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MAJOR ARTICLE

Dalbavancin for the Treatment of Acute Bacterial Skin and Skin Structure Infection in Patients With Obesity or Diabetes: A Subgroup Analysis of Pooled Phase 3 Clinical Trials

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Background. We assessed the efficacy and safety of dalbavancin, a long-acting lipoglycopeptide with activity against Gram-positive pathogens, for treatment of acute bacterial skin and skin structure infections (ABSSSI) in patients with high body mass index (BMI) and/or diabetes.

Methods. Data from two phase 3 trials of dalbavancin (1000 mg intravenous [IV], day 1; 500 mg IV, day 8) versus comparator and one phase 3b trial of single-dose (1500 mg IV, day 1) versus 2-dose (1000 mg IV, day 1; 500 mg IV, day 8) dalbavancin in adults with ABSSSI were pooled and summarized separately by baseline BMI and diabetes status. Clinical success at 48 to 72 hours (≥20% reduction in lesion size), end of treatment ([EOT] day 14), and day 28 was evaluated in the intent-to-treat (ITT) and microbiological ITT (microITT) populations. Safety data were reported in patients who received ≥1 dose of study drug.

Results. In the dalbavancin ITT population (BMI, n = 2001; diabetes, n = 2010), at 48 to 72 hours (and EOT) clinical success was achieved in 89.3% (EOT, 90.9%) of patients with normal BMI and 78.9% to 87.6% (EOT, 91.0% to 95.2%) of patients with elevated BMI. Clinical success after dalbavancin treatment was achieved in 82.4% (EOT, 90.8%) of patients with diabetes and 86.0% (EOT, 91.6%) of patients without diabetes. Similar trends were observed for infections due to methicillin-resistant *Staphylococcus aureus* or methicillin-susceptible *S aureus* (microITT population).

Conclusions. Dalbavancin is effective, with sustained clinical success rates in patients with obesity or diabetes, with a similar safety profile across patient groups.

Keywords. acute bacterial skin and skin structure infection; dalbavancin; diabetes; obesity.

The incidence and severity of acute bacterial skin and skin structure infections (ABSSSI), including infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), have increased in recent years [1, 2]. Studies have shown that risk factors such as obesity and diabetes can predict poor outcomes, resulting in increased treatment costs and hospitalizations [3–5]. Furthermore, complications and subsequent hospitalizations for skin and soft tissue infections are significantly more common in patients with versus without diabetes [6].

Dalbavancin, a long-acting lipoglycopeptide antibiotic, is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency [7, 8] as a single-dose or 2-dose treatment for ABSSSI in adults and children and has been shown to be efficacious in treating ABSSSI caused by Gram-positive organisms, including MRSA and *Streptococcus* species [9–11]. Once-weekly intravenous (IV) dalbavancin has been shown to be noninferior to twice-daily IV vancomycin with an optional switch to oral linezolid [9], and a single 1500-mg dose of dalbavancin was shown to be noninferior to the 2-dose regimen [10]. Use of dalbavancin in an outpatient setting was shown to provide high patient satisfaction, making it an attractive treatment option for ABSSSI [12]. In this study, we present the results of a pooled analysis of 3 phase 3 clinical trials of dalbavancin treatment for ABSSSI: DUR001-301, DUR001-302, and DUR001-303.

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METHODS

Data from 2 double-blind, phase 3 trials of dalbavancin (1000 mg IV over 30 minutes on day 1 and 500 mg IV on day 8) versus comparator (vancomycin 1000 mg IV over 120 minutes every 12 hours for 3 days, with potential switch to oral linezolid 600 mg every 12 hours from day 4 until treatment completion [10–14 days]; DUR001-301 and DUR001-302) and 1 phase 3b trial of dalbavancin as a single dose (1500 mg IV on day 1) versus 2 doses (1000 mg IV on day 1, 500 mg IV on day 8; DUR001-303) for the treatment of ABSSSI in adults (Supplementary Table 1) were pooled and summarized separately by baseline body mass index ([BMI] healthy weight, <25 kg/m^2; overweight, 25–<30 kg/m^2; obesity class 1, 30–<35 kg/m^2; obesity class 2 or 3, ≥35 kg/m^2) and diabetes status (with/without; determination of diabetes by study is provided in Supplementary Table 1). Because study DUR001-303 demonstrated noninferiority of single-dose versus 2-dose dalbavancin, with a similar safety profile, data from both arms were pooled with the dalbavancin data from the other 2 studies [9, 10]. These studies have been previously described in detail [9, 10] (trial registration NCT01339091, NCT01431339, NCT02127970).

