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The Safety and Efficacy of Dalbavancin and Active Comparator in Pediatric Patients With Acute Bacterial Skin and Skin Structure Infections

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Background: Acute bacterial skin and skin structure infections (ABSSSIs) are a significant source of morbidity in children. Dalbavancin, approved for the treatment of adults and children with ABSSSI, has a well-established safety profile in adults. We report safety and descriptive efficacy data for the treatment of ABSSSI in children.

Methods: Children with ABSSSI (birth–<18 years old) or sepsis (<3 months old) known/suspected to be caused by susceptible Gram-positive organisms were enrolled in this phase 3, multicenter, open-label, comparator-controlled study (NCT02814916). Children ≥3 months old were randomized 3:3:1 to receive single-dose dalbavancin, 2-dose dalbavancin, or a comparator antibiotic in 4 age cohorts; those <3 months old received single-dose dalbavancin. Clinical response and microbiologic efficacy were evaluated 48–72 hours and 14, 28 and 54 days posttreatment. Bowel flora testing and audiology were collected in a subset of patients at baseline and day 28. Adverse events (AEs) were collected throughout the study.

Results: Treatment-emergent AEs occurred in 7.2%, 9.0% and 3.3% of patients in dalbavancin single-dose, dalbavancin 2-dose and comparator arms, respectively. Three serious AEs occurred in the dalbavancin single-dose arm; no treatment-related AEs, serious AEs, or AEs leading to study discontinuation were reported. Favorable clinical response at 48–72 hours was documented in 97.4%, 98.6% and 89.7% of patients. Safety and efficacy were comparable across age cohorts. The microbiologic intent-to-treat population had comparable clinical response for all baseline pathogens, including methicillin-resistant *Staphylococcus aureus*.

Conclusion: The safety profile of dalbavancin was consistent in children and adults with ABSSSI. No new safety signals were identified.

Key Words: acute bacterial skin and skin structure infection, dalbavancin, safety, pediatric

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Acute bacterial skin and skin structure infections (ABSSSIs) are a significant source of morbidity in children.[1,2] Studies have shown that among culture-positive skin and soft tissue infections in the United States, the majority were caused by *Staphylococcus aureus*, and nearly half of those were methicillin resistant (MRSA).[3,4] Community-acquired MRSA appears to have initially emerged and spread in children and is now one of the most common SSSI pathogens affecting children and adults.[5,6] The epidemiology of *S. aureus*, characterized by successive emergence of regionally predominant strains, is reflected in other regions of the world,[7,8] resulting in an increased need for antibiotics with a spectrum of activity that includes MRSA for the empiric treatment of ABSSSI.[9,10]

The long-acting, second-generation lipoglycopeptide antibiotic dalbavancin has been approved for use in adults and children by the US Food and Drug Administration (FDA) and for use in adults by the European Medicines Agency for intravenous (IV) treatment of ABSSSI caused by susceptible strains of *S. aureus* (including methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, *S. agalactiae*, *S. dysgalactiae*, *S. anginosus* (including *S. intermedius, S. constellatus*), and vancomycin-susceptible strains of *Enterococcus faecalis*.[11,12]

The safety and efficacy of IV dalbavancin in adults have been demonstrated in several phase 2[13,14] and pivotal phase 3[15–17] trials. Previous pediatric trials reported no serious adverse events (SAEs) or deaths related to dalbavancin treatment. In addition, audiograms showed no evidence of ototoxicity due to dalbavancin administration in those patients for whom results were obtained and evaluable.

The pharmacokinetics (PK) of dalbavancin is well characterized in adults and shown to be linear, with low variability and long terminal elimination half-life (>14 days), allowing for simplified dosing regimens.[18–20] In adults, the standard treatment regimen is 1500 mg, either as a single dose or as 1000 mg followed 1 week later by a 500-mg dose, administered by IV infusion over 30 minutes.

