treatment option for complicated SAB

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- The use of ceftobiprole medocaril in the indication of *S. aureus* bacteremia is investigational and has not been approved by a regulatory authority.

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