Clinical Trial Protocol: DUR001-306

Study Title:	A Phase 3, Multicenter, Open-Label, Randomized, Comparator Controlled Trial of the Safety and Efficacy of Dalbavancin versus Active Comparator in Pediatric Subjects with Acute Bacterial Skin and Skin Structure Infections
Study Number:	DUR001-306
Study Phase:	Phase 3
Product Name:	Dalbavancin
IND Number:	60,613
EudraCT Number	2014-005281-30
Indication:	Acute Bacterial Skin and Skin Structure Infections in Pediatric Patients
Sponsor:	AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064 USA AbbVie Deutschland GmbH & Co. KG Knollstrasse 50 Ludwigshafen 67061 Germany

	Date
Original Protocol	23 December 2014
Amendment 1	26 February 2015
Amendment 2	02 March 2016
Amendment 3	13 June 2016
Amendment 4	09 March 2017
Amendment 5	27 June 2017
Amendment 6	26 April 2018
Amendment 7	29 March 2022
Amendment 8	18 November 2022

Confidentiality Statement

SYNOPSIS

Sponsor:

AbbVie Inc. and AbbVie Deutschland GmbH & Co. KG

Name of Finished Product:

Dalbavancin (DUR001) for Injection, 500 mg (US)

Name of Active Ingredient:

Dalbavancin hydrochloride

Study Title:

A Phase 3, Multicenter, Open-Label, Randomized, Comparator Controlled Trial of the Safety and Efficacy of Dalbavancin versus Active Comparator in Pediatric Subjects with Acute Bacterial Skin and Skin Structure Infections

Study Number:

DUR001-306

Study Phase: Phase 3

Primary Objective(s):

To determine the safety and descriptive efficacy of dalbavancin for the treatment of acute bacterial skin and skin structure infections in children, from birth to 17 years (inclusive), known or suspected to be caused by susceptible Gram-positive organisms, including methicillin-resistant strains of *Staphylococcus aureus*

Secondary Objective(s):

- To assess clinical response at 48-72 hours post randomization (defined as ≥ 20% reduction in lesion size compared to baseline) measured in patients who did not receive rescue therapy and are alive, and clinical response based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of therapy), at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy). In Cohort 5 (birth to < 3 months), clinical response in patients with acute bacterial skin and skin structure infections (ABSSSI) at 48-72 hours post-randomization is defined as cessation of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions. In patients diagnosed with sepsis in Cohort 5, clinical response at 48-72 hours post-randomization is defined as improvement of at least one abnormal clinical and laboratory parameter related to sepsis. For later timepoints, clinical response in Cohort 5 is based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of therapy), at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy).
- To assess clinical response by baseline pathogen at 48-72 hours post randomization (defined as ≥ 20% reduction in lesion size compared to baseline), and clinical response by baseline pathogen based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of therapy), at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy). In Cohort 5 (birth to < 3 months), clinical response by baseline pathogen in patients with ABSSSI is defined as cessation of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions. In patients diagnosed with sepsis in Cohort 5, clinical response by baseline pathogen at 48-72 hours post-randomization is defined as improvement of at least one abnormal clinical and laboratory parameters related to sepsis. For later timepoints, clinical response by baseline pathogen is based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of therapy), at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy).
- Cohort 5 (birth to < 3 months): to assess all-cause mortality at test of cure visit (28 ± 2 days after start of therapy).
- To evaluate the pharmacokinetics (PK) of dalbavancin in pediatric patients from birth to 17 years of age (inclusive).

Study Design:

This is a Phase 3, multicenter, open-label, randomized, comparator controlled trial evaluating the safety and efficacy of a single dose of intravenous (IV) dalbavancin and a two-dose regimen of once weekly IV dalbavancin (for a total of 14 days of coverage) for the treatment of acute bacterial skin and skin structure infections known or suspected to be due to susceptible Gram-positive organisms in children, from birth to 17 years (inclusive). The comparators are either IV vancomycin (for methicillin-resistant Gram-positive infections) or IV oxacillin or flucloxacillin (for methicillin-susceptible Gram-positive infections) for 10-14 days. Patients may be switched from IV oxacillin or flucloxacillin to oral cefadroxil after at least 72 hours of study drug treatment, if they meet specified criteria for oral therapy. Similarly, if infection with methicillin-resistant *S. aureus* is documented, then patients may be switched from IV vancomycin to oral clindamycin after at least 72 hours of parenteral antibiotic therapy, if they meet specified criteria for oral therapy. If an alternate comparator regimen is indicated by local susceptibility patterns or recommended by local treatment guidelines, this must be discussed with the medical monitor.

In Cohort 5 (birth to < 3 months) only the single-dose regimen of dalbavancin (22.5 mg/kg) will be evaluated. At the discretion of the investigator, concomitant therapy based on local standard of care may be added to the single-dose regimen of dalbavancin, as clinically indicated, in Cohort 5. Cohort 5 will be initiated based on review of initial results from patients > 28 days to < 3 months in study DAL-PK-02 (DUR001-107).

Eligible patients from birth to 17 years of age (inclusive) with acute bacterial skin and skin structure infection will be enrolled. Approximately 188 patients will be enrolled, with 178 patients 3 months or older randomized to receive dalbavancin (single-dose or two-dose regimen) or comparator, in a 3:3:1 randomization scheme: 76 patients will be randomized to dalbavancin (single-dose IV), 76 patients will be randomized to dalbavancin (2 IV doses one week apart), and 26 patients will be randomized to comparator (IV vancomycin or IV oxacillin or flucloxacillin). The randomization scheme will not include the youngest age cohort (birth to < 3 months of age), as all 10 patients in this cohort will receive the single-dose regimen of dalbavancin, bringing the total number of patients enrolled in the study to approximately 188 patients. No patient in Cohort 5 (birth to < 3 months) will be randomized to the comparator arm.

The enrollment target of 10 patients for Cohort 5 includes at least 5 patients ≤ 28 days (including pre-term neonates).

There will be 5 age cohorts:

- Cohort 1 --12 years to 17 years old, inclusive,
- Cohort 2 -- 6 years to < 12 years old,
- Cohort 3 -- 2 years to < 6 years old,
- Cohort 4 -- 3 months to < 2 years old, and
- Cohort 5 -- birth to < 3 months of age (including pre-term neonates with gestational age ≥ 32 weeks).

With the exception of Cohort 5, patients will be randomized 3:3:1 to each of the three treatment groups.

In Cohorts 3 and 4 (enrolling patients aged 2 years to < 6 years old, and 3 months to < 2 years old, respectively), there will be approximately 15 patients in each dalbavancin arm, and 5 patients in each comparator arm. In Cohorts 1 and 2 (enrolling patients 12 years to 17 years old, inclusive and 6 years to < 12 years old, respectively), there will be approximately 23 patients in each dalbavancin arm, and 8 patients in each comparator arm.

Study Population:

Patients, from birth to 17 years (inclusive) with ABSSSI. For Cohort 5 (birth to < 3 months), patients with suspected or confirmed sepsis will be allowed.

Inclusion Criteria:

For Cohorts 1 – 4, ages 3 months to 17 years, inclusive, each patient must meet the following criteria to be enrolled in this study.

1. Male or female patients 3 months to 17 years of age (inclusive)
2. A clinical picture compatible with an ABSSSI suspected or confirmed to be caused by Gram-positive bacteria, including MRSA.

3. In addition to local signs of ABSSSI, the patient has at least one of the following:
   - Fever, defined as body temperature ≥ 38.4°C (101.2°F) taken orally, ≥ 38.7°C (101.6°F) tympanically, or ≥ 39°C (102.2°F) rectally (core temperature)
   - Leukocytosis (WBC > 10,000 mm^3) or leukopenia (WBC < 2,000 mm^3) or left shift of >10% band neutrophils
4. Infection either involving deeper soft tissue or requiring significant surgical intervention:

(a) Major cutaneous abscess characterized as a collection of pus within the dermis or deeper that is accompanied by erythema, edema and/or induration which:
   i. requires surgical incision and drainage, and
   ii. is associated with cellulitis such that the total affected area involves at least 35 cm^2 of erythema, or total affected area of erythema is at least BSA (m^2) x 43.0 (cm^2/m^2), OR
   iii. alternatively, involves the central face and is associated with an area of erythema of at least 15 cm^2

(b) Surgical site or traumatic wound infection characterized by purulent drainage with surrounding erythema, edema and/or induration which occurred within 30 days after the trauma or surgery and is associated with cellulitis such that
   i. the total affected area involves at least 35 cm^2 of erythema, or total affected area of erythema is at least BSA (m^2) x 43.0 (cm^2/m^2), OR
   ii. alternatively, involves the central face and is associated with an affected area of at least 15 cm^2

(c) Cellulitis, defined as a diffuse skin infection characterized by spreading areas of erythema, edema and/or induration and
   i. is associated with erythema that involves at least 35 cm^2 of surface area, or surface area of erythema is at least BSA (m^2) x 43.0 (cm^2/m^2), OR
   ii. alternatively, cellulitis of the central face that is associated with an affected area of at least 15 cm^2

5. In addition to the requirement for erythema, all patients are required to have at least two (2) of the following signs of ABSSSI:

(a) Purulent drainage/discharge
(b) Fluctuance
(c) Heat/localized warmth

(d) Tenderness to palpation
(e) Swelling/induration

6. A signed and dated informed consent document indicating that a legally acceptable representative or the patient's parent(s)/legal guardian(s) has been informed of all pertinent aspects of the trial. If required by the local IRB/IEC, a child assent will be obtained, as applicable.
7. Patients, and if required by local/site regulations, their parent(s)/legal guardian(s), must be willing and able, if discharged from the hospital, to return to the hospital or a designated clinic for scheduled visits, treatment, laboratory test and other outpatient procedures as required by the protocol.
8. Patients must be expected to survive with appropriate antibiotic therapy and appropriate supportive care throughout the study.

For Cohort 5 (birth to < 3 months), each patient must meet the following inclusion criteria to be enrolled in this study.

1. Male or female patients from birth to < 3 months of age, including pre-term neonates (gestational age ≥ 32 weeks)
2. A clinical picture compatible with an ABSSSI suspected or confirmed to be caused by Gram-positive bacteria, including MRSA.

   OR

   Suspected or confirmed sepsis including any of the following clinical criteria:

   (a) Hypothermia (<36°C) OR fever (>38.5°C)
   (b) Bradycardia OR tachycardia OR rhythm instability
   (c) Hypotension OR mottled skin OR impaired peripheral perfusion
   (d) Petechial rash
   (e) New onset or worsening of apnea episodes OR tachypnea episodes OR increased oxygen requirements OR requirement for ventilation support
   (f) Feeding intolerance OR poor sucking OR abdominal distension
   (g) Irritability
   (h) Lethargy
   (i) Hypotonia

3. In addition, patients must meet <u>at least one</u> of the following laboratory criteria:
   (a) White blood cell count ≤4.0×10^9/L OR ≥20.0×10^9/L
   (b) Immature to total neutrophil ratio >0.2
   (c) Platelet count ≤100×10^9/L
   (d) C-reactive protein (CRP) >15 mg/L OR procalcitonin ≥ 2 ng/mL

(e) Hyperglycemia OR Hypoglycemia
(f) Metabolic acidosis

4. Infections must be of sufficient severity to merit hospitalization and parenteral antibiotic therapy. These infections may include:

   (a) Cutaneous or subcutaneous abscess

   (b) Surgical site or traumatic wound infection

   (c) Cellulitis, Erysipelas

   (d) Omphalitis

   (e) Impetigo and bullous impetigo

   (f) Pustular folliculitis

   (g) Scarlet fever

   (h) Staphylococcal scalded skin syndrome

   (i) Streptococcal toxic shock syndrome

   (j) Erythematous based-erosion

   (k) Other infections originating in the skin or subcutaneous tissue and associated with signs and symptoms of sepsis as defined in Inclusion Criterion 2.