Based on the findings of study DUR001-306, a phase 3 pediatric study in patients with ABSSSI (NCT02814916), 3 PK studies

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These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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in pediatric subjects (A8841004, NCT00678106; DUR001-106, NCT01946568; DAL-PK-02, NCT02688790), and PK/pharmacodynamics (PD) modeling and simulations, dalbavancin received FDA approval (July 2021) for treatment of ABSSSI in pediatric patients. PK data from these 4 studies were used to develop a population PK model for dalbavancin in pediatric patients that was used to conduct simulations supporting the approved pediatric dose regimens.[19,21–23]

We now report the safety and descriptive efficacy for study DUR001-306.

MATERIALS AND METHODS

Objectives

The primary objective was to determine the safety of dalbavancin in children from birth to <18 years of age for the treatment of ABSSSI caused by susceptible Gram-positive organisms, including MRSA. Secondary objectives included descriptive efficacy of dalbavancin for treating pediatric patients with ABSSSI based on clinical response at 48–72 hours, end of treatment (EOT), and test of cure (TOC) and evaluation of the PK of dalbavancin in pediatric patients with ABSSSI.

Study Design and Patients

Study DUR001-306 was a multicenter, open-label, randomized, comparator-controlled trial evaluating the safety and efficacy of a single dose of IV dalbavancin and a 2-dose regimen of once-weekly IV dalbavancin versus comparator for the treatment of ABSSSI in children known or suspected to be due to susceptible Gram-positive organisms.

Pediatric patients with ABSSSI (birth to <18 years old) or sepsis (<3 months old only) were eligible for enrollment (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/E893). Patients ≥3 months old were enrolled in 1 of 4 age cohorts (cohort 1, 12–<18 years; cohort 2, 6–<12 years; cohort 3, 2–<6 years; and cohort 4, 3 months to <2 years) and randomized to dalbavancin (single-dose or 2-dose regimen) or comparator (IV vancomycin, oxacillin or flucloxacillin). Patients in a fifth cohort (birth to <3 months old) were not included in the randomization scheme and were all assigned to single-dose dalbavancin.

Patients randomized to the single-dose regimen of dalbavancin received dalbavancin IV administered over 30 ± 5 minutes: cohorts 1 and 2, 18 mg/kg (maximum 1500 mg) on day 1; cohorts 3 and 4, 22.5 mg/kg (maximum 1500 mg) on day 1. Patients randomized to the 2-dose regimen of dalbavancin also received dalbavancin IV administered over 30 ± 5 minutes: cohorts 1 and 2, 12 mg/kg (maximum 1000 mg) on day 1, and 6 mg/kg (maximum 500 mg) on day 8; cohorts 3 and 4, 15 mg/kg (maximum 1000 mg) on day 1, and 7.5 mg/kg (maximum 500 mg) on day 8. Patients in cohort 5 received a single-dose regimen of dalbavancin 22.5 mg/kg IV on day 1 administered over 30 ± 5 minutes. Patients in cohorts 1–4 randomized to comparator antibiotic received a 10- to 14-day course of IV vancomycin (for methicillin-resistant Gram-positive infections) or oxacillin or flucloxacillin (for methicillin-susceptible Gram-positive infections based on local practice patterns and approvals for clinical use in pediatric patients): vancomycin 10–15 mg/kg/dose, administered over 60 ± 10 minutes every 6 ± 1 hours (maximum dose, 4000 mg/d); oxacillin 30 mg/kg/dose, administered over 60 ± 10 minutes every 6 ± 1 hour; flucloxacillin 50 mg/kg/dose, administered over 60 ± 10 minutes every 6 ± 1 hours (maximum dose, 2000 mg/d). Patients who, after ≥72 hours of IV comparator antibiotic treatment, met study criteria for oral therapy could be switched to oral cefadroxil (from IV oxacillin or flucloxacillin) or oral clindamycin (from IV vancomycin for MRSA). Total planned enrollment was approximately 188 patients (cohorts 1–4, n = 178; cohort 5, n = 10, with ≥5 patients ≤28 days old including preterm infants).