Patient Selection Criteria

Full details of inclusion and exclusion criteria are given in Supplementary Table 2. Adult patients (≥18 years old) with ABSSSI who required significant surgical intervention or had infections involving deeper soft tissue were enrolled if they had the following: major cutaneous abscess, cellulitis, or surgical site/traumatic wound infection with an accompanying area of erythema ≥75 cm^2; ≥2 localized signs or symptoms of ABSSSI (purulent drainage/discharge, fluctuance, heat/localized warmth, tenderness to palpation, or swelling/induration); and ≥1 systemic sign of inflammation (eg, elevated body temperature [≥38°C/100.4°F], white blood cell count >12 000 cells/mm^3, or white blood cell differential count with ≥10% band forms). Patients were excluded if they (1) received antibiotics with a Gram-positive spectrum ≤14 days before randomization (except as a single dose of a short-acting antibiotic), (2) had infections caused by an organism known to be resistant to dalbavancin or vancomycin or due exclusively to Gram-negative bacteria, or (3) had burns, diabetic foot infection, decubitus ulcer, evidence of meningitis, necrotizing fasciitis, gangrene, osteomyelitis, endovascular infection, infected device, or venous catheter entry site infection.

Patient Populations and Endpoints

For DUR001-301 and DUR001-302, the primary efficacy endpoint was clinical response at 48 to 72 hours after study drug initiation, defined as no increase in lesion area and a temperature stable at ≤37.6°C. For DUR001-303, the primary endpoint was clinical response defined as a ≥20% reduction in lesion area relative to baseline and no need for rescue antibiotic therapy for ABSSSI before the 48- to 72-hour assessment. The proportion of patients with a ≥20% reduction in lesion area at 48 to 72 hours after study drug initiation relative to baseline was included as a key sensitivity analysis in studies DUR001-301 and DUR001-302. Because this endpoint was common to all 3 studies and is consistent with FDA guidance on developing drugs for ABSSSI treatment, it was used for the pooled analyses in addition to investigator assessment at end of treatment (14 days) and at 28 days (Supplementary Table 3).

Statistical Analysis

Post hoc analyses of the 3 study endpoints (≥20% reduction in lesion area at 48 to 72 hours with no rescue antibiotic therapy [9, 10] and investigator assessment of clinical response at end of treatment [day 14] and at day 28) were carried out using pooled data in the intent-to-treat ([ITT] all randomized patients) and microbiological ITTs ([microITTs] patients in the ITT population with a pathogen identified at baseline). Data were stratified by baseline pathogen (*S aureus*, including MRSA and methicillin-susceptible *S aureus* [MSSA] and *Streptococcus pyogenes*) and by treatment and BMI/diabetes subgroup. Response rates and corresponding confidence intervals based on the Clopper-Pearson exact method were calculated [13]. Patients with missing data at 48 to 72 hours or lack of investigator assessment of clinical response at 28 days were considered nonresponders.

In addition, response rates were estimated based on logistic regression models using outcome variables of clinical response at 48 to 72 hours, or investigator assessment of clinical response at end of treatment or at 28 days, and covariates of treatment, BMI or diabetes status, and infection type. Logistic regression analysis was applied to the ITT and microITT populations as well as each baseline pathogen. Wald tests, odds ratios (OR), and corresponding 95% confidence intervals (CIs) obtained from these models were also reported.

Safety

In all studies, safety was assessed in patients who received ≥1 dose of study drug at day 3 or 4, day 8 (at administration of a second dose of study drug), day 14 (defined as end-of-treatment visit), and day 28. An additional safety evaluation was carried out at day 70 in DUR001-301 and DUR001-302 [9, 10].

Patient Consent Statement

Analyses presented in this manuscript are post hoc analyses of previously published data and as such do not require de novo patient consent. This article is based on previously conducted studies the design of the which were approved by the institutional review board or ethics committee at each study site.

Table 1. Patient Demographics and Baseline Disease Characteristics by BMI Category (ITT Population)[a]