5. A signed and dated informed consent document indicating that a legally acceptable representative or the patient's parent(s)/legal guardian(s) has been informed of all pertinent aspects of the trial.

6. Each patients' parent(s)/legal guardian(s) must be willing and able, if discharged from the hospital, to return to the hospital or a designated clinic for scheduled visits, treatment, laboratory test and other outpatient procedures as required by the protocol.

7. Patients must be expected to survive with appropriate antibiotic therapy and appropriate supportive care throughout the study.

Exclusion Criteria:

Patients who meet any of the following will be excluded from the study:

1. Patients in Cohort 1-4: Clinically significant renal impairment, defined as creatinine clearance < 30 mL/min (calculated by the Schwartz "bedside" formula). Patients in Cohort 5 (birth to < 3 months of age): Moderate or severe renal impairment defined as serum creatinine ≥ 2 times the upper limit of normal (× ULN) for age OR urine output < 0.5 mL/kg/h (measured over at least 8 hours prior to dosing) OR requirement for dialysis.
2. Clinically significant hepatic impairment, defined as serum bilirubin or alkaline phosphatase > 2X ULN for age, and/or serum AST or ALT > 3X ULN for age (neonates with elevated total bilirubin can participate if conjugated or direct bilirubin were normal per age).
3. Treatment with an investigational drug within 30 days preceding the first dose of study medication.
4. Patients with sustained shock defined as systolic blood pressure < 90 mm Hg in children ≥ 10 years old, < 70 mm Hg + [2 x age in years] in children 1 to < 10 years, or < 70 mm Hg in infants 3 to < 12 months old for more than 2 hours despite adequate fluid resuscitation, with evidence of hypoperfusion or need for sympathomimetic agents to maintain blood pressure.
5. More than 24 hours of any systemic antibacterial therapy within 96 hours before randomization. EXCEPTION: Microbiological or clinical treatment failure with a systemic antibiotic other than IV study drug that was administered for at least 48 hours. Failure must be confirmed by either a microbiological laboratory report or documented worsening clinical signs or symptoms.
6. Infection due to an organism known prior to study entry to be resistant to dalbavancin (dalbavancin MIC > 0.25 μg/mL) or vancomycin (vancomycin MIC > 2 μg/mL).
7. Patients with necrotizing fasciitis, or deep-seated infections that would require > 2 weeks of antibiotics (e.g., endocarditis, osteomyelitis or septic arthritis).
8. Infections caused exclusively by Gram-negative bacteria (without Gram-positive bacteria present) and infections caused by fungi, whether alone or in combination with a bacterial pathogen.
9. Venous catheter entry site infection.

10. Infections involving diabetic foot ulceration, perirectal abscess or a decubitus ulcer.
11. Patient with an infected device, even if the device is removed. Examples include infection of: prosthetic cardiac valve, vascular graft, a pacemaker battery pack, joint prosthesis, implantable pacemaker or defibrillator, intra-aortic balloon pump, left ventricular assist device, or a neurosurgical device such as a ventricular peritoneal shunt, intra-cranial pressure monitor, or epidural catheter.
12. Gram-negative bacteremia, even in the presence of Gram-positive infection or Gram-positive bacteremia. Note: If a Gram-negative bacteremia develops during the study, or is subsequently found to have been present at Baseline, the patient should be removed from study treatment and receive appropriate antibiotic(s) to treat the Gram-negative bacteremia.
13. Patients whose skin infection is the result of having sustained full or partial thickness burns.
14. Patients in Cohorts 1 - 4 with uncomplicated skin infections such as superficial/simple cellulitis/erysipelas, impetiginous lesion, furuncle, or simple abscess that only requires surgical drainage for cure. Patients in Cohort 5 (birth to < 3 months of age) may be enrolled if they have uncomplicated skin infections of sufficient severity to require hospitalization and parenteral antibiotic therapy.
15. For Cohorts 1 – 4 (3 months to 17 years of age, inclusive): Concomitant condition requiring any antibiotic therapy that would interfere with the assessment of study drug for the condition under study.
16. Sickle cell anemia
17. Cystic fibrosis
18. Anticipated need of antibiotic therapy for longer than 14 days.
19. Patients who are placed in a hyperbaric chamber as adjunctive therapy for the ABSSSI.
20. More than 2 surgical interventions (defined as procedures conducted under sterile technique and typically unable to be performed at the bedside) for the skin infection, or patients who are expected to require more than 2 such interventions.
21. Medical conditions in which chronic inflammation may preclude assessment of clinical response to therapy even after successful treatment (e.g., chronic stasis dermatitis of the lower extremity).

22. Immunosuppression/immune deficiency, including hematologic malignancy, recent bone marrow transplant (in post-transplant hospital stay), absolute neutrophil count < 500 cells/mm^3, receiving immunosuppressant drugs after organ transplantation, receiving oral steroids ≥ 20 mg prednisolone per day (or equivalent) for > 14 days prior to enrollment, and known or suspected human immunodeficiency virus (HIV) infected patients with a CD4 cell count < 200 cells/mm^3 or with a past or current acquired immunodeficiency syndrome (AIDS)-defining condition and unknown CD4 count.
23. Known or suspected hypersensitivity to glycopeptide antibiotics, beta-lactam agents, aztreonam, or cephalosporins.
24. Patients with a rapidly fatal illness, who are not expected to survive for 3 months.
25. Positive urine (or serum) pregnancy test at screening (post-menarchal females only) or after admission (prior to dosing).
26. Pregnant or nursing females; sexually active females of childbearing potential who are unwilling or unable to use adequate contraceptive precautions. Female patients to have pregnancy testing are those who are at least 10 years old with menarche and/or thelarche (beginning of breast development).
27. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
28. Unwilling or unable to follow study procedures.

Test Product, Dose, and Mode of Administration:

Patients randomized to the single-dose regimen of dalbavancin will receive dalbavancin administered intravenously over 30 (± 5) minutes as follows:

- **3 months to < 6 years old:** 22.5 mg/kg (maximum 1500 mg) on Day 1;
- **≥ 6 years to 17 years old (inclusive):** 18 mg/kg (maximum 1500 mg) on Day 1

Patients randomized to the two-dose regimen of dalbavancin will receive dalbavancin administered intravenously over 30 (± 5) minutes as follows:

- **3 months to < 6 years old:** 15 mg/kg (maximum 1000 mg) on Day 1, and 7.5 mg/kg (maximum 500 mg) on Day 8;
- **≥ 6 years to 17 years old (inclusive):** 12 mg/kg (maximum 1000 mg) on Day 1, and 6 mg/kg (maximum 500 mg) on Day 8

Patients in Cohort 5 (**birth to < 3 months of age**) will receive the single-dose regimen of dalbavancin 22.5 mg/kg on Day 1 administered intravenously over 30 (± 5) minutes. Cohort 5 will be initiated based on review of initial results from patients > 28 days to < 3 months in study DAL-PK-02 (DUR001-107).

Comparator Systemic Antibiotics:

Patients randomized to the comparator arm will receive a 10-14 day course of either vancomycin 10 *to 15* mg/kg/dose, infused over 60 minutes (± 10) every 6 hours (± 1 hour), not to exceed a total daily dose of 4000 mg; or oxacillin 30 mg/kg/dose, infused over 60 minutes (± 10) every 6 hours (± 1 hour); or flucloxacillin 50 mg/kg/dose, infused over 60 minutes (± 10) every 6 hours (± 1 hour), not to exceed a total daily dose of 2000 mg.

No patient in Cohort 5 (birth to < 3 months of age) will be randomized to the comparator arm.

Patients on IV oxacillin or flucloxacillin may be switched to oral cefadroxil (dose for infants and children: 15 mg/kg/dose every 12 hours, maximum 2 g/day; dose for adolescents:
500 -1000 mg every 12 hours), and if infection with methicillin-resistant *S. aureus* is documented, the patient may be switched from IV vancomycin to oral therapy with clindamycin 10 mg/kg every 8 hours, at the discretion of the investigator after at least 72 hours of IV therapy if the patient meets the following criteria:

- The patient has been afebrile for 48 hours
- Local signs and symptoms of infection are improving
- The patient has the ability to swallow, retain, and absorb the oral medication

If patients randomized to comparator are initially placed on empiric IV vancomycin and their baseline pathogen is a methicillin-susceptible Gram-positive organism, they may be switched to IV oxacillin or flucloxacillin (or oral cefadroxil if criteria for oral therapy are met), and continue in the study. If patients are initially placed on empiric IV oxacillin or flucloxacillin, and their baseline pathogen is a methicillin-resistant Gram-positive organism, they should be switched to IV vancomycin (or oral clindamycin for documented MRSA and if criteria for oral therapy are met), and continue in the study. If an alternate comparator regimen is indicated by local susceptibility patterns or recommended by local treatment guidelines, this must be discussed with the medical monitor.

Adjunctive Systemic Antibiotics:

Aztreonam may be administered at randomization for presumed co-infection with a Gram-negative pathogen and could be discontinued if a Gram-negative pathogen is not documented by culture. For suspected anaerobic pathogens, metronidazole oral/IV may be used. Patients in Cohort 5 (birth to < 3 months) will be allowed concomitant antibacterial therapy in addition to dalbavancin, based on local standard of care.

Additional, Non-Study Therapy Antibiotics:

For *Clostridium difficile* infections, metronidazole (IV or oral) or oral vancomycin may be used in all treatment groups.

Other antibiotics that do not achieve significant therapeutic concentrations in the serum (e.g., nitrofurantoin) may be considered for treatment of other concomitant infections. Close consultation with the medical monitor is advised prior to use of these antibiotics.

If a Gram-negative bacteremia develops during the study, or is subsequently found to have been present at Baseline, the patient should be removed from study treatment and receive appropriate antibiotic(s) to treat the Gram-negative bacteremia.

Statistical Methods:

The proposed sample size is approximately 188 patients, such that 188 patients are included in the Safety Population: 76 in the single-dose arm of dalbavancin, 76 in the two-dose arm of dalbavancin, and 26 in the comparator arm. The enrollment target of 10 patients for Cohort 5 (birth to < 3 months), includes at least 5 patients ≤ 28 days (including pre-term neonates) bringing the total number of patients enrolled in the study to approximately 188 patients.

General Statistical Considerations:

The study is primarily a safety study. Safety results and adverse events will be tabulated by separate treatment regimens, including those who did and did not receive additional agents (such as aztreonam and/or metronidazole). Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Summaries of efficacy variables will be done by age and treatment group for all patients who receive at least one dose of study medication, who have values available at the appropriate visits. Exploratory analyses may also be performed. Listings of individual patient's data will be produced.

A comprehensive Statistical Analysis Plan (SAP) will be finalized prior to closure of the database.

Primary Analysis (Safety)

Safety will be assessed by means of physical examination and vital signs, collection of adverse events and clinical laboratory tests. Physical examination will be performed at Baseline; vital signs will be collected at Baseline, and at Day 1, 48-72 hours post randomization, Day 8 (± 1 day), Day 14 (± 2 days), Day 28 (± 2 days), Day 54 (± 7 days), or at premature discontinuation. Adverse events will be collected at every visit, beginning from the signing of Informed Consent. Clinical laboratory tests needed to determine eligibility will be collected during screening, if not already collected as standard of care. Data from clinical laboratory tests performed as standard of care during the study will be collected.