Study Assessments

Safety and efficacy were evaluated in the following patient populations: intent-to-treat (ITT); safety; modified ITT [mITT; randomized patients who received ≥1 dose of study drug and had a diagnosis of ABSSSI (or, in cohort 5, suspected/confirmed sepsis) not known to be caused exclusively by a Gram-negative organism]; clinically evaluable (CE); microbiologic ITT (micro-ITT); and microbiologically evaluable according to definitions shown in Table, Supplemental Digital Content 2, http://links.lww.com/INF/E893. Healthcare resource utilization data were collected on days 14 ± 2 and 28 ± 2. Patient and parent/guardian therapy satisfaction was assessed using the Skin and Soft Tissue

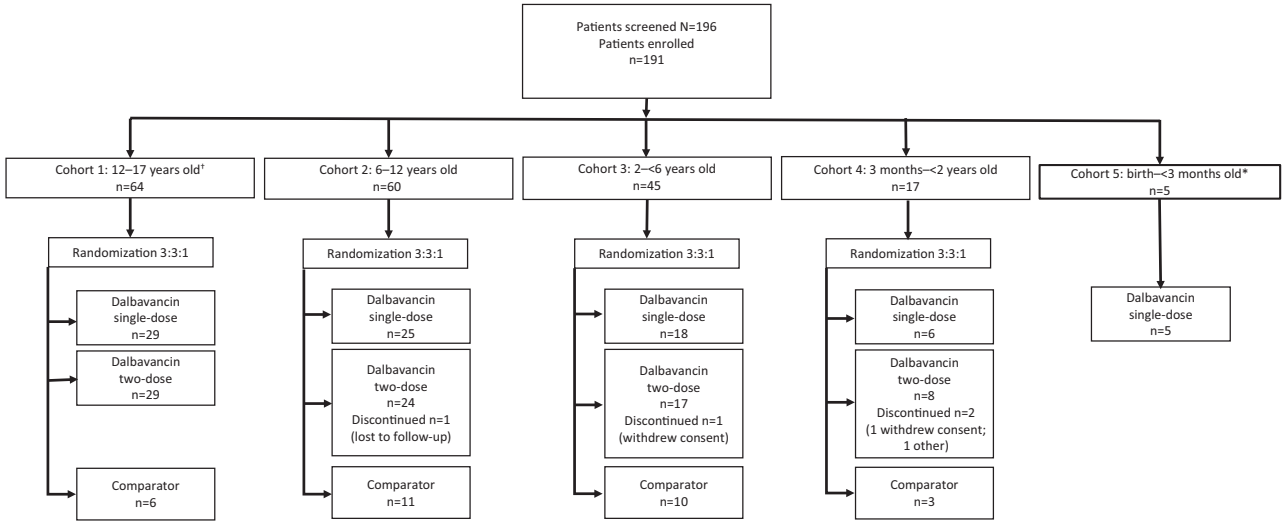

FIGURE 1. Study design. *Including preterm neonates with gestational age ≥32 weeks. †Inclusive.

Infection Convenience questionnaire at day 14 ± 2 and premature discontinuation.

Safety

The primary endpoint of safety and tolerability was evaluated by physical examination (cohorts 1–4, baseline; cohort 5, baseline, 48–72 hours, day 8, EOT, TOC, follow-up visit, and premature discontinuation), vital signs (every visit), AEs (every visit), deaths (cohort 5), clinical laboratory tests [baseline, 48–72 hours (cohort 5), EOT, premature discontinuation], audiology testing and effect of dalbavancin on bowel flora. Audiologic testing was conducted in a subset of children at baseline and at the TOC visit. Audiologic testing included evoked otoacoustic emissions testing, acoustic immittance measures, optional threshold auditory brainstem responses (infants <12 months old), and age-appropriate behavioral audiologic threshold assessment (older children). Patients with any abnormality at TOC visit that had increased from baseline by a clinically significant margin were to be followed up at 3 months and 6 months postdose, as needed, or until return to baseline. The effect of dalbavancin on bowel flora was determined in all patients from birth to <2 years by polymerase chain reaction for *Clostridium difficile* and culture for vancomycin-resistant enterococci (VRE).