	BMI, kg/m^2							
	Dalbavancin (n = 1350)				Vancomycin (n = 651)			
Characteristic	<25 (n = 419)	25–<30 (n = 460)	30–<35 (n = 244)	≥35 (n = 227)	<25 (n = 212)	25–<30 (n = 199)	30–<35 (n = 130)	≥35 (n = 110)
Age, median (range), years	45.0 (18–85)	51.0 (18–84)	52.0 (19–85)	52.0 (18–85)	48.5 (18–84)	51.0 (19–84)	52.0 (19–85)	52.0 (18–85)
Male, n (%)	273 (65.2)	290 (63.0)	132 (54.1)	100 (44.1)	129 (60.8)	133 (66.8)	71 (54.6)	40 (36.4)
Race, n (%)								
White	377 (90.0)	415 (90.2)	219 (89.8)	199 (87.7)	185 (87.3)	174 (87.4)	120 (92.3)	99 (90.0)
Black	24 (5.7)	25 (5.4)	17 (7.0)	21 (9.3)	8 (3.8)	14 (7.0)	3 (2.3)	10 (9.1)
Other	18 (4.3)	20 (4.3)	8 (3.3)	7 (3.1)	19 (9.0)	11 (5.5)	7 (5.4)	1 (0.9)
Diabetes, n (%)								
No	400 (95.5)	418 (90.9)	215 (88.1)	166 (73.1)	199 (93.9)	187 (94.0)	97 (74.6)	76 (69.1)
Yes	19 (4.5)	42 (9.1)	29 (11.9)	61 (26.9)	13 (6.1)	12 (6.0)	33 (25.4)	34 (30.9)
Creatinine Clearance, mL/min								
Mean (SD)	104.2 (38.5)	90.3 (33.5)	84.8 (34.5)	84.7 (35.3)	96.4 (36.8)	94.8 (37.0)	83.2 (34.9)	89.0 (44.4)
Median (range)	101.6 (17.2–255.1)	89.8 (14.6–206.1)	83.7 (17.5–234.8)	81.4 (12.4–203.8)	96.4 (20.9–198.2)	92.4 (10.6–210.3)	79.8 (21.0–176.2)	78.9 (22.0–224.9)
C-Reactive Protein								
n[b]	411	452	235	224	202	196	127	106
Median (range), mg/L	52.8 (0.2–300.0)	52.6 (0.6–361.9)	60.3 (0.4–443.7)	79.1 (0.1–435.5)	69.2 (0.5–300.0)	56.0 (0.3–300.0)	78.1 (3.1–300.0)	74.1 (1.9–300.0)
Infection Type, n (%)								
Cellulitis	162 (38.7)	226 (49.1)	132 (54.1)	156 (68.7)	102 (48.1)	85 (42.7)	79 (60.8)	75 (68.2)
Major abscess	117 (27.9)	134 (29.1)	57 (23.4)	46 (20.3)	65 (30.7)	66 (33.2)	26 (20.0)	26 (23.6)
Traumatic wound/surgical site infection	140 (33.4)	100 (21.7)	55 (22.5)	25 (11.0)	45 (21.2)	48 (24.1)	25 (19.2)	9 (8.2)
SIRS Criteria at Baseline[c]								
n[b]	419	458	244	227				
n (%)	178 (42.5)	205 (44.8)	126 (51.6)	125 (55.1)	107 (50.5)	100 (50.3)	71 (54.6)	58 (52.7)
Temperature								
n[b]	417	457	243	227	212	196	130	110
≥38°C, n (%)	339 (81.3)	393 (86.0)	206 (84.8)	184 (81.1)	172 (81.1)	164 (83.7)	118 (90.8)	98 (89.1)
WBC Count								
n[b]	413	445	239	220	200	192	123	105
>12 000 Cells/mm^3, n (%)	171 (41.4)	153 (34.4)	92 (38.5)	89 (40.5)	85 (42.5)	77 (40.1)	46 (37.4)	41 (39.0)
Bandemia								
n[b]	326	346	176	162	156	160	83	78
≥10%, n (%)	72 (22.1)	66 (19.1)	35 (19.9)	40 (24.7)	38 (24.4)	34 (21.3)	20 (24.1)	16 (20.5)
Infection Area, cm^2								
n[b]	418	458	244	227	212	199	130	110
Mean (SD)	385.5 (383.2)	459.7 (484.4)	476.4 (436.4)	737.6 (796.0)	477.6 (486.0)	473.4 (407.3)	707.3 (689.7)	681.1 (674.5)

Table 1. Continued

Characteristic	BMI, kg/m^2							
	Dalbavancin (n = 1350)				Vancomycin (n = 651)			
	<25 (n = 419)	25–<30 (n = 460)	30–<35 (n = 244)	≥35 (n = 227)	<25 (n = 212)	25–<30 (n = 199)	30–<35 (n = 130)	≥35 (n = 110)
Median (range)	289.0 (60.5–5100.0)	303.4 (56.0–4774.0)	304.3 (25.6–2667.6)	410.0 (88.4–4235.0)	310.0 (80.1–3675.0)	371.0 (80.1–2484.0)	420.8 (72.0–3922.0)	405.4 (82.5–3688.1)

Abbreviations: BMI, body mass index; ITT, intent to treat; SD, standard deviation; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

[a]Analysis was completed on patients with nonmissing BMI data.

[b]For characteristics where n differs from subgroup total owing to missing data.

[c]Defined as having ≥2 of the following: temperature <36°C or >38°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute; WBC count <4000 or >12 000 cells/mm^3; or >10% bandemia.

Ethics

All studies were performed in accordance with the following: the Declaration of Helsinki; the study protocols; the International Council on Harmonisation tripartite guideline E6(R1), Good Clinical Practice (ICH E6[R1]); and the institutional review board or ethics committee at each study site.