Audiologic testing will be conducted in at least 20 children < 12 years old (in selected centers), of which at least 9 children will be < 2 years old. Audiologic testing will be performed at Baseline and repeated at Day 28 (± 2 days). Testing (as specified in the protocol) performed within 7 days prior to study drug administration can be used as the Baseline assessment. If the audiologic assessment at Day 28 shows an abnormality that exceeds by a clinically significant margin any abnormality observed in the pre-study assessment, follow-up assessments will be performed at 3 months and 6 months post-dose, as needed or until returned to baseline.

The impact of dalbavancin on the bowel flora will be determined in all patients from birth to < 2 years, by performing PCR for Clostridium difficile (C. diff) and culture for vancomycin-resistant enterococci (VRE) on a stool specimen or rectal swab at Baseline

and Day 28 (± 2 days). The testing of bowel flora in this age group will be done in all study arms.

All safety analyses will be based on the Safety population and will be summarized by treatment group.

Secondary Analyses:

The study is designed to determine the safety and descriptive efficacy of a single- or a two-dose regimen of IV dalbavancin administered one week apart, relative to the comparator regimen (IV vancomycin or IV oxacillin or flucloxacillin with option to switch to oral cefadroxil or clindamycin, as noted). Of note, all patients in Cohort 5 (birth to < 3 months) will receive the single-dose regimen of dalbavancin.

Clinical response at 48-72 hours post randomization is defined as ≥ 20% reduction in lesion size compared to baseline, measured in patients who did not receive rescue therapy and are alive (Cohorts 1 – 4). In Cohort 5 (birth to < 3 months), clinical response in patients with ABSSSI at 48-72 hours post-randomization is defined as cessation of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions. In patients diagnosed with sepsis in Cohort 5, clinical response at 48-72 hours post-randomization is defined as improvement of at least one abnormal clinical and laboratory parameter related to sepsis. Clinical response, in each of the 5 cohorts, will be assessed in patients who did not receive rescue therapy and are alive (in Cohort 5, rescue therapy is defined as additional antibiotic therapy initiated after at least 48 hours of start of study treatment).

Clinical response at remaining time-points will be based primarily on the global clinical assessment of the patient made by the investigator at that evaluation time-point.

Clinical response at the End of Treatment (EOT) visit (14 ± 2 days) is defined as Cure, Improvement, Failure, or Unknown;

Clinical response at the TOC visit (28 ± 2 days), and at the follow-up visit (54 ± 7 days) is defined as Cure, Failure or Unknown.

Cure: Resolution of the clinical signs and symptoms of infection, when compared to baseline. No additional antibacterial treatment is required for disease under study.

Improvement: Reduction in severity of two or more, but not all, clinical signs and symptoms of infection, when compared with baseline (Cohorts 1-4, and ABSSSI patients

in Cohort 5). In sepsis patients in Cohort 5 (birth to < 3 months), improvement is defined as reduction in severity of at least one abnormal clinical and laboratory parameter related to sepsis (see Inclusion Criteria for Cohort 5), when compared with baseline. No additional antibacterial treatment is required for disease under study. This outcome category will only be used at the EOT evaluation. For Cohort 5, no rescue medication is required after at least 48 hours of start of study treatment.

Failure: Persistence or progression of baseline clinical signs and symptoms of infection after at least 2 days (48 hours) of treatment or development of new clinical findings consistent with active infection.

Unknown: Extenuating circumstances preclude classification to one of the above.

When classifying the patient's clinical response using the criteria listed above, "no additional antibacterial treatment is required for the disease under study" refers to: no additional treatment with an antibacterial agent with activity against the patient's isolate is required for the disease under study. The occurrence of any of the following conditions will result in reassignment by the Sponsor as follows:

- Patients previously assessed as a clinical failure: the outcome will always be clinical failure at subsequent time-points.
- For Cohorts 1 – 4 (3 months to 17 years of age, inclusive): Patients who were given a concomitant antibiotic with activity against the patient's isolate for the disease under study prior to the evaluation time-points will be classified as a failure. For Cohort 5 (birth to < 3 months): Patients who are given rescue therapy (additional antibiotic therapy initiated after at least 48 hours of start of study treatment) will be classified as a failure.
- If a patient undergoes an unplanned surgical procedure (e.g., incision and drainage of abscess, major debridement, amputation) for non-improving or worsening infection after 3 days (72 hours) of study drug treatment, the clinical response should be considered a failure.

Microbiological outcomes: Clinical response will also be determined by baseline pathogen at 48-72 hours post randomization, EOT, TOC, and the last follow-up visit, as described above. Direct demonstration of eradication or persistence of the causative organism must be attempted, if feasible, in all patients where it is considered standard practice. However, this must be done in all patients who are considered treatment failures.

All-cause mortality: For Cohort 5 only (birth to < 3 months), all-cause mortality will be determined at test of cure visit (28 ± 2 days after start of therapy).

Pharmacokinetic outcome: Concentration of dalbavancin in plasma. The population PK profile of dalbavancin will be assessed using a sparse sampling approach, and will be reported separately.

Other Endpoints/Assessments:

For Cohorts 1-4 and ABSSSI patients in Cohort 5: Infection site assessment includes the following: purulence/drainage, erythema, heat/localized warmth, pain/tenderness to palpation, fluctuance and swelling/induration at Baseline (within four hours prior to the first dose of study drug), 48-72 hours post randomization, Day 8 (± 1 day), Day 14 (± 2 days), Day 28 (± 2 days), and Day 54 (± 7 days). Ruler measurements of the area of erythema will also be obtained at Baseline and at 48-72 hours post randomization in Cohorts 1 – 4 and ABSSSI patients in Cohort 5. Length of the area of erythema will be measured as the longest length. Width will be measured as the widest width perpendicular to the longest length.

Resource utilization will be collected at Day 14 (± 2 days) and Day 28 (± 2 days), as well as other data available (e.g., length of hospitalization, or need for additional outpatient visits including Emergency Department visits, tests and procedures).

Patient and parent/guardian **satisfaction** with therapy will be assessed using the SSTI-Convenience questionnaire at Day 14 (± 2 days).

Date of Original Approved Protocol: 23 December 2014

Date of Most Recent Protocol Amendment (if applicable): Amendment 7:
29 March 2022

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABSSSI	Acute Bacterial Skin and Skin Structure Infections
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC_{0-24}	Area under the curve from zero to 24 hours
BUN	Blood Urea Nitrogen
C_{max}	Maximum concentration
CA	Community-associated
CE	Clinically Evaluable
CrCl	Creatinine Clearance
CRF	Case Report Form
CTA	Clinical Trial Application
DSMB	Data and Safety Monitoring Board
EOT	End of Treatment Visit
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transpeptidase
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
hs-CRP	High-sensitivity C-reactive Protein
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IRB/IEC	Institutional Review Board /Independent Ethics Committee
ITT	Intent-to-Treat
IUD	Intrauterine Device
IV	Intravenous
IWRS	Interactive Web Randomization System
LDH	Lactate Dehydrogenase
ME	Microbiologically Evaluable
MRSA	Methicillin-resistant Staphylococcus aureus
NI	Non-inferior
PK	Pharmacokinetic
PK/PD	Pharmacokinetic / Pharmacodynamic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TOC	Test of Cure (visit)
WBC	White Blood Cell

1 INTRODUCTION

Acute bacterial skin and skin structure infections (ABSSSI) are a significant source of morbidity in children; cutaneous abscesses and cellulitis are the predominant types of skin infections evaluated by pediatricians [1]. In the US, ABSSSI lead to 3 million pediatric health care visits per year, placing a heavy burden on the health care system [2,3]. Hospitalizations for ABSSSI in children now exceed 70,000 per year, more than double the rate from 15 years ago [4,5]. The increased rate of hospitalization occurred with the emergence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA). The prevalence of CA-MRSA in the US is greater than 50% in most areas, and as high as 70-80% in cities such as Chicago, Houston, and San Francisco [6-11]. Recent surveillance data shows that areas of Europe and South America have similar prevalence of CA-MRSA to the US [12-16]. This changing epidemiology has led to an increased need for antibiotic treatment with a spectrum of activity that includes MRSA for the empiric treatment of ABSSSI.

Dalbavancin is a lipoglycopeptide approved in the United States and European Union for the treatment of ABSSSI in adults. Dalbavancin is highly active against Gram-positive bacteria, including streptococci and *S. aureus*, including MRSA; the MIC_{90} for *S. aureus* is 0.06 µg/mL.

In adults, dalbavancin (given intravenously as 1000 mg on Day 1 followed by 500 mg on Day 8), has been shown to be non-inferior (NI) both to linezolid alone and to a comparator regimen including vancomycin followed by linezolid in the treatment of acute bacterial skin and skin structure infections (ABSSSI)/complicated skin and skin structure infections (cSSSI) in multiple randomized, double-blinded studies (VER001-9, DUR001-301 and DUR001-302). A single-dose intravenous administration of dalbavancin (1500 mg) in adults with ABSSSI has also been studied (DUR001-303). This study demonstrated that a single 1500 mg infusion was non-inferior to the same total dose delivered as 2 infusions 1 week apart. In addition, dalbavancin has a half-life of approximately 14 days, allowing for a single-dose and a two-dose, once weekly dosing regimen. Dalbavancin was well tolerated in these studies, with a higher proportion of patients in the comparator group reporting an adverse event (AE) as compared with dalbavancin. The most common AEs reported with dalbavancin were gastrointestinal complaints (nausea, diarrhea) and headache.

Dalbavancin in Children

The safety and pharmacokinetics of dalbavancin in adolescents have been studied in a study (A8841004) which included 10 subjects ages 12-16 years, and a second study (DUR001-106), which enrolled 36 patients, of which 34 received drug.

Study A8841004: The pharmacokinetics of dalbavancin in adolescents aged 12 to 17 years inclusive were evaluated in an open-label, multi-center study conducted to investigate the pharmacokinetics (PK), safety and tolerability of a single dose of intravenous (IV) dalbavancin. Dalbavancin was administered to hospitalized patients in addition to background anti-infective treatment for a known or suspected bacterial infection. In this study, mean plasma exposures for dalbavancin, based on AUC_{inf} and C_{max}, were similar when administered as 1000 mg to pediatric patients (12-16 years) weighing > 60 kg (range: 61.9-105.2 kg) or as 15 mg/kg to pediatric patients weighing <60 kg (range: 47.9-58.9 kg). Apparent terminal $t_{1/2}$ was similar for dalbavancin dosages of 1000 mg and 15 mg/kg, with mean values of 227 and 202 hours, respectively. The safety profile of dalbavancin in patients in this study is as follows: five patients in the dalbavancin 1000 mg group and 4 patients in the 15 mg/kg group experienced AEs. There was one serious adverse event (SAE) of mild ileus not related to treatment experienced by one patient in the 15 mg/kg group. There were no temporary or permanent discontinuations or dose reductions of treatment due to AEs. Headache, experienced by one patient in each group, was the only AE reported by more than one patient. AEs reported in the 1000 mg group were diarrhea, nausea, vomiting, increased bilirubin, headache, nasal congestion and hypotension. AEs reported in the 15 mg/kg group were abdominal pain, constipation, ileus, hyperbilirubinemia, skin laceration, wound, dehydration, dizziness, headache and rash macular. The only AE reported of moderate severity was headache in the 1000 mg group; all other AEs reported were of mild severity.

Study DUR001-106: Study DUR001-106 was an open-label, multi-center study conducted to investigate the PK, safety and tolerability of a single dose of IV dalbavancin in children. Dalbavancin was administered to hospitalized patients in addition to background anti-infective treatment for a known or suspected bacterial infection. Of the 36 patients enrolled, 34 received treatment: 11 in Cohort 1 (6-11 years of age inclusive), 12 in Cohort 2 (2 to < 6 years of age), and 11 in Cohort 3 (3 months to < 2 years of age).