Efficacy

As a secondary endpoint, the descriptive efficacy of a single- or 2-dose regimen of dalbavancin IV was compared with the comparator based on clinical response at 48–72 hours, EOT, and TOC according to clinical and microbiologic parameters (Table, Supplemental Digital Content 3, http://links.lww.com/INF/E893). Clinical response at 48–72 hours post-randomization was defined as ≥20% reduction in lesion size compared with baseline in patients who did not receive rescue therapy and were alive (cohorts 1–4). In cohort 5, clinical response in patients with ABSSSI at 48–72 hours post-randomization was defined as cessation of increase in lesion size and decreased erythema or tenderness compared with baseline with no appearance of new lesions. In patients diagnosed with sepsis in cohort 5, clinical response at 48–72 hours post-randomization was defined as an improvement of ≥1 abnormal clinical and laboratory parameter related to sepsis.

Ethics

The study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Patients (2013), the International Conference on Harmonization E6 guideline on Good Clinical Practice, and applicable local laws. All patients and/or their legally authorized representative provided written informed consent/assent and privacy-related documentation in accordance with applicable regulations.

RESULTS

Patient Disposition and Baseline Characteristics

Of 196 patients screened, 191 were enrolled, 98.4% completed the study intervention, and 97.9% completed the treatment and follow-up periods (Fig. 1). Three patients in the dalbavancin 2-dose arm prematurely discontinued the study: 2 withdrew consent (1 each in cohorts 3 and 4) and 1 discontinued for other reasons (cohort 4); 1 patient was lost to follow up (cohort 2). Patient demographics are presented in Table 1.

Baseline Disease Characteristics

In the mITT population (n = 186), ABSSSI types at baseline were major cutaneous abscess, cellulitis, and surgical site/traumatic wound infection. Most patients had erythema ≥35 cm^2 or body surface area (m^2) × 43 cm^2/m^2. The most frequent site of infection was the central face [n = 40 (21.5%)]. The infection area ranged between 4 and 512 cm^2 (median, 55.3 cm^2; Table 1). Clinical signs and symptoms included erythema, purulent discharge, swelling/induration, fluctuance, pain/tenderness to palpation, and heat/localized warmth; erythema and pain/tenderness to palpation were severe in >70% of patients.

Baseline Microbiology

All patients in the microITT population had ≥1 Gram-positive (aerobic) pathogen isolated from the ABSSSI site or blood at baseline, most commonly oxacillin-susceptible *S. aureus* (n = 104; 83.9%). *S. pyogenes* was identified in 12 patients (9.7%), MRSA in 6 (4.8%), *E. faecalis* in 4 (3.2%) and *S. mitis*/*S. oralis* in 3 (2.4%). For all isolates deemed to be pathogens in this study, the minimum inhibitory concentration was below the Clinical and Laboratory Standards Institute/FDA susceptibility breakpoint (0.25 mg/L) for dalbavancin, consistent with previous clinical trials in adult patients with ABSSSI.[13–17]

Baseline bowel flora testing identified 5 patients positive for *C. difficile* and 4 patients positive for VRE in the subset of patients tested (2 patients who tested positive for VRE at baseline were >2 years old).

Safety

Overall, 7.2%, 9.0% and 3.3% in dalbavancin single-dose, dalbavancin 2-dose and comparator arms, respectively, experienced a treatment-emergent AE (TEAE; Table 2). At least 1 patient in every age cohort except cohort 2 experienced a TEAE in each of the dalbavancin treatment arms. The TEAE in the comparator arm was reported in cohort 3. No treatment-related TEAEs were reported. Three serious TEAEs were reported, all in the dalbavancin single-dose arm, with 1 each in cohorts 1 (bacterial osteomyelitis), 4 (convulsion) and 5 (bacterial abscess); these recovered/resolved and were considered unrelated to the study drug. No treatment-related SAEs, AEs leading to discontinuation, or SAEs leading to death were reported. Most TEAEs were mild or moderate in severity.

TEAEs that occurred in >1 patient were pyrexia and cough (each in 2 patients in the dalbavancin 2-dose arm) and postoperative anemia (1 patient in the dalbavancin 2-dose arm and 1 in the comparator arm). All other TEAEs occurred in ≤1 patient in any treatment arm (Table, Supplemental Digital Content 4, http://links.lww.com/INF/E893).

Changes in laboratory parameters (mean white blood cell counts, neutrophils, and high-sensitivity C-reactive protein) from baseline to EOT and end of the study were consistent with the reduction in systemic immune response. There were no clinically significant mean changes in other hematology or chemistry parameters. Changes in vital signs (mean pulse rate, respiratory rate and temperature) decreased from baseline at all study visits and were also consistent with the reduction in systemic immune response. No other clinically meaningful mean changes for vital signs were observed. Audiology parameters at baseline and day 28 in all tested patients showed no signal of ototoxicity; test results at day 28 remained within the clinically normal range. No bone conduction tests were required.

Evaluation of baseline bowel flora in patients <2 years old was repeated at TOC: of 5 patients who tested positive for *C. difficile* at baseline (dalbavancin treatment), 2 tested negative and 3 had missing values. Of the 4 patients who tested positive for VRE at baseline, 1 remained positive and 1 had a missing value at TOC; the remaining 2 were >2 years old and therefore not tested at the TOC visit. All patients who tested negative (or had missing values) for *C. difficile* or VRE at baseline remained negative (or had missing values) at TOC.

TABLE 1. Patient Demographics and Baseline Characteristics, Safety Population

Demographics and Characteristics	Dalbavancin Single-dose (n = 83)	Dalbavancin 2-Dose (n = 78)	Comparator (n = 30)	Total (N = 191)
Age (yr)				
Mean (SD)	8.3 (5.2)	8.9 (4.9)	6.8 (4.2)	8.3 (5.0)
Median (range)	8.0 (0.04–17.0)	9.0 (0.3–17.0)	7.0 (0.8–15.0)	8.0 (0.04–17.0)
Age cohort, n (%)				
Birth to <3 mo	5 (6.0)	NA	NA	5 (2.6)
Birth to ≤28 d	3 (3.6)	NA	NA	3 (1.6)
>28 d to <3 mo	2 (2.4)	NA	NA	2 (1.0)
3 mo to <2 yr	6 (7.2)	8 (10.3)	3 (10.0)	17 (8.9)
2 yr to <6 yr	18 (21.7)	17 (21.8)	10 (33.3)	45 (23.6)
6 yr to <12 yr	25 (30.1)	24 (30.8)	11 (36.7)	60 (31.4)
12 yr to <18 yr	29 (34.9)	29 (37.2)	6 (20.0)	64 (33.5)
Sex, n (%)				
Male	48 (57.8)	53 (67.9)	18 (60.0)	119 (62.3)
Female	35 (42.2)	25 (32.1)	12 (40.0)	72 (37.7)
Race, n (%)				
White	72 (86.7)	69 (88.5)	29 (96.7)	170 (89.0)
Black	4 (4.8)	6 (7.7)	0 (0.0)	10 (5.2)
Asian	1 (1.2)	1 (1.3)	0 (0.0)	2 (1.0)
American Indian or Alaska Native	3 (3.6)	1 (1.3)	1 (3.3)	5 (2.6)
Multiple	3 (3.6)	1 (1.3)	0 (0.0)	4 (2.1)
Ethnicity, n (%)				
Hispanic or Latino	4 (4.8)	7 (9.0)	1 (3.3)	12 (6.3)
Not Hispanic or Latino	79 (95.2)	71 (91.0)	29 (96.7)	179 (93.7)
Weight (kg)				
Mean (SD)	32.9 (20.5)	35.6 (20.6)	27.1 (15.4)	33.1 (19.9)
Median (range)	30.0 (3.2–83.7)	31.6 (7.0–85.0)	20.0 (8.0–56.0)	28.4 (3.2–85.0)
BMI, kg/m^2				
Mean (SD)	18.0 (4.5)	18.4 (4.1)	17.3 (3.0)	18.1 (4.1)
Median (range)	17.1 (11.0–31.6)	17.5 (9.3–29.4)	17.0 (10.8–23.1)	17.2 (9.3–31.6)
Creatinine clearance, mL/min/1.73 m^2				
Mean (SD)	125.3 (26.4)	122.7 (50.9)	126.7 (22.5)	124.4 (38.1)
Median (range)	124.5 (54.0–211.0)	121.0 (42.0–486.0)	127.0 (76.0–175.0)	123.0 (42.0–486.0)
Infection type, n (%)				
Cellulitis	22 (26.5)	19 (24.4)	12 (40.0)	53 (27.7)
Major cutaneous abscess	42 (50.6)	45 (57.7)	14 (46.7)	101 (52.9)
Surgical site/traumatic wound infection	18 (21.7)	14 (17.9)	4 (13.3)	36 (18.8)
Missing	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.5)
Area of infection, cm^2*				
n	78	78	30	186
Mean (SD)	78.6 (62.8)	78.9 (75.6)	80.3 (41.7)	79.0 (65.6)
Median (range)	51.5 (4.0–306.0)	52.3 (15.0–512.0)	77.0 (20.0–180.0)	55.3 (4.0–512.0)

*Modified intent-to-treat population.
BMI indicates body mass index; NA, not applicable.

TABLE 2. Summary of Treatment-Emergent Adverse Events, Safety Population

AEs, n (%)	Dalbavancin Single-Dose (n = 83)	Dalbavancin 2-Dose (n = 78)	Comparator (n = 30)
Overall AEs	6 (7.2)	8 (10.3)	1 (3.3)
TEAEs	6 (7.2)	7 (9.0)	1 (3.3)
Serious TEAEs	3 (3.6)	0 (0.0)	0 (0.0)
AEs leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Cohort 1, ages 12 to <18 yr	n = 29	n = 29	n = 6
TEAEs	1 (3.4)	2 (6.9)	0 (0.0)
Serious TEAEs	1 (3.4)	0 (0.0)	0 (0.0)
Cohort 2, ages 6 to <12 yr	n = 25	n = 24	n = 11
TEAEs	1 (4.0)	0 (0.0)	0 (0.0)
Serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)
Cohort 3, ages 2 to <6 yr	n = 18	n = 17	n = 10
TEAEs	1 (5.6)	1 (5.9)	1 (10.0)
Serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)
Cohort 4, ages 3 mo to <2 yr	n = 6	n = 8	n = 3
TEAEs	1 (16.7)	4 (50.0)	0 (0.0)
Serious TEAEs	1 (16.7)	0 (0.0)	0 (0.0)
Cohort 5, ages birth to <3 mo	n=5	n=0	n=0
TEAEs	2 (40.0)	–	–
Serious TEAEs	1 (20.0)	–	–

TABLE 3. Clinical Response* in Pediatric Patients, All Cohorts, mITT Population

Clinical Response, n (%)	Dalbavancin Single-Dose (n = 78)	Dalbavancin 2-Dose (n = 78)	Comparator (n = 30)
48–72 h	n = 78	n = 74	n = 29
Clinical responder	76 (97.4)	73 (98.6)	26 (89.7)
Clinical non-responder	2 (2.6)	1 (1.4)	3 (10.3)
EOT	n = 77	n = 74	n = 30
Clinical cure	73 (94.8)	68 (91.9)	30 (100)
Improvement	3 (3.9)	4 (5.4)	0 (0.0)
Clinical failure	1 (1.3)	2 (2.7)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
TOC	n = 76	n = 74	n = 30
Clinical cure	73 (96.1)	72 (97.3)	30 (100.0)
Clinical failure	1(1.3)	2 (2.7)	0 (0.0)
Unknown	2 (2.6)	0 (0.0)	0 (0.0)
Follow-up	n = 77	n = 73	n = 30
Clinical cure	75 (97.4)	71 (97.3)	30 (100.0)
Clinical failure	1 (1.3)	2 (2.7)	0 (0.0)
Unknown	1 (1.3)	0 (0.0)	0 (0.0)

*Sponsor assessment.

Efficacy

Clinical Outcomes

Clinical response in the mITT and CE populations (assessed by the sponsor) at 48–72 hours was 97.4%, 98.6% and 89.7% in the dalbavancin single-dose, dalbavancin 2-dose and comparator arms, respectively (Table 3). At this time, the area of erythema had decreased by ≥70% from baseline in 53.8% and 60.3% of the single- and 2-dose dalbavancin-treated patients, respectively, versus 36.7% of comparator-treated patients. At EOT, clinical cure rate was 94.8%, 91.9% and 100.0% in the dalbavancin single-dose, dalbavancin 2-dose and comparator arms, respectively, with all baseline signs of systemic infection resolved (Table 3). At TOC visit, clinical cure rate in the mITT population was 96.1%, 97.3% and 100.0%. There was no relapse or recurrence by time of follow-up in patients with clinical success at TOC.

Clinical outcomes assessed by the investigator and sponsor were similar across mITT and CE populations and most age cohorts at all time points. Concordance between clinical responders at 48–72 hours and a clinical status of cure/improvement at EOT visit was >97% overall in all cohorts.

Clinical Response by Baseline Pathogen

Favorable clinical response in the microITT population at 48–72 hours was similar across pathogens, including MRSA. The majority of patients had a clinical outcome of cure/improvement regardless of baseline pathogen at EOT, TOC and follow-up visits (Table 4).

TABLE 4. Clinical Response* at 48–72 Hours by Key Target Pathogen at Baseline: microITT Population

Clinical Response, n (%)†	Dalbavancin Single-Dose (n = 51)	Dalbavancin 2-Dose (n = 55)	Comparator (n = 18)
Staphylococcus aureus; oxacillin susceptible, MSSA	n = 46	n = 44	n = 14
Clinical responder	45 (97.8)	42 (95.5)	12 (85.7)
Clinical non-responder	1 (2.2)	1 (2.3)	1 (7.1)
Missing	0 (0.0)	1 (2.3)	1 (7.1)
Staphylococcus aureus; oxacillin resistant, MRSA	n = 2	n = 4	n = 0
Clinical responder	2 (100.0)	4 (100.0)	0 (NA)
Clinical non-responder	0 (0.0)	1 (1.9)	0 (NA)
Streptococcus agalactiae	n = 0	n = 1	n = 0
Clinical responder	0 (NA)	1 (100.0)	0 (NA)
Clinical non-responder	0 (NA)	0 (0.0)	0 (NA)
Streptococcus anginosus	n = 1	n = 0	n = 0
Clinical responder	1 (100.0)	0 (NA)	0 (NA)
Clinical non-responder	0 (0.0)	0 (NA)	0 (NA)
Streptococcus constellatus	n = 0	n = 1	n = 0
Clinical responder	0 (NA)	1 (100.0)	0 (NA)
Clinical non-responder	0 (NA)	0 (0.0)	0 (NA)
Streptococcus intermedius	n = 0	n = 1	n = 0
Clinical responder	0 (NA)	1 (100.0)	0 (NA)
Clinical non-responder	0 (NA)	0 (0.0)	0 (NA)
Streptococcus pyogenes	n = 5	n = 4	n = 3
Clinical responder	4 (80.0)	3 (75.0)	3 (100.0)
Clinical non-responder	1 (20.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	1 (25.0)	0 (0.0)
Enterococcus faecalis	n = 2	n = 2	n = 0
Clinical responder	2 (100.0)	2 (100.0)	0 (NA)
Clinical non-responder	0 (0.0)	0 (0.0)	0 (NA)

*Sponsor assessment.

†The very small numbers of patients in some subgroups precludes meaningful comparison, and data should be considered descriptive.

MSSA indicates methicillin-susceptible *Staphylococcus aureus*; NA, not applicable.

Microbiologic Outcomes

In the dalbavancin single-dose, dalbavancin 2-dose, and comparator arms, microbiologic eradication/presumed eradication was achieved in 98.0%, 96.3% and 88.9% of patients, respectively, in the microITT population at 48–72 hours; 96.1%, 94.4% and 100% at EOT; 92.2%, 94.4% and 100% at TOC; and 94.1%, 90.7% and 100% at follow up. Comparable microbiologic response was observed across all cohorts in microITT and microbiologically evaluable populations at 48–72 hours and was consistent across pathogens.

Healthcare Utilization

Healthcare resource utilization was comparable across treatment arms. More than 84% of patients in all treatment arms were hospitalized; readmission rates were <4%. Fewer dalbavancin-treated patients required an indwelling catheter (32.5% single-dose; 41.0% 2-dose) versus comparator-treated patients (60.0%), and the median number of days for catheter placement was 0 (range, 0–9) for dalbavancin-treated patients versus 4.5 (range, 0–15) for comparator.

The Skin and Soft Tissue Infection Convenience questionnaire showed that the majority of patients or parent/guardians in all treatment arms were satisfied with their treatment. More dalbavancin-treated patients reported that treatment did not interfere with their (or their child's) usual daily activities at all (single-dose, 80.8%; 2-dose, 87.0%) versus comparator-treated patients (47.6%; Table, Supplemental Digital Content 5, http://links.lww.com/INF/E893).

DISCUSSION

Dalbavancin was generally safe and well tolerated in pediatric patients with ABSSSI, and resulted in clinical responses of 97.4% and 98.6% at 48–72 hours post-randomization in the single- and 2-dose study arms, respectively. Clinical cure was achieved in >96% of patients treated with dalbavancin by TOC visit. Importantly, the safety and efficacy of dalbavancin single-dose was comparable with the 2-dose regimen, highlighting the strength of single-dose dalbavancin for the treatment of ABSSSI.

This study is the first to report safety and efficacy outcomes in children with ABSSSI treated with dalbavancin. The safety profile of dalbavancin in pediatric patients was consistent with that in adults with ABSSSI, with no new clinically relevant safety signals identified. Clinical response at 48–72 hours post-infusion, EOT, and TOC were favorable. The clinical cure rate was sustained at the follow-up visit.

Clinical responses were similar across dalbavancin single-dose and 2-dose regimens and age cohorts and similar to comparator treatments in this study. The rate of favorable clinical and microbiologic response in the microITT population at all time points was similar regardless of baseline pathogen. In addition, all signs of local and systemic inflammation resolved in most patients. The robust clinical responses observed in patients with *S. aureus*, notable decrease in lesion size in the majority of patients, improvement of laboratory test values and indicators of systemic infection, and resolution of lesion site symptoms at EOT and TOC all provide evidence of the efficacy of dalbavancin in pediatric patients.

Healthcare resource utilization was comparable across treatment arms; fewer dalbavancin-treated patients required an indwelling catheter and the median number of days for catheter placement was lower versus comparator. Most patients or parent/guardians reported satisfaction with treatment across all study arms, with more dalbavancin-treated patients reporting that treatment did not negatively affect daily activities.

Safety, efficacy, and microbiologic outcomes in this study were consistent across the 5 age cohorts. However, a study limitation is the small number of patients in some cohorts, particularly cohorts 4 and 5, which preclude further analysis and meaningful comparison. This study is ongoing to enroll additional preterm neonates in cohort 5. Additional limitations include the descriptive analysis of efficacy results because the study was not powered for statistical testing of efficacy, and the open-label study design.

Extrapolation of clinical efficacy and safety from adults to pediatric patients using PK data has been applied to other antibiotics approved for ABSSSI in children. This is based on assumptions that the disease, mechanism of action of antibiotic, and PK/PD are similar between pediatric patients and adults. Extensive PK sampling data from this study were pooled with data from 3 PK studies in pediatric subjects and used to develop a robust population PK model for dalbavancin in pediatric patients. The model was then used to confirm drug exposure and PK/PD target attainment for the approved pediatric doses.[23] The long half-life of dalbavancin, along with PK/PD modeling and simulation showing adequate target attainment, justifies the approved single-dose regimen for pediatric patients and offers an opportunity to improve the compliance with therapy relative to daily administrations of either IV or oral drugs.

Study DUR001-306 is one of the studies supporting the recent pediatric indication approval for dalbavancin and demonstrates the safety and efficacy of both the single-dose and 2-dose dalbavancin for the treatment of pediatric patients with ABSSSI known or suspected to be caused by susceptible microorganisms.

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