RESULTS

Patients and Disease Characteristics

Across the 3 clinical trials, BMI data were available for 2001 patients (dalbavancin, n = 1350; vancomycin, n = 651) (Table 1). Approximately 30% of patients had BMI <25 kg/m^2 (healthy weight) or 25–30 kg/m^2 (overweight), and approximately 20% each had BMI of 30–<35 kg/m^2 (obesity class 1) or ≥35 kg/m^2 (obesity class 2 or 3) (Table 1). Diabetes status was available for 2010 patients (dalbavancin, n = 1357; vancomycin, n = 653); approximately 12% had diabetes (Table 2). Baseline demographic and disease characteristics were broadly similar across the 3 trials [9, 10] and across treatment groups in the pooled dataset. The proportion of patients with diabetes in the dalbavancin and vancomycin groups increased with increasing BMI category (<25 kg/m^2, 4.5% and 6.1%, respectively; ≥35 kg/m^2, 26.9% and 30.9%) (Table 1). More patients with diabetes were obesity class 2 or 3 BMI category than those without (dalbavancin, 39.9% vs 13.8%; vancomycin, 37.0% vs 13.5%). Median creatinine clearance rate showed a decreasing trend with increasing BMI and was numerically lower among patients with versus without diabetes (Table 2). Mean infection area was larger with increasing BMI category and was also larger in patients with diabetes (Tables 1 and 2).

In both treatment groups, cellulitis was the most common reason for treatment across all BMI and diabetes strata; the proportion of patients with cellulitis was higher in patients with higher BMI and in those with diabetes (Tables 1 and 2). In the dalbavancin treatment group, 38.7% of patients with BMI <25 kg/m^2 had cellulitis, compared with 68.7% of patients with BMI ≥35 kg/m^2. In the vancomycin treatment group, 48.1% of patients with BMI <25 kg/m^2 had cellulitis, compared with 68.2% of patients with BMI ≥35 kg/m^2. Cellulitis was the infection type for 48.9% and 50.3% of patients without diabetes in the dalbavancin and vancomycin treatment groups, respectively, compared with 58.2% and 66.3% of patients with diabetes.

In the microITT population, ABSSSI pathogens isolated from the ABSSSI site or blood were predominantly *S aureus* in patients treated with dalbavancin (72.0%, 69.3%, 80.7%, and 68.2% for BMI <25 kg/m^2, 25–<30 kg/m^2, 30–<35 kg/m^2, and ≥35 kg/m^2, respectively) (Table 3). MRSA were isolated in a larger proportion of patients with BMI ≥35 kg/m^2 (dalbavancin-treated, 31.8%) than patients with lower BMI (eg, BMI <25 kg/m^2, 24.8%). There was no difference in the

Table 2. Patient Demographics and Baseline Disease Characteristics by Diabetes Status (ITT Population)[a]

Characteristic	Dalbavancin (n = 1357)		Vancomycin (n = 653)	
	With Diabetes (n = 153)	Without Diabetes (n = 1204)	With Diabetes (n = 92)	Without Diabetes (n = 561)
Age, median (range), years	57.0 (19–85)	48.5 (18–85)	57.0 (20–84)	50.0 (18–84)
Male, n (%)	80 (52.3)	720 (59.8)	39 (42.4)	335 (59.7)
Race, n (%)				
White	131 (85.6)	1084 (90.0)	75 (81.5)	504 (89.8)
Black	13 (8.5)	75 (6.2)	7 (7.6)	29 (5.2)
Other	9 (5.9)	45 (3.7)	10 (10.9)	28 (5.0)
Body Mass Index, kg/m^2, n (%)				
<25	19 (12.4)	400 (33.2)	13 (14.1)	199 (35.5)
25–<30	42 (27.5)	418 (34.7)	12 (13.0)	187 (33.3)
30–<35	29 (19.0)	215 (17.9)	33 (35.9)	97 (17.3)
≥35	61 (39.9)	166 (13.8)	34 (37.0)	76 (13.5)
Creatinine Clearance, mL/min				
Mean (SD)	77.9 (34.1)	94.5 (36.3)	78.9 (38.9)	94.2 (37.6)
Median (range)	74.4 (14.6–199.0)	92.6 (12.4–255.1)	71.0 (10.6–224.9)	92.0 (20.6–210.3)
C-Reactive Protein				
n[b]	151	1171	88	544
Median (range), mg/L	84.5 (0.2–300.0)	53.6 (0.1–433.7)	86.7 (2.8–300.0)	60.4 (0.3–300.0)
Infection Type, n (%)				
Cellulitis	89 (58.2)	589 (48.9)	61 (66.3)	282 (50.3)
Major abscess	34 (22.2)	324 (26.9)	23 (25.0)	160 (28.5)
Traumatic wound/surgical site infection	30 (19.6)	291 (24.2)	8 (8.7)	119 (21.2)
SIRS Criteria at Baseline[c]				
n[b]	151	1197	92	560
n (%)	74 (49.0)	560 (46.8)	55 (59.8)	281 (50.2)
Temperature				
n[b]	151	1193	92	557
≥38°C, n (%)	118 (78.1)	1004 (84.2)	77 (83.7)	475 (85.3)
WBC Count				
n[b]	149	1168	87	534
>12 000 cells/mm^3, n (%)	64 (43.0)	441 (37.8)	44 (50.6)	206 (38.6)
Bandemia				
n[b]	108	902	59	419
≥10%, n (%)	28 (25.9)	185 (20.5)	13 (22.0)	95 (22.7)
Infection Area, cm^2				
n	151	1196	92	560
Mean (SD)	524.3 (606.7)	481.8 (518.6)	737.1 (805.1)	530.1 (503.6)
Median (range)	300.0 (77.4–3128.0)	311.9 (25.6–5100.0)	393.0 (72.0–3922.0)	363.3 (77.6–3675.0)

Abbreviations: ITT, intent to treat; SD, standard deviation; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

[a]Analysis was completed on patients with nonmissing diabetes status.

[b]For characteristics where n differs from subgroup total owing to missing data.

[c]Defined as having ≥2 of the following: temperature <36°C or >38°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute; WBC count <4000 or >12 000 cells/mm^3; or >10% bandemia.

predominant pathogens isolated from patients with diabetes at baseline versus those without. Pathogens isolated at baseline from patients treated with vancomycin were comparable to those of dalbavancin-treated patients across BMI and diabetes categories.

Clinical Outcomes

In the overall ITT population, clinical response rates 48 to 72 hours after dalbavancin administration were 89.3% (95% CI, 86.3–92.2), 87.6% (95% CI, 84.6–90.6), 84.4% (95% CI, 79.9–89.0), and 78.9% (95% CI, 73.5–84.2) in BMI categories <25 kg/m^2, 25–<30 kg/m^2, 30–<35 kg/m^2, and ≥35 kg/m^2, respectively. Clinical response rates for the overall microITT population and for patients with *S aureus* isolated at baseline followed a similar pattern; patients with BMI ≥35 kg/m^2 had a slightly lower response rate (overall microITT, 83.2% [95% CI, 76.1–90.3]; *S aureus*, 86.3% [95% CI, 78.4–94.2]) than those with BMI <25 kg/m^2 (overall microITT, 91.8% [95% CI, 88.6–

Table 3. ABSSSI Pathogens Isolated From the ABSSSI Site or Blood at Baseline by BMI Subgroup and Diabetes Status (microITT Population)

Organisms Isolated at Baseline	Dalbavancin (n = 765)				Vancomycin (n = 327)				Dalbavancin (n = 767)		Vancomycin (n = 329)	
	Healthy Weight <25 kg/m^2 (n = 282)	Overweight 25–<30 kg/m^2 (n = 257)	Obese 30–<35 kg/m^2 (n = 119)	Obese ≥35 kg/m^2 (n = 107)	Healthy Weight <25 kg/m^2 (n = 123)	Overweight 25–<30 kg/m^2 (n = 105)	Obese 30–<35 kg/m^2 (n = 57)	Obese ≥35 kg/m^2 (n = 42)	With diabetes (n = 80)	Without diabetes (n = 687)	With diabetes (n = 38)	Without diabetes (n = 291)
Patients with ≥1 Gram-positive organism, n (%)	271 (96.1)	240 (93.4)	114 (95.8)	95 (88.8)	117 (95.1)	102 (97.1)	54 (94.7)	38 (90.5)	74 (92.5)	648 (94.3)	36 (94.7)	277 (95.2)
Staphylococcus aureus	203 (72.0)	178 (69.3)	96 (80.7)	73 (68.2)	90 (73.2)	86 (81.9)	46 (80.7)	33 (78.6)	58 (72.5)	494 (71.9)	29 (76.3)	227 (78.0)
MSSA[a]	134 (47.5)	124 (48.2)	67 (56.3)	39 (36.4)	72 (58.5)	60 (57.1)	37 (64.9)	20 (47.6)	39 (48.8)	327 (47.6)	21 (55.3)	168 (57.7)
MRSA[b]	70 (24.8)	54 (21.0)	29 (24.4)	34 (31.8)	19 (15.4)	25 (23.8)	9 (15.8)	13 (31.0)	19 (23.8)	168 (24.5)	8 (21.1)	59 (20.3)
Streptococcus pyogenes	32 (11.3)	23 (8.9)	7 (5.9)	11 (10.3)	21 (17.1)	10 (9.5)	3 (5.3)	2 (4.8)	4 (5.0)	69 (10.0)	3 (7.9)	33 (11.3)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; BMI, body mass index; microITT, microbiological intent to treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S aureus*.

[a]Eleven patients had MSSA bacteremia at baseline [26].

[b]Four patients had MRSA bacteremia at baseline [26].

95.0]; *S aureus*, 91.1% [95% CI, 87.2–95.0]) (Figure 1*A*; Supplementary Table 4).

At end of dalbavancin treatment, investigator-assessed clinical response rates in the ITT population were 90.9% (95% CI, 88.2–93.7), 92.0% (95% CI, 89.5–94.4), 91.0% (95% CI, 87.4–94.6), and 95.2% (95% CI, 92.4–97.9) in BMI categories <25 kg/m^2, 25–30 kg/m^2, 30–<35 kg/m^2, and ≥35 kg/m^2, respectively. At the 28-day timepoint after dalbavancin treatment, response rates were slightly lower across all BMI strata, but they remained at 94.3% for patients with BMI ≥35 kg/m^2 (Figure 1*A*; Supplementary Table 4). Clinical response to vancomycin followed a similar pattern. Patients in the microITT population with infections due to MRSA and MSSA also had slightly numerically lower clinical response rates at 48 to 72 hours with increasing BMI, but they had numerically higher clinical success rates per investigator assessment at end of treatment (Supplementary Table 4).

In the ITT population, clinical response rates to dalbavancin treatment among patients with diabetes were 82.4% (95% CI, 76.3–88.4) compared with 86.0% (95% CI, 84.1–88.0) for patients without diabetes (Figure 1*B*; Supplementary Table 5). Similar to the data stratified by BMI, clinical response rates were slightly higher at end of treatment than at 48 to 72 hours (90.8% [95% CI, 86.3–95.4] and 91.6% [95% CI, 90.0–93.2] for patients with and without diabetes, respectively). At the 28-day timepoint, clinical response rate was slightly lower than at end of treatment. Clinical response rates to vancomycin followed a similar pattern.

Trends in the proportion of patients achieving success for these endpoints were similar in the microITT population and in the by-pathogen analyses for the 2 treatment groups (Supplementary Table 5). However, because these analyses were carried out post hoc, it is not possible to evaluate the statistical significance of any differences in clinical response rate between groups.

Safety

The incidence of treatment-emergent adverse events (TEAEs) overall was lower in patients treated with dalbavancin compared with vancomycin across BMI strata (Table 4). In both treatment groups, the proportion of patients experiencing TEAEs increased with increasing BMI; 31.7% and 47.7% of patients with BMI ≥35 kg/m^2 treated with dalbavancin and vancomycin, respectively, experienced 1 or more TEAEs. The incidence of drug-related TEAEs, serious TEAEs, and TEAEs leading to study drug discontinuation among dalbavancin-treated patients was comparable across BMI categories. Among vancomycin-treated patients, those in the highest BMI category (≥35 kg/m^2) reported more drug-related TEAEs, serious TEAEs, and TEAEs leading to study drug discontinuation than those in the lower BMI categories.

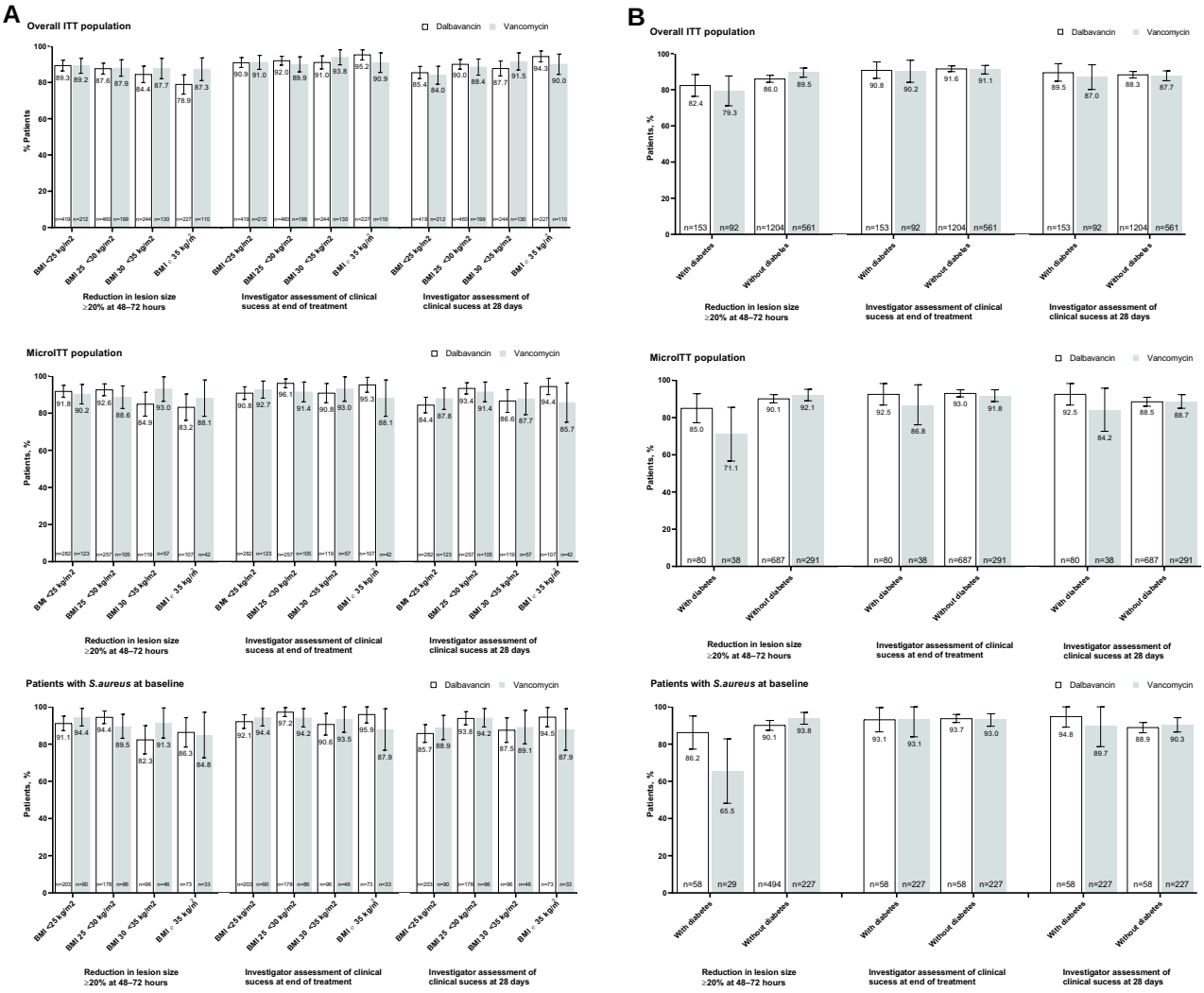

Figure 1. Outcomes stratified by (*A*) body mass index (BMI) category and (*B*) diabetes status for the overall intent-to-treat (ITT) population, the microbiological ITT (microITT) population, and patients with *Staphylococcus aureus* at baseline.

Incidences of TEAEs in patients with and without diabetes were 31.1% and 25.6%, respectively, for dalbavancin-treated patients, and 48.9% and 36.1% for vancomycin-treated patients (Table 4). In patients with and without diabetes, drug-related TEAEs were reported in 10.6% and 9.6% of dalbavancin-treated patients and 15.2% and 13.4% of vancomycin-treated patients, respectively. Few patients discontinued treatment because of TEAEs (dalbavancin, 2.0% with vs 1.8% without diabetes; vancomycin, 3.3% vs 1.8%, respectively).

DISCUSSION

This post hoc analysis of pooled phase 3 trial data demonstrates that treatment of ABSSSI with dalbavancin is effective across BMI strata and in patients with and without diabetes.

Owing to the small sample size of some subgroups, the high response rate to both study drugs, and the post hoc nature of the analysis, the statistical power of comparisons between dalbavancin and vancomycin and between BMI and diabetes status is low. However, we did use the results of our logistic regression model (Supplementary Table 6) to calculate OR for clinical response for comparisons between BMI subgroups, infection types, and the presence or absence of diabetes (Supplementary Table 7). The OR for clinical response in patients with BMI <25 kg/m^2 compared with patients with BMI ≥35 kg/m^2 was 1.54 (95% CI, 1.05–2.26) at 48 to 72 hours in the ITT population; the OR for this comparison at end of treatment was 0.68 (95% CI, 0.40–1.15), indicating that patients with higher BMI had a higher odds of clinical response than those of healthy weight at end of treatment but not after 48 to 72 hours. Similarly, the presence of diabetes was associated

Table 4. Safety of Dalbavancin Stratified by BMI Category and Diabetes Status (Safety Population)

Adverse Event, n (%)	Dalbavancin (n = 1347)				Vancomycin (n = 650)				Dalbavancin (n = 1347)		Vancomycin (n = 650)	
	<25 kg/m^2 (n = 418)	25–<30 kg/m^2 (n = 458)	30–<35 kg/m^2 (n = 244)	≥35 kg/m^2 (n = 227)	<25 kg/m^2 (n = 212)	25–<30 kg/m^2 (n = 199)	30–<35 kg/m^2 (n = 130)	≥35 kg/m^2 (n = 109)	With Diabetes (n = 151)	Without Diabetes (n = 1196)	With Diabetes (n = 92)	Without Diabetes (n = 559)
Any TEAE	113 (27.0)	107 (23.4)	61 (25.0)	72 (31.7)	78 (36.8)	67 (33.7)	49 (37.7)	52 (47.7)	47 (31.1)	306 (25.6)	45 (48.9)	202 (36.1)
Drug-related TEAE	43 (10.3)	35 (7.6)	26 (10.7)	27 (11.9)	24 (11.3)	27 (13.6)	18 (13.8)	20 (18.3)	16 (10.6)	115 (9.6)	14 (15.2)	75 (13.4)
Serious TEAE	6 (1.4)	14 (3.1)	5 (2.0)	4 (1.8)	8 (3.8)	9 (4.5)	3 (2.3)	6 (5.5)	7 (4.6)	22 (1.8)	11 (12.0)	15 (2.7)
TEAE leading to premature discontinuation of study drug	6 (1.4)	14 (3.1)	3 (1.2)	2 (0.9)	4 (1.9)	3 (1.5)	2 (1.5)	4 (3.7)	3 (2.0)	22 (1.8)	3 (3.3)	10 (1.8)

Abbreviations: BMI, body mass index; TEAE, treatment-emergent adverse event.

with lower odds of a clinical response at 48 to 72 hours after dalbavancin treatment compared with patients without diabetes (OR = 0.69 [95% CI, 0.48–0.99]) and at later timepoints approached equivalence. Comparisons between infection types showed that patients with cellulitis have lower odds of achieving clinical success at 48 to 72 hours post-dalbavancin treatment than patients with major cutaneous abscess (ITT population; 0.48 [95% CI, 0.34–0.68]) or surgical site/traumatic wound infection (0.48 [95% CI, 0.33–0.68]), whereas at later timepoints the OR approached equivalence. Taken together, these 3 comparisons suggest that the lower clinical response rate at the earlier timepoint is due to the higher incidence of cellulitis at baseline among patients with higher BMI or diabetes (dalbavancin; < 25 kg/m^2, 38.7%; 25-$<$30 kg/m^2, 49.1%; 30-$<$35 kg/m^2, 54.1%; $\geq$35 kg/m^2, 68.7%; with diabetes, 58.2%; without diabetes, 48.9%). Cellulitis is an acute inflammatory response to microbial infection of the dermis and/or subcutaneous tissues, commonly due to skin commensals, which are able to invade due to deficiencies in skin integrity, immunity, or vasculature, all 3 of which are compromised in patients with obesity or diabetes [14]. Obesity is an independent risk factor for cellulitis regardless of metabolic phenotype, and poor glycemic control is associated with the development of cellulitis [15, 16]. A small number of retrospective and case-control studies have shown that obesity is associated with poorer outcomes of antimicrobial treatment of cellulitis [17, 18]. It is known that resolution of cellulitis after administration of intravenous antibiotics can be slow, and fever and inflammation may persist during the first 72 hours [19]. For this reason, clinical response rate at the end of treatment may be a more appropriate endpoint for patients with cellulitis.

The safety profile of dalbavancin was comparable across all BMI strata. However, among patients treated with vancomycin, those with higher BMI or with diabetes reported a higher incidence of TEAEs and drug-related TEAEs. This is likely due to the higher rates of nephrotoxicity in patients treated with vancomycin compared with those treated with dalbavancin, as shown in a previous analysis of pooled data from the same 3 studies [20].

The findings of these subgroup analyses support the use of dalbavancin in patients with ABSSSI and significant comorbidities, such as high BMI and diabetes. Dalbavancin offers health resource and cost savings over vancomycin in the treatment of ABSSSI: its extended terminal half-life of 14.4 days allows administration as a single dose, with a short infusion time, and thus may be used in an ambulatory setting [9, 10].

In similar analyses, researchers have evaluated the safety and efficacy of antibiotics, such as oritavancin, omadacycline, and delafloxacin, for the treatment of ABSSSI in patients with higher BMI and diabetes. A subgroup analysis of SOLO-I, a double-blind study comparing the efficacy and safety of a single IV dose of oritavancin with IV vancomycin in adults with

ABSSSI, showed that there was no significant difference in outcomes based on BMI or diabetes status [21]. A pooled subgroup analysis of SOLO-I and SOLO-II (similar design to SOLO-I) showed that high-risk patients (based on the Eron classification system) in the oritavancin and vancomycin treatment groups had comparable clinical efficacy [22]. Subgroup analysis of OASIS 1 showed that the transition from IV to oral omadacycline was well tolerated and effective in patients regardless of BMI or diabetes status [23]; these results were supported by pooled subgroup analyses of OASIS 1 and 2 by diabetes [24] and BMI [24] status. A pooled subgroup analysis showed that delafloxacin had similar efficacy and safety outcomes to vancomycin in patients with obesity [25].

Limitations

Data from the DUR001-303 study were pooled across the 2 dalbavancin-dosing regimens (single- and 2-dose) and combined with data from DUR001-301 and DUR001-302 (2-dose regimen); because the single-dose regimen has been shown to be noninferior to the 2-dose regimen, this was considered acceptable for the purpose of the analysis [10].

Given differences in the definition of programmatically determined clinical success at end of treatment and day 28 among the 3 studies, investigator assessment of clinical success was used. Across treatment groups and strata, the investigator assessment of clinical success at 28 days was generally several percentage points higher than programmatically determined success based on the definitions.

Finally, the data presented here show patients stratified according to BMI or diabetes status but not both. When the data were stratified according to both BMI and diabetes status, slight numerical decreases were noted in the proportions of patients achieving ≥20% reduction in lesion area at 48 to 72 hours as BMI increased in patients with and without diabetes treated with dalbavancin (Supplementary Table 8), consistent with the overall analysis. This trend was not apparent at the later endpoints assessed by the investigator in the dalbavancin group; the numbers of patients included, particularly in the diabetes subgroups, were too small in the vancomycin group to allow meaningful comparisons.

CONCLUSIONS

The results of this study show that dalbavancin is effective with sustained clinical success rates in patients with obesity or diabetes, with a similar safety profile across patient groups.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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