At the beginning of the study, the dalbavancin doses were 15 mg/kg (not to exceed the adult dose of 1000 mg) as a single 30 minute infusion for patients ≥ 5 years of age and 25 mg/kg for patients < 5 years of age. However, based on the results of an interim PK analysis that included data from 11 patients in Cohort 1 and 7 patients in Cohort 2, the dalbavancin dose for patients in the youngest age group (3 months to < 2 years of age) was changed to 10 mg/kg (maximum of 1000 mg). One patient in Cohort 2 received the 10 mg/kg dose after protocol amendment 2.

Treatment with dalbavancin was safe with respect to adverse events and laboratory abnormalities. There were no serious adverse events considered related to treatment with

dalbavancin, and no deaths were reported. There were no unexpected adverse events relative to the known safety profile of dalbavancin in adult patients. Additionally, baseline and EOS audiograms were within normal limits. There was no evidence of ototoxicity due to dalbavancin administration in a majority of patients; for the remainder, no determination could be made.

Dose rationale for dalbavancin: Upon completion of Study DUR001-106, a population PK analysis was conducted to support justification of the dosing regimen in pediatric patients [17]. The population PK analysis was based on a pooled pediatric PK dataset from 43 subjects aged 3 months to 16 years. Incorporation of the covariates body weight and serum albumin were together able to account for the age-related differences in PK compartmental model parameters. Results of Monte Carlo simulations of exposure, represented by $AUC_{0\text{-}120}$, over the age range of 3 months to 18 years are shown in Figure 1 for dosing regimens of 12 mg/kg and 15 mg/kg, respectively. Based upon these results and the stated goal of attaining expected exposures equivalent to those attained in adults, the following two-dose regimen was chosen for equivalence to the 1000/500 mg adult regimen:

- Age ≥ 3 months to <6 years: 15 mg/kg on day 1, 7.5 mg/kg on day 8 (maximum 1000 mg day 1; maximum 500 mg on day 8)
- Age ≥ 6 years to <18 years: 12 mg/kg on day 1, 6 mg/kg on day 8 (maximum 1000 mg day 1; maximum 500 mg on day 8)

In keeping with the observed dose-proportionality of exposures over the range of doses tested in adults and pediatric patients, the corresponding single-dose regimen would be a single-dose equivalent to the sum of two-dose regimen, as has been proposed for adults. Therefore, the following regimen was chosen based on projected exposure equivalence to the 1500 mg adult regimen:

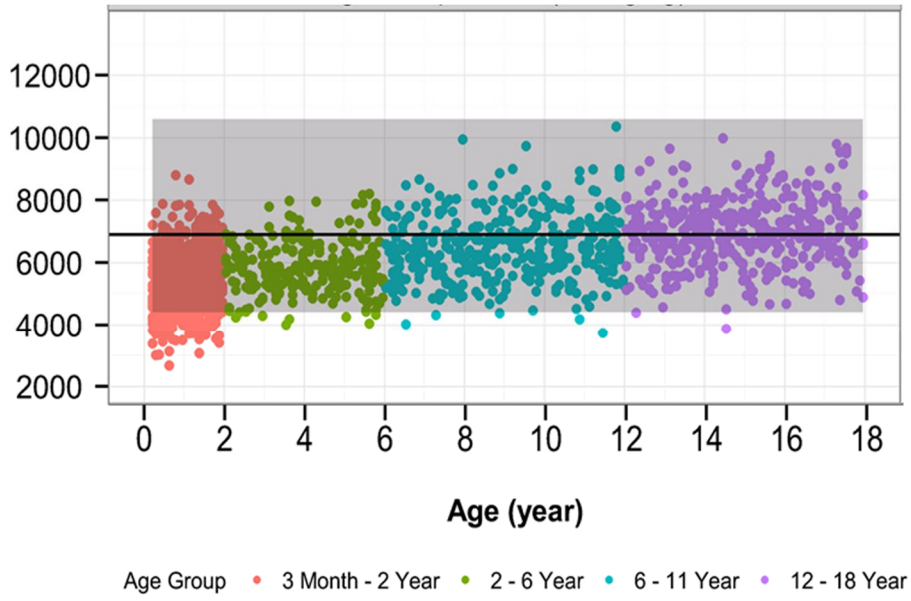
- Age ≥ 3 months to < 6 years: 22.5 mg/kg on day 1 (maximum 1500 mg)
- Age ≥ 6 years to < 18 years: 18 mg/kg on day 1 (maximum 1500 mg)

Simulations were also performed to find a single dose regimen for children aged birth to 3 months that would provide exposures similar to those expected in adult patients administered a single 1500 mg dose. The results of these simulations indicated that the following dose regimen was appropriate for children younger than 3 months of age:

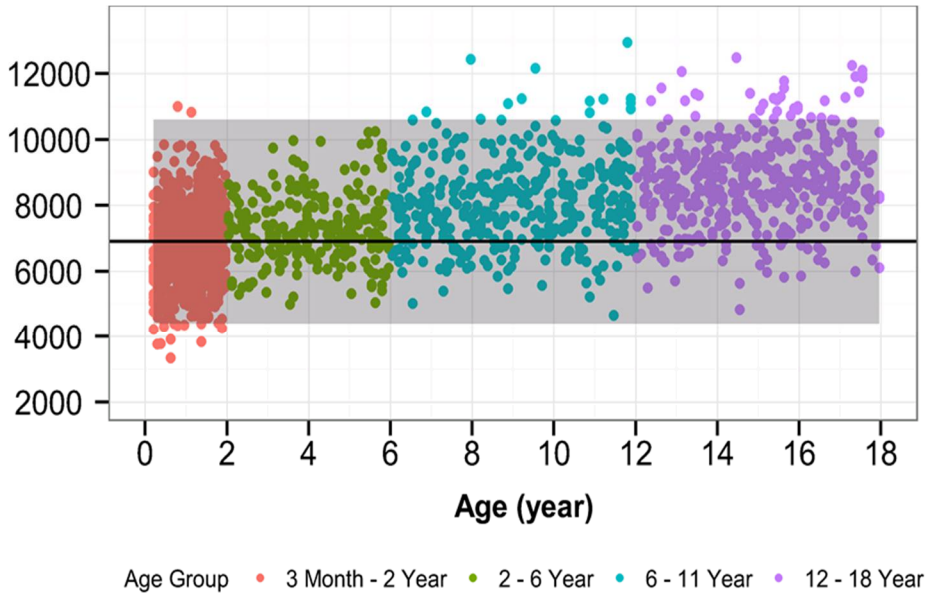
- Age birth to < 3 months: 22.5 mg/kg on day 1 (maximum 1500 mg)

Figure 1 Dalbavancin AUC_{0-120} Estimates for 2,000 Simulated Subjects Using the Revised Population PK Model [18]

(a) Dalbavancin AUC_{0-120} (µg*hr/mL) for a 12 mg/kg dose



(b) Dalbavancin AUC_{0-120} (µg*hr/mL) for a 15 mg/kg dose



(Solid line/shaded region is median/90% variability interval of AUC_{0-120} in adults administered a 1000 mg dose in Phase 3, per adult population PK model)

ABSSSI in children provides an opportunity to study the relative safety and efficacy of dalbavancin in a well-defined patient population with Gram-positive infections [19]. The prolonged half-life of dalbavancin allows for once weekly dosing to maintain serum concentrations above the MIC_{90} for most Gram-positive pathogens, including *S. aureus* for the entire duration of treatment. The single-dose regimen or the two-dose, once weekly dosing regimen offers advantages to patients, parents and physicians, obviating the need for prolonged intravenous access and simplifying adherence to an anti-infective treatment course.

In order to support enrolment of patients < 3 months of age, Cohort 5 will recruit patients with either ABSSSI or neonatal sepsis.

More complete information about dalbavancin is found in the current Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Objectives

The **primary objective** of this study is to determine the safety and descriptive efficacy of dalbavancin for the treatment of acute bacterial skin and skin structure infections in children, from birth to 17 years (inclusive), known or suspected to be caused by susceptible Gram-positive organisms, including methicillin-resistant strains of *Staphylococcus aureus.*

The **secondary objectives** of this study are:

- To assess clinical response at 48-72 hours post randomization (defined as ≥ 20% reduction in lesion size compared to baseline) measured in patients who did not receive rescue therapy and are alive; and clinical response based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of therapy); at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy). In Cohort 5 (birth to < 3 months), clinical response in patients with ABSSSI at 48-72 hours post-randomization is defined as cessation of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions. In patients diagnosed with sepsis in Cohort 5, clinical response at 48-72 hours post-randomization is defined as improvement of at least one abnormal clinical and laboratory parameter related to sepsis. For later timepoints, clinical response in Cohort 5 is based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of

therapy), at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy).

- To assess clinical response by baseline pathogen at 48-72 hours post randomization (defined as ≥ 20% reduction in lesion size compared to baseline); and clinical response based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of therapy), at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy). In Cohort 5 (birth to < 3 months), clinical response by baseline pathogen in patients with ABSSSI is defined as cessation of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions. In patients diagnosed with sepsis in Cohort 5, clinical response by baseline pathogen at 48-72 hours post-randomization is defined as improvement of at least one abnormal clinical and laboratory parameters related to sepsis. For later timepoints, clinical response by baseline pathogen is based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of therapy), at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy).
- Cohort 5 (birth to < 3 months): to assess all-cause mortality at test of cure visit (28 ± 2 days after start of therapy).
- To evaluate the pharmacokinetics (PK) of dalbavancin in pediatric patients from birth to 17 years of age (inclusive).

2.1.1 Primary Evaluations (Safety)

The primary outcome measure is the safety of dalbavancin for the treatment of ABSSSI in children including the following:

- Audiologic testing will be conducted in at least 20 children < 12 years old (in selected centers), of which at least 9 children will be < 2 years old. Audiologic testing will be performed at Baseline and repeated at Day 28 (± 2 days). Testing (as specified in the protocol) performed within 7 days prior to study drug administration can be used as the Baseline assessment.
- The impact of dalbavancin on **bowel flora**, to be evaluated in all patients from birth to < 2 years, by performing PCR for *Clostridium difficile* (C. diff) and culture for vancomycin-resistant enterococci (VRE) on a stool specimen or rectal swab at Baseline and Day 28 (± 2 days). The testing of bowel flora in this age group will be done in the dalbavancin arm and the comparator arm.

2.1.2 Secondary Evaluations

Clinical response at 48-72 hours after randomization defined as ≥ 20% reduction in lesion size compared to baseline, in patients who did not receive rescue therapy and are alive (Cohorts 1-4). In Cohort 5 (birth to < 3 months), clinical response in patients with ABSSSI at 48-72 hours post-randomization is defined as cessation of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions. In patients diagnosed with sepsis in Cohort 5, clinical response at 48-72 hours post-randomization is defined as improvement of at least one abnormal clinical and laboratory parameter related to sepsis. Clinical response, in each of the 5 cohorts, will be assessed in patients who did not receive rescue therapy and are alive. In Cohort 5, rescue therapy is defined as additional antibiotic therapy initiated after at least 48 hours of start of study. Length of the area of erythema will be measured as the longest length. Width will be measured as the widest width perpendicular to the longest length. Ruler measurements are to be performed at Baseline (within four hours prior to the first dose of study drug) and repeated at 48-72 hours post randomization in Cohorts 1 – 4 and ABSSSI patients in Cohort 5.

Clinical response at remaining time-points will be based primarily on the global clinical assessment of the patient made by the investigator at that evaluation time-point.

Clinical response at the EOT visit (14 ± 2 days)

- Defined as Cure, Improvement, Failure, or Unknown

Clinical response at the TOC visit (28 ± 2 days) and at the follow-up visit (54 ± 7 days)

- Defined as Cure, Failure or Unknown

Cure: Resolution of the clinical signs and symptoms of infection, when compared to baseline. No additional antibacterial treatment is required for disease under study.

Improvement: Reduction in severity of two or more, but not all, clinical signs and symptoms of infection, when compared with baseline (Cohorts 1-4, and ABSSSI patients in Cohort 5). In sepsis patients in Cohort 5 (birth to < 3 months), improvement is defined as reduction in severity of at least one abnormal clinical and laboratory parameter related to sepsis (see Inclusion Criteria for Cohort 5), when compared with baseline. For Cohorts 1 – 4 only, no additional antibacterial treatment is required for disease under study. This outcome category will only be used at the EOT evaluation. For Cohort 5, no rescue medication is required after at least 48 hours of start of study treatment.

Failure: Persistence or progression of baseline clinical signs and symptoms of infection after at least 2 days (48 hours) of treatment or development of new clinical findings consistent with active infection.

Unknown: Extenuating circumstances preclude classification to one of the above.

When classifying the patient's clinical response using the criteria listed above, "no additional antibacterial treatment is required for the disease under study" refers to: no additional treatment with an antibacterial agent with activity against the patient's isolate is required for the disease under study.

The occurrence of any of the following conditions will result in reassignment by the Sponsor as a **failure**:

- Patients **previously** assessed as a **clinical failure**: the outcome will always be clinical failure at subsequent time-points.
- For Cohorts 1 – 4 only: Patients who were given a **concomitant antibiotic with activity** against the patient's isolate for the disease under study **prior to the evaluation time-points** will be classified as a **failure**. For Cohort 5 (birth to < 3 months): Patients who are given rescue therapy (additional antibiotic therapy initiated after at least 48 hours of start of study treatment) will be classified as a failure.
- If a patient undergoes an **unplanned surgical procedure** (e.g., incision and drainage of abscess, major debridement, amputation) for non-improving or worsening infection **after 3 days** (72 hours) of study drug treatment, the clinical response should be considered a **failure**.

Microbiological outcomes: Clinical **response** will also be determined **by baseline pathogen** at 48-72 hours post randomization, EOT, TOC, and last follow-up visit, as described above. Direct demonstration of eradication or persistence of the causative organism must be attempted in all patients where it is considered standard practice. However, this must be done in all patients who are considered treatment failures.

All-cause mortality: For Cohort 5 only (birth to < 3 months), all-cause mortality will be determined at test of cure visit (28 ± 2 days after start of therapy).

Pharmacokinetic (PK) outcomes: Concentration of dalbavancin in plasma. The population PK profile of dalbavancin will be assessed using a sparse sampling approach, and will be reported separately.

For all safety analyses, patient data will be analyzed in the treatment group based on the actual study drug received (Safety Population). For all efficacy analyses, patient data will be analyzed based on the study arm to which they were randomized.

2.1.3 Additional Efficacy Evaluations

For Cohorts 1-4 and ABSSSI patients in Cohort 5: Infection site assessment includes the following: purulence/drainage, erythema, heat/localized warmth, pain/tenderness to palpation, fluctuance and swelling/induration at Baseline, 48-72 hours post randomization, Day 8 (± 1 day), Day 14 (± 2 days), Day 28 (± 2 days) and Day 54 (± 7 days). Ruler measurements of the area of erythema will also be obtained at Baseline and at 48-72 hours post randomization in Cohorts 1-4 and ABSSSI patients in Cohort 5. Length of the area of erythema will be measured as the longest length. Width will be measured as the widest width perpendicular to the longest length.

Resource utilization will be collected at Day 14 (± 2 days) and Day 28 (± 2 days), as well as other data available (e.g., length of hospitalization, or need for additional outpatient visits including Emergency Department visits, tests and procedures).

Patient and parent/guardian **satisfaction** with therapy will be assessed using the SSTI-Convenience questionnaire at Day 14 (± 2 days).

3 STUDY DESIGN

3.1 Overall Study Design and Plan

This is a Phase 3, multicenter, open-label, randomized, comparator controlled trial evaluating the safety and efficacy of a single dose of IV dalbavancin and a two-dose regimen of once weekly IV dalbavancin (for a total of 14 days of coverage) for the treatment of acute bacterial skin and skin structure infections known or suspected to be due to susceptible Gram-positive organisms in children. The comparators are either IV vancomycin (for methicillin-resistant Gram-positive infections) or IV oxacillin or flucloxacillin (for methicillin-susceptible Gram-positive infections) for 10-14 days. Patients may be switched from IV oxacillin or flucloxacillin to oral cefadroxil after at least 72 hours of study drug treatment, if they meet specified criteria for oral therapy. Similarly, if infection with methicillin-resistant S. aureus is documented, then patients may be switched from IV vancomycin to oral clindamycin after at least 72 hours of parenteral antibiotic therapy, if they meet specified criteria for oral therapy. If an alternate comparator regimen is indicated by local susceptibility patterns or recommended by local treatment guidelines, this must be discussed with the medical monitor.

Eligible patients, from birth to 17 years of age (inclusive) with acute bacterial skin and skin structure infection will be enrolled. Approximately 188 patients will be enrolled (such that 188 patients will be included in the Safety Population), with 178 patients 3 months or older randomized to receive dalbavancin (single-dose or two-dose regimen) or comparator, in a 3:3:1 randomization scheme: 76 patients will be randomized to dalbavancin (single-dose IV), 76 patients will be randomized to dalbavancin (2 doses once weekly IV therapy), and 26 patients will be randomized to comparator (IV vancomycin or IV oxacillin or flucloxacillin).The randomization scheme will not include the youngest age cohort (birth to < 3 months of age), as all 10 patients in this cohort will receive the single-dose regimen of dalbavancin, bringing the total number of patients enrolled in the study to approximately 188 patients.

The enrollment target of 10 patients for Cohort 5 includes at least 5 patients ≤ 28 days (including pre-term neonates).

There will be 5 age cohorts:

- Cohort 1 –12 years to 17 years old, inclusive,
- Cohort 2 – 6 years to < 12 years old,
- Cohort 3 – 2 years to < 6 years old,
- Cohort 4 – 3 months to < 2 years old, and
- Cohort 5 – birth to < 3 months of age (including pre-term neonates with gestational age ≥ 32 weeks).

With the exception of Cohort 5, patients will be randomized 3:3:1 to each of the three treatment groups. In Cohorts 3 and 4 (enrolling patients aged 2 years to < 6 years old and 3 months to < 2 years old, respectively), there will be approximately 15 patients in each dalbavancin arm, and 5 patients in each comparator arm. In Cohorts 1 and 2 (enrolling patients 12 years to 17 years old, inclusive, and 6 years to < 12 years old, respectively), there will be approximately 23 patients in each dalbavancin arm and 8 patients in each comparator arm.

A Data and Safety Monitoring Board (DSMB) will be chartered to review data on safety at pre-specified intervals to assure the well-being of patients. The specific responsibilities and activities of the DSMB will be detailed in a separate DSMB Charter.

3.2 Investigational Study Medications

3.2.1 Dalbavancin Group

Patients randomized to the single-dose regimen of dalbavancin will receive dalbavancin administered intravenously over 30 (± 5) minutes as follows:

- **3 months to < 6 years old:** 22.5 mg/kg (maximum 1500 mg) on Day 1;
- **≥ 6 years to 17 years old (inclusive):** 18 mg/kg (maximum 1500 mg) on Day 1

Patients randomized to the two-dose regimen of dalbavancin will receive dalbavancin administered intravenously over 30 (± 5) minutes as follows:

- **3 months to < 6 years old:** 15 mg/kg (maximum 1000 mg) on Day 1, and 7.5 mg/kg (maximum 500 mg) on Day 8;
- **≥ 6 years to 17 years old (inclusive):** 12 mg/kg (maximum 1000 mg) on Day 1, and 6 mg/kg (maximum 500 mg) on Day 8

Patients in Cohort 5 (birth to < 3 months of age) will receive the single-dose regimen of dalbavancin 22.5 mg/kg on Day 1 administered intravenously over 30 (± 5) minutes. Cohort 5 will be initiated based on review of initial results from patients > 28 days to < 3 months in study DAL-PK-02 (DUR001-107).

If clinically improving, patients may be discharged home as long as they return for protocol-specified assessments (48-72 hours, Days 8, 14, 28 and 54).

3.2.2 Comparator Group

For patients randomized to the comparator arm, patients will receive a 10-14 day course of either vancomycin 10 *to 15* mg/kg/dose, infused over 60 minutes (± 10) every 6 hours (± 1 hour), not to exceed a total daily dose of 4000 mg; or oxacillin 30 mg/kg/dose, infused over 60 minutes (± 10) every 6 hours (± 1 hour); or flucloxacillin 50 mg/kg/dose, infused over 60 minutes (± 10) every 6 hours (± 1 hour), not to exceed a total daily dose of 2000 mg. Based on local practice patterns and approvals for clinical use in the pediatric population, oxacillin or flucloxacillin will be supplied as an IV comparator.

No patient in Cohort 5 (birth to < 3 months of age) will be randomized to the comparator arm.

If clinically improving, patients may be discharged home to continue IV/oral therapy per standard of care, as long as they return for protocol-specified assessments (48-72 hours, Days 8, 14, 28 and 54).

The choice of empiric vancomycin or oxacillin or flucloxacillin will be based on investigator judgment based on the local incidence of MRSA in the community. If MRSA rates are > 10%, vancomycin will be encouraged as the initial treatment. Serum trough concentrations of vancomycin may be checked based on investigator judgment and local standard of care and the dose of vancomycin may be adjusted as needed.

Patients on oxacillin or flucloxacillin may be switched to oral cefadroxil (dose for infants and children: 15 mg/kg/dose every 12 hours, maximum 2 g/day; dose for adolescents: 500-1000 mg every 12 hours), and if infection with methicillin-resistant *S. aureus* is documented, patients may be switched from IV vancomycin to oral therapy with clindamycin 10 mg/kg every 8 hours at the discretion of the investigator after at least 72 hours of IV therapy if the patient meets the following criteria:

- The patient has been afebrile for 48 hours
- Local signs and symptoms of infection are improving
- The patient has the ability to swallow, retain, and absorb the oral medication

If patients randomized to comparator are initially placed on empiric IV vancomycin and their baseline pathogen is a methicillin-susceptible Gram-positive organism, they may be switched to IV oxacillin or flucloxacillin (or oral cefadroxil if criteria for oral therapy are met), and continue in the study. If patients are initially placed on empiric IV oxacillin or flucloxacillin and their baseline pathogen is a methicillin-resistant Gram-positive organism, they should be

switched to IV vancomycin (or oral clindamycin for documented MRSA and if criteria for oral therapy are met), and continue in the study. If an alternate comparator regimen is indicated by local susceptibility patterns or recommended by local treatment guidelines, this must be discussed with the medical monitor.

3.2.3 Method for Determination of Creatinine Clearance

Patients with estimated serum creatinine clearance values < 30 mL/min are excluded from this study (Exclusion Criterion 1, Section 4.2). However, the dosage of vancomycin may need to be adjusted in patients with moderate to mild renal impairment. Serum creatinine clearance will be calculated as follows (also see Appendix 4 [20]):

Schwartz "bedside" equation for ages 3 months to 17 yrs (inclusive):

$$\text{CrCl (mL/min/1.73 m}^2\text{)} = \frac{0.413 \times \text{Height (length) (cm)}}{\text{Serum creatinine (mg/dL)}}$$

3.3 Rationale for Study Design and Comparator Group

The purpose of this trial is to determine the safety and descriptive efficacy of dalbavancin for the treatment of ABSSSI known or suspected to be caused by susceptible Gram-positive organisms, including MRSA, in pediatric patients.

Comparator agents used commonly in clinical practice are dosed multiple times a day and given intravenously in hospitalized pediatric patients. While oral therapy is common after an initial intravenous course of treatment, oral agents are not uniformly well tolerated in children and adherence with treatment regimens after discharge may be uncertain. Regimens targeted at Gram-positive organisms, which deliver effective drug exposures for the entire treatment duration, require limited intravenous access, minimize any risk of non-adherence, and are well tolerated would represent a significant advance in the treatment of this disease.

3.4 Adjunctive Systemic Antibiotics

- **Aztreonam** may be administered at randomization for presumed co-infection with a Gram-negative pathogen and could be discontinued if a Gram-negative pathogen is not documented by culture.
- For suspected **anaerobic** pathogens, **metronidazole** oral/IV may be used.
- Cohort 5 (birth to < 3 months) will be allowed concomitant antibacterial therapy in addition to dalbavancin, based on local standard of care.

3.5 Additional, Non-Study Therapy Antibiotics

- For *Clostridium difficile* infections, **metronidazole** (IV or oral) or **oral vancomycin** may be used in all treatment groups.
- Other antibiotics that do not achieve significant therapeutic concentrations in the serum (e.g., nitrofurantoin) may be considered for treatment of other concomitant infections. Close consultation with the medical monitor is advised prior to use of these antibiotics.

If a **Gram-negative bacteremia** develops during the study, even in the presence of a Gram-positive infection or Gram-positive bacteremia, or is subsequently found to have been present at Baseline, the patient should be removed from study treatment and receive appropriate antibiotic(s) to treat the Gram-negative bacteremia. Such patients must have a Premature Discontinuation Visit performed within 3 calendar days after discontinuing study medication but are required to have AEs reported through Day 54 and a Final Visit at Day 54. Similarly, patients who withdraw from the study for other reasons must also have a Premature Discontinuation Visit performed within three calendar days and AEs reported through Day 54 and a patient status assessment at Day 54 (see Section 6.3).

Patients subsequently discovered to have had a Gram-positive organism at baseline resistant to dalbavancin may remain on study therapy based on the investigator's impression of the patient's clinical response to therapy.

4 STUDY POPULATION SELECTION

Male or female patients who present with ABSSSI and who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study. Additionally, for Cohort 5 only, patients may present with suspected or confirmed sepsis.

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for enrollment under this protocol.

4.1 Inclusion Criteria

For Cohorts 1 – 4, ages 3 months to 17 years inclusive, each patient must meet the following criteria to be enrolled in this study:

1. Male or female patients 3 months to 17 years of age (inclusive)
2. A clinical picture compatible with ABSSSI suspected or confirmed to be caused by Gram-positive bacteria, including MRSA.
3. In addition to local signs of ABSSSI, the patient has at least one of the following:
   - Fever, defined as body temperature ≥ 38.4°C (101.2°F) taken orally, ≥ 38.7°C (101.6°F) tympanically, or ≥ 39°C (102.2°F) rectally (core temperature)
   - Leukocytosis (WBC > 10,000 mm^3) or leukopenia (WBC < 2,000 mm^3) or left shift of > 10% band neutrophils
4. Infection either involving deeper soft tissue or requiring significant surgical intervention:

(a) Major cutaneous abscess characterized as a collection of pus within the dermis or deeper that is accompanied by erythema, edema and/or induration which:
   i. requires surgical incision and drainage, and
   ii. is associated with cellulitis such that the total affected area involves at least 35 cm^2 of erythema, or total affected area of erythema is at least BSA (m^2) x 43.0 (cm^2/m^2), OR
   iii. alternatively, involves the central face and is associated with an area of erythema of at least 15 cm^2

(b) Surgical site or traumatic wound infection characterized by purulent drainage with surrounding erythema, edema and/or induration which occurred within 30 days after the trauma or surgery and is associated with cellulitis such that
   i. the total affected area involves at least 35 cm^2 of erythema, or total affected area of erythema is at least BSA (m^2) x 43.0 (cm^2/m^2), OR
   ii. alternatively, involves the central face and is associated with an affected area of at least 15 cm^2

(c) Cellulitis, defined as a diffuse skin infection characterized by spreading areas of erythema, edema and/or induration and
   i. is associated with erythema that involves at least 35 cm^2 of surface area, or surface area of erythema is at least BSA (m^2) x 43.0 (cm^2/m^2), OR

ii. alternatively, cellulitis of the central face that is associated with an affected area of at least 15 cm^2

5. In addition to the requirement for erythema, all patients are required to have at least two (2) of the following signs of ABSSSI:

(a) Purulent drainage/discharge
(b) Fluctuance
(c) Heat/localized warmth
(d) Tenderness to palpation
(e) Swelling/induration

6. A signed and dated informed consent document indicating that the legally acceptable representative or the patient's parent(s)/legal guardian(s)) has been informed of all pertinent aspects of the trial. If required by the local IRB/IEC, a child assent will be obtained, as applicable.

7. Patients, and if required by local/site regulations, their parent(s)/legal guardian(s), must be willing and able, if discharged from the hospital, to return to the hospital or a designated clinic for scheduled visits, treatment, laboratory test and other outpatient procedures as required by the protocol.

8. Patients must be expected to survive with appropriate antibiotic therapy and appropriate supportive care throughout the study.

For Cohort 5 (birth to < 3 months), each patient must meet the following inclusion criteria to be enrolled in this study:

1. Male or female patients from birth to < 3 months of age, including pre-term neonates (gestational age ≥ 32 weeks)

2. A clinical picture compatible with an ABSSSI suspected or confirmed to be caused by Gram-positive bacteria, including MRSA

   OR

   Suspected or confirmed sepsis including any of the following clinical criteria:

   (a) Hypothermia (<36°C) OR fever (>38.5°C)
   (b) Bradycardia OR tachycardia OR rhythm instability
   (c) Hypotension OR mottled skin OR impaired peripheral perfusion
   (d) Petechial rash
   (e) New onset or worsening of apnea episodes OR tachypnea episodes OR increased oxygen requirements OR requirement for ventilation support
   (f) Feeding intolerance OR poor sucking OR abdominal distension
   (g) Irritability

(h) Lethargy
(i) Hypotonia

3. In addition, patients must meet <u>at least one</u> of the following laboratory criteria:
   (a) White blood cell count $\leq 4.0 \times 10^9$/L OR $\geq 20.0 \times 10^9$/L
   (b) Immature to total neutrophil ratio >0.2
   (c) Platelet count $\leq 100 \times 10^9$/L
   (d) C-reactive protein (CRP) >15 mg/L OR procalcitonin ≥ 2 ng/mL
   (e) Hyperglycemia OR Hypoglycemia
   (f) Metabolic acidosis
4. Infections must be of sufficient severity to merit hospitalization and parenteral antibiotic therapy. These infections may include:

   (a) Cutaneous or subcutaneous abscess

   (b) Surgical site or traumatic wound infection

   (c) Cellulitis, Erysipelas

   (d) Omphalitis

   (e) Impetigo and bullous impetigo

   (f) Pustular folliculitis

   (g) Scarlet fever

   (h) Staphylococcal scalded skin syndrome

   (i) Streptococcal toxic shock syndrome

   (j) Erythematous based-erosion

   (k) Other infections originating in the skin or subcutaneous tissue and associated with signs and symptoms of sepsis as defined in Inclusion Criterion 2.
5. A signed and dated informed consent document indicating that a legally acceptable representative or the patient's parent(s)/legal guardian(s) has been informed of all pertinent aspects of the trial.
6. Each patients' parent(s)/legal guardian(s) must be willing and able, if discharged from the hospital, to return to the hospital or a designated clinic for scheduled visits, treatment, laboratory test and other outpatient procedures as required by the protocol.
7. Patients must be expected to survive with appropriate antibiotic therapy and appropriate supportive care throughout the study.

4.2 Exclusion Criteria

Patients who meet any of the following will be excluded from the study:

1. Patients in Cohort 1-4: Clinically significant renal impairment, defined as creatinine clearance < 30 mL/min (calculated by the Schwartz "bedside" formula). Patients in Cohort 5 (birth to < 3 months of age): Moderate or severe renal impairment defined as serum creatinine ≥ 2 times the upper limit of normal (× ULN) for age OR urine output < 0.5 mL/kg/h (measured over at least 8 hours prior to dosing) OR requirement for dialysis.
2. Clinically significant hepatic impairment, defined as serum bilirubin or alkaline phosphatase > 2X ULN for age, and/or serum AST or ALT > 3X ULN for age (neonates with elevated total bilirubin can participate if conjugated or direct bilirubin were normal per age).
3. Treatment with an investigational drug within 30 days preceding the first dose of study medication.
4. Patients with sustained shock defined as systolic blood pressure < 90 mm Hg in children ≥ 10 years old, < 70 mm Hg + [2 x age in years] in children 1 to < 10 years, or < 70 mm Hg in infants 3 to < 12 months old for more than 2 hours despite adequate fluid resuscitation, with evidence of hypoperfusion or need for sympathomimetic agents to maintain blood pressure.
5. More than 24 hours of any systemic antibacterial therapy within 96 hours before randomization. EXCEPTION: Microbiological or clinical treatment failure with a systemic antibiotic other than IV study drug that was administered for at least 48 hours. Failure must be confirmed by either a microbiological laboratory report or documented worsening clinical signs or symptoms.
6. Infection due to an organism known prior to study entry to be resistant to dalbavancin (dalbavancin MIC > 0.25 μg/mL) or vancomycin (vancomycin MIC > 2 μg/mL).
7. Patients with necrotizing fasciitis, or deep-seated infections that would require > 2 weeks of antibiotics (e.g., endocarditis, osteomyelitis or septic arthritis).
8. Infections caused exclusively by Gram-negative bacteria (without Gram-positive bacteria present) and infections caused by fungi, whether alone or in combination with a bacterial pathogen.
9. Venous catheter entry site infection.
10. Infections involving diabetic foot ulceration, perirectal abscess or a decubitus ulcer.

11. Patient with an infected device, even if the device is removed. Examples include infection of: prosthetic cardiac valve, vascular graft, a pacemaker battery pack, joint prosthesis, implantable pacemaker or defibrillator, intra-aortic balloon pump, left ventricular assist device, or a neurosurgical device such as a ventricular peritoneal shunt, intra-cranial pressure monitor, or epidural catheter.
12. Gram-negative bacteremia, even in the presence of Gram-positive infection or Gram-positive bacteremia. Note: If a Gram-negative bacteremia develops during the study, or is subsequently found to have been present at Baseline, the patient should be removed from study treatment and receive appropriate antibiotic(s) to treat the Gram-negative bacteremia.
13. Patients whose skin infection is the result of having sustained full or partial thickness burns.
14. Patients in Cohorts 1 – 4 with uncomplicated skin infections such as superficial/simple cellulitis/erysipelas, impetiginous lesion, furuncle, or simple abscess that only requires surgical drainage for cure. For Cohort 5 (birth to < 3 months of age) these patients may be enrolled if they have uncomplicated skin infections of sufficient severity to require hospitalization and parenteral antibiotic therapy.
15. For Cohorts 1 – 4 (3 months to 17 years of age, inclusive): Concomitant condition requiring any antibiotic therapy that would interfere with the assessment of study drug for the condition under study.
16. Sickle cell anemia
17. Cystic fibrosis
18. Anticipated need of antibiotic therapy for longer than 14 days.
19. Patients who are placed in a hyperbaric chamber as adjunctive therapy for the ABSSSI.
20. More than 2 surgical interventions (defined as procedures conducted under sterile technique and typically unable to be performed at the bedside) for the skin infection, or patients who are expected to require more than 2 such interventions.
21. Medical conditions in which chronic inflammation may preclude assessment of clinical response to therapy even after successful treatment (e.g., chronic stasis dermatitis of the lower extremity).

22. Immunosuppression/immune deficiency, including hematologic malignancy, recent bone marrow transplant (in post-transplant hospital stay), absolute neutrophil count < 500 cells/mm^3, receiving immunosuppressant drugs after organ transplantation, receiving oral steroids ≥ 20 mg prednisolone per day (or equivalent) for > 14 days prior to enrollment, and known or suspected human immunodeficiency virus (HIV) infected patients with a CD4 cell count < 200 cells/mm^3 or with a past or current acquired immunodeficiency syndrome (AIDS)-defining condition and unknown CD4 count.
23. Known or suspected hypersensitivity to glycopeptide antibiotics, beta-lactam agents, aztreonam, or cephalosporins.
24. Patients with a rapidly fatal illness, who are not expected to survive for 3 months.
25. Positive urine (or serum) pregnancy test at screening (post-menarchal females only) or after admission (prior to dosing).
26. Pregnant or nursing females; sexually active females of childbearing potential who are unwilling or unable to use adequate contraceptive precautions. Female patients to have pregnancy testing are those who are at least 10 years old with menarche and/or thelarche (beginning of breast development).
27. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
28. Unwilling or unable to follow study procedures.

4.3 Randomization Criteria

Patients will be randomized using an Interactive Web Randomization System (IWRS) into the study provided they have satisfied all patient selection criteria.

4.4 Females of Child-Bearing Potential

If the patient is a female of childbearing potential, she must be willing to practice complete abstinence, or she and any male partner are required to simultaneously use 2 effective contraceptive methods, from the following list of 5:

1. A barrier (condoms, diaphragm or cervical cap) with spermicide;
2. A second, different barrier method (condoms, diaphragm or cervical cap);

3. Oral or similar contraceptive, which includes, but is not limited to: injectable, implanted, or patch hormone therapy, and intrauterine device (IUD);
4. Documented surgical sterilization at least 4 weeks prior to baseline;
5. Partner vasectomy at least 6 months prior to baseline.

5 STUDY TREATMENTS

5.1 Allocation to Treatment

This is a randomized open-label study evaluating dalbavancin with a comparator regimen in the treatment of pediatric ABSSSI.

The study is planned to enroll approximately 188 patients, such that 188 patients will be included in the Safety Population. After a patient signs the ICF at the baseline visit, study personnel will register the patient in the IWRS, and the system will assign the patient a sequential Patient Identification (PID) number. The first patient to sign the ICF at each study center will be assigned the first number in the sequence by the system.

Patients ≥ 3 months will then be randomized to receive dalbavancin (single-dose or two-dose regimen) or a comparator, in a 3:3:1 randomization scheme: 76 patients will be randomized to dalbavancin (single-dose IV), 76 patients will be randomized to dalbavancin (2 IV doses one week apart), and 26 patients will be randomized to comparator (IV vancomycin or IV oxacillin or flucloxacillin), based on an IWRS-generated randomization schedule. The randomization scheme will not include the youngest age cohort (birth to < 3 months of age), as all 10 patients in this cohort will receive the single-dose regimen of dalbavancin, bringing the total number of patients enrolled in the study to approximately 188 patients.

There will be 5 age cohorts: 12 years to 17 years old, inclusive (Cohort 1); 6 years to < 12 years old (Cohort 2), 2 years to < 6 years old (Cohort 3), 3 months to < 2 years old (Cohort 4), and from birth to < 3 months (Cohort 5). With the exception of Cohort 5, patients will be randomized 3:3:1 to each of the three treatment groups.

In Cohorts 3 and 4 (enrolling patients aged 2 years to < 6 years old and 3 months to < 2 years old, respectively), there will be approximately 15 patients in each dalbavancin arm. In Cohorts 1 and 2 (12 years to 17 years old, inclusive and 6 years to < 12 years old, respectively), there will be approximately 23 patients in each dalbavancin arm, and 8 patients in each comparator arm. The enrollment target of 10 patients for Cohort 5 includes at least 5 patients ≤ 28 days (including pre-term neonates).

A patient will be eligible for randomization once it has been determined that she/he meets all inclusion criteria and none of the exclusion criteria. On the day the patient is to receive the first dose of study drug, a designated member of the clinical pharmacy staff will contact the IWRS to obtain the study treatment assignment and dispense therapy accordingly. The IWRS will associate that patient with the next available treatment in the appropriate stratum on the randomization schedule. A patient is considered randomized when the pharmacist or designee receives the treatment assignment associated with the patient entered into the IWRS.

5.2 Drug Supplies

5.2.1 Dalbavancin

5.2.1.1 Formulation and Packaging

The study drug dalbavancin is supplied as a single-use vial of sterile, lyophilized preservative-free, powder containing 500 mg of dalbavancin. Each 500 mg vial of dalbavancin for injection should be reconstituted and further diluted by addition of 5% Dextrose Injection (D5W) prior to administration, in accordance with the study pharmacy manual. Each participating site is responsible for providing D5W required for preparation and administration of IV dalbavancin.

All supplies packed and labeled will be formally released in accordance with both Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

5.2.1.2 Preparation and Dispensing

All unit doses of dalbavancin will be prepared at the study site. Dalbavancin will be prepared and documented in accordance with the treatment schedule as outlined in the study protocol. Preparation instructions will be provided to each study site in a study pharmacy manual.

5.2.1.3 Administration

Study drug administration will be documented in accordance with the Pharmacy Manual.

5.2.1.4 Compliance

Intravenous treatment will be administered under the supervision of investigative site personnel and infusion date, start, and stop time will be documented on the CRF.

5.2.2 Vancomycin, Oxacillin, Flucloxacillin, Cefadroxil, or Clindamycin

5.2.2.1 Formulation and Packaging

The IV comparators will be supplied as Vancomycin Hydrochloride for Injection, 500 mg vials (powder for reconstitution), Oxacillin for Injection, 1 g vials (powder for reconstitution), and Flucloxacillin Powder for Solution for Injection or Infusion, 500 mg vials. Based on local practice patterns and approvals for clinical use in the pediatric population, oxacillin or flucloxacillin will be supplied. Each participating site is responsible for providing the appropriate reconstitution diluents required for preparation and administration of IV infusions.

Oral Cefadroxil will be supplied in 500 mg capsules and as a suspension (250mg/5mL). Oral Clindamycin will be supplied in 150 mg and 300 mg capsules and as a suspension (75mg/5mL).

All supplies packed and labeled will be formally released in accordance with both Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

5.2.2.2 Preparation and Dispensing

The IV comparators, Vancomycin, Oxacillin, and Flucloxacillin are to be prepared according to the commercial label and in accordance with the study pharmacy manual.

Cefadroxil and Clindamycin suspensions will be prepared according to label directions prior to dispensing. All oral Cefadroxil and Clindamycin will be dispensed in accordance with the pharmacy manual.

5.2.2.3 Administration

Comparator will be administered in accordance with the treatment schedule outlined in the study protocol.

5.2.2.4 Compliance

Intravenous treatment will be administered under the supervision of investigative site personnel.

Upon discharge, patients/parents should be informed that compliance with taking all oral medication as instructed is imperative. Patients/parents will be asked to report oral dosing date and frequency which will be recorded on the CRF to monitor compliance to comparator.

In case of inadequate compliance (defined as < 80% or > 120% of the expected number of doses to be taken from randomization to subsequent study visits), the patient will first be reinstructed on importance of dosing adherence by the PI, or a qualified designee. In the event that treatment compliance remains unsatisfactory, patients may be discontinued at the discretion of the PI after close consultation with Sponsor.

5.3 Drug Storage and Drug Accountability

The investigator, or an approved representative, e.g., pharmacist/designee, will ensure that all study drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements.

Adequate records must be maintained documenting the receipt and administration of all drug supplies.

5.3.1 Unreconstituted Dalbavancin for Injection, 500 mg vials

Dalbavancin for Injection, 500 mg unreconstituted vials should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

5.3.2 Reconstituted and Diluted Dalbavancin for Injection

Reconstituted vials may be stored either refrigerated at 2-8°C (36-46°F), or at controlled room temperature 20-25°C (68-77°F). Do not freeze.

The total time from reconstitution to dilution to administration should not exceed 48 hours.

5.3.3 Comparators

The active comparators, Vancomycin Hydrochloride for Injection, Oxacillin for Injection, Flucloxacillin Powder for Solution for Injection or Infusion, and Cefadroxil and Clindamycin capsules and suspensions are to be stored according to the commercial label instructions.

5.4 Concomitant Medication(s), Adjunctive Therapy and Non-drug Therapy

5.4.1 Concomitant Medications

Any medication taken by the patient, other than study drug, is considered concomitant medication. All concomitant medications from Screening (Day -1) through the Follow-up Visit (Day 54 ± 7) must be recorded in the patient's medical record and on the CRFs.

At each visit, the investigator will obtain information on any therapeutic interventions (e.g., drug and non-drug therapy, surgery, etc.) provided. The use of any other investigational drug is prohibited, and patients may not participate in any other studies involving marketed products concomitantly while in this study.

The use of other (non-antibacterial) medications should be limited to those essential for the care of the patient. All medications required by the patient to manage underlying illnesses, other than infection under study, and any drugs that may be required for emergency treatments must be recorded on the CRF.

5.4.2 Concomitant Antibacterial Medications

Concomitant systemic and topical antibacterials are prohibited during the study, up to the Final visit, with the following exceptions:

- Vancomycin oral may be used in all treatment groups for the treatment of *Clostridium difficile* infections and may be continued as required throughout the duration of the study. The Sponsor will not provide oral vancomycin.
- Metronidazole IV or oral may be used in all treatment groups for the treatment of *Clostridium difficile* infections and may be continued as required throughout the duration of the study. The Sponsor will not provide metronidazole.
- Other antibacterials that do not achieve therapeutic levels in the serum (e.g., nitrofurantoin) may be considered. Close consultation with the medical monitor is advised prior to use of these antibiotics.

Concomitant antibacterial medications allowed for patients in Cohort 5 are described in Section 5.4.3.

5.4.3 Adjunctive Antibacterial Therapy

Systemic and topical antibacterials are prohibited during the study, up to the EOT visit (14 ± 2 days), with the following exceptions:

- **Metronidazole** oral/IV may be used in all treatment groups for suspected anaerobic pathogens and may be continued as required throughout the duration of the study. The Sponsor will not provide metronidazole.

- **Aztreonam** for the treatment of ABSSSI caused by Gram-negative bacteria: ONLY systemic aztreonam may be administered empirically at randomization for a presumed Gram-negative contribution to the ABSSSI and could be discontinued if a Gram-negative pathogen is not documented by culture. Empiric use of aztreonam post-randomization is not permitted. Use of aztreonam to treat a culture-confirmed infection at any time during the study is acceptable. Aztreonam will be provided in those countries where it is not commercially available.
- For patients in Cohort 5 (birth to < 3 months), concomitant antibacterial therapy will be allowed in addition to dalbavancin, based on local standard of care.

5.4.4 Non-drug Adjunctive Therapy

The potential need for surgical intervention in patients with ABSSSI during the study must be prospectively defined at Baseline. Patients expected to require more than 2 surgical interventions for the ABSSSI under study are not to be enrolled.

The following adjunctive therapies are permitted for the treatment of ABSSSI:

- Debridement at the bedside;
- Topical solutions including antiseptic agents such as povidine-iodine;
- Local bedside wound care as per hospital protocol.

6 STUDY PROCEDURES

6.1 Baseline (Day -1 to 1) – Within 24 Hours Prior to First Dose

The investigator (or an appropriate delegate at the investigator site) will obtain written informed consent from parent(s)/legal guardian(s) and assent from patient (when appropriate) prior to the initiation of any study related activities. IWRS will then be accessed to obtain a sequential Patient Identification (PID) number.

The following procedures will be performed (also see Appendix 1):

- Review Inclusion and Exclusion criteria
- Demographics and medical history (including history of drug allergies, alcohol, drug and tobacco use)
- Complete physical examination (including general appearance, examination of head, eyes, ears, nose, throat, neck, skin, heart, lungs, abdomen, neurologic system, and extremities)

- Targeted examination of infection site assessment and ruler measurements; the assessment should occur within 4 hours prior to the first dose of study drug (Section 7.3.1.2, Appendix 5)
- Vital signs: blood pressure, respiratory rate, heart rate and temperature (oral, rectal, or tympanic), and height and weight
- Blood for laboratory testing: Standard of care laboratory tests obtained within 72 hours prior to first dose can be used to determine eligibility. If not already collected per standard of care, during screening, clinical laboratory tests needed to determine eligibility and serum or urine pregnancy testing (for post-menarchal females) will be done locally in order to qualify the patient for the study. All efforts should be made to utilize standard of care clinical laboratory tests if available to minimize blood collection. Data from clinical laboratory tests performed as standard of care during the study will be collected.
- An additional 2 mL whole blood sample will be obtained in children ≥ 2 years old **and** ≥ 12 kg to test for the bacteria that cause ABSSSI (EDTA whole blood, frozen).
- **For Cohorts 1-4 (3 months to 17 years inclusive):** Estimate creatinine clearance with Schwartz "bedside" equation
- **For Cohort 5 (birth to < 3 months) only:** Determine urine output (measured over at least 8 hours prior to dosing)
- Infection site specimen collection (including Gram-stain, culture and susceptibility [Appendix 3])
- Audiologic testing will be conducted in at least 20 children < 12 years old (in selected centers), of which at least 9 children will be < 2 years old. Audiologic testing to be conducted on infants (< 12 months old) will include: evoked otoacoustic emissions testing, acoustic immittance measures (tympanometry and contra and ipsilateral acoustic reflex thresholds) and (optional) threshold auditory brainstem responses. For the older children, testing will include evoked otoacoustic emissions testing, acoustic immittance measures (tympanometry and contra ipsilateral acoustic reflex thresholds), and age appropriate behavioral audiologic threshold assessment. Testing (as specified in the protocol) performed within 7 days prior to study drug administration can be used as the Baseline assessment
- Bowel flora testing: PCR for *Clostridium difficile* (C diff) and culture for vancomycin-resistant enterococci (VRE) on stool specimen or rectal swab will be done only in all patients from birth to < 2 years.

- Review and record previous (defined as within the prior 30 days) drug and non-drug treatments
- Review and record concomitant medications
- Review and record concomitant non-drug adjunctive therapy
- Record adverse events that occur after ICF is signed

6.2 Treatment Period

6.2.1 Day 1

- Randomize the patient
- Administer study drug within 4 hours after randomization and record dosing
- Vital signs: blood pressure, respiratory rate, heart rate, and temperature (oral, rectal, or tympanic)
- Review and record concomitant medications
- Review and record concomitant non-drug adjunctive therapy
- Record adverse events
- Obtain plasma PK measurement on patients on dalbavancin arm (single dose and two-dose), at 30 minutes (end of infusion) and at 2 hours after the start of the IV infusion.

6.2.2 48-72 hours after randomization

- Targeted examination of infection site with ruler measurements, including Clinical Status (Section 7.3.1.2)
- Vital signs: blood pressure, respiratory rate, heart rate, and temperature (oral, rectal, or tympanic)
- Review and record concomitant medications
- Review and record concomitant non-drug adjunctive therapy
- Administer comparator (in comparator arm) and record dosing
- Record adverse events
- Obtain plasma PK measurement on patients on dalbavancin arm (single dose and two-dose) at 48-72 hours after start of IV infusion

6.2.3 Day 8 (± 1 day)

- Targeted examination of infection site (Section 7.3.1.2)
- Vital signs: blood pressure, respiratory rate, heart rate, and temperature (oral, rectal, or tympanic)
- Review and record concomitant medications
- Review and record concomitant non-drug adjunctive therapy
- Obtain plasma PK measurement on patients in the dalbavancin arms (single dose and two-dose) at 168 ± 24 hours after start of IV infusion on Day 1 (but before the Day 8 dose)
- Administer second dose of dalbavancin (or administer comparator) if applicable and record dosing
- Record adverse events

6.2.4 Day 14 (± 2 days): End of Treatment Visit (EOT)

The EOT visit is to occur at Day 14 (± 2) for patients completing the study treatment.

- Targeted examination of infection site, including Clinical Status (Section 7.3.1.2)
- Vital signs: blood pressure, respiratory rate, heart rate, and temperature (oral, rectal, or tympanic)
- Obtain plasma PK measurement on patients on dalbavancin arm (single dose and two-dose) at 312 ± 48 hours after start of IV infusion on Day 1
- Review and record concomitant medications
- Review and record concomitant non-drug adjunctive therapy
- Investigator assessment of clinical response (Section 2.1.2)
- Administer parent/caregiver satisfaction using the SSTI-Convenience questionnaire (Appendix 6)
- Resource Utilization
- Record adverse events
- If on comparator, record oral dosing

6.2.5 Day 28 (± 2 days): Test of Cure Visit

- Targeted examination of infection site, including Clinical Status (Section 7.3.1.2)
- Vital signs: blood pressure, respiratory rate, heart rate, and temperature (oral, rectal, or tympanic)
- Serum or urine pregnancy test for post-menarchal female patients
- Audiologic testing will be conducted in at least 20 children < 12 years old (in selected centers), of which at least 9 children will be < 2 years old. Audiologic testing to be conducted on infants (< 12 months old) will include: evoked otoacoustic emissions testing, acoustic immittance measures (tympanometry and contra and ipsilateral acoustic reflex thresholds) and (optional) threshold auditory brainstem responses. For the older children, testing will include evoked otoacoustic emissions testing, acoustic immittance measures (tympanometry and contra ipsilateral acoustic reflex thresholds), and age appropriate behavioral audiologic threshold assessment
- Bowel flora testing: PCR for *Clostridium difficile* (C. diff) and culture for vancomycin-resistant enterococci (VRE) on stool specimen or rectal swab will be done only in all patients from birth to < 2 years.
- Review and record concomitant medications
- Review and record concomitant non-drug adjunctive therapy
- Investigator assessment of clinical response (Section 2.1.2)
- Resource Utilization
- Record adverse events

6.2.6 Day 54 (± 7 days): Follow-up Visit

- Targeted examination of infection site, including Clinical Status (Section 7.3.1.2)
- Vital signs: blood pressure, respiratory rate, heart rate, and temperature (oral, rectal, or tympanic)
- Review and record concomitant medications
- Review and record concomitant non-drug adjunctive therapy
- Investigator assessment of clinical response (Section 2.1.2)
- Record adverse events

6.2.7 Premature Discontinuation Visit

The premature discontinuation visit should occur within 3 calendar days of the discontinuation. Specimens or measurements listed below should be obtained at time of discontinuation, if patient discontinues earlier than the last scheduled assessment for that particular activity.

- Targeted examination of infection site, including Clinical Status (Section 7.3.1.2)
- Vital signs: blood pressure, respiratory rate, heart rate, and temperature (oral, rectal, or tympanic)
- Obtain plasma PK measurement on patients on dalbavancin arm (single dose and two-dose) only if premature discontinuation visit occurs prior to Day 14
- Serum or urine pregnancy test for post-menarchal female patients
- Audiologic testing will be conducted in at least 20 children < 12 years old (in selected centers), of which at least 9 children will be < 2 years old. Audiologic testing to be conducted on infants (< 12 months old) will include: evoked otoacoustic emissions testing, acoustic immittance measures (tympanometry and contra and ipsilateral acoustic reflex thresholds) and (optional) threshold auditory brainstem responses. For the older children, testing will include evoked otoacoustic emissions testing, acoustic immittance measures (tympanometry and contra ipsilateral acoustic reflex thresholds), and age appropriate behavioral audiologic threshold assessment
- Bowel flora testing: PCR for *Clostridium difficile* (C. diff) and culture for vancomycin-resistant enterococci (VRE) on stool specimen or rectal swab will be done only in all patients from birth to < 2 years
- Review and record concomitant medications
- Review and record concomitant non-drug adjunctive therapy
- Investigator assessment of clinical response (Section 2.1.2)
- Administer parent/caregiver satisfaction using the SSTI-Convenience questionnaire (Appendix 6)
- Resource Utilization
- Record adverse events
- If on comparator, record oral dosing

6.3 Patient Withdrawal from Treatment or Study

Patients may withdraw from the study or study drug at any time at their own request or at the request of their parents/legal guardians, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. If the patient withdraws or is withdrawn from study drug treatment, the investigator should inquire about the reason for withdrawal, request the patient to return for all protocol-specified assessments, if possible, and follow-up with the patient regarding any unresolved AEs through Day 54.

For patients who withdraw from the study early, a final visit should be performed within 3 calendar days after decision to discontinue.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further study-specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7 ASSESSMENTS

7.1 Safety

7.1.1 Physical Examination

A complete physical examination will be performed at Baseline which includes: height, weight, general appearance, examination of head, eyes, ears, nose, throat, neck, skin, heart, lungs, abdomen, neurologic exam, extremities and a targeted exam of the infection site.

A targeted exam of the infection site will also be performed at 48-72 hours post randomization, on Day 8 (± 1 day), Day 14 (± 2 days), Day 28 (± 2 days), Day 54 (± 7 days), and at time of premature discontinuation.

7.1.2 Vital Signs (Blood Pressure, Respiratory Rate, Heart Rate and Temperature)

Vital signs are performed as noted below while admitted, and at each visit. These include: blood pressure, respiratory rate, heart rate, and temperature.

Temperature may be recorded as oral, rectal or tympanic (ear). If possible, temperature should be obtained using the same method each day. Temperature measurements should be taken at Baseline, at Day 1, 48-72 hours post randomization, Day 8 (± 1 day), Day 14 (± 2 days), Day 28 (± 2 days), Day 54 (± 7 days), and at time of premature discontinuation.

7.1.3 Clinical Laboratory Assays

Patients will be in a seated or supine position during protocol required blood collection.

Standard of care laboratory tests obtained within 72 hours prior to first dose can be used to determine eligibility. Clinical laboratory tests needed to determine eligibility will be collected during screening, if not already collected as standard of care. All efforts should be made to utilize standard of care clinical laboratory tests if available to minimize blood collection.

Data from clinical laboratory tests performed as standard of care during the study will be collected.

For female patients of childbearing potential: a urine or serum pregnancy test must be performed at Screening Visit prior to study drug administration. Results of screening pregnancy test must be negative in order for the patient to receive study drug. Urine or serum pregnancy test must be repeated on Day 28 (± 2 days), and at time of premature discontinuation.

Data from any peripheral blood cultures performed as standard of care during the study will be collected.

Whole blood sample (only in children ≥ 2 years old **and** ≥ 12 kg): Baseline only, to identify bacteria that cause ABSSSI (for data analysis only), EDTA frozen.

Plasma samples (0.25 mL of blood per sample) for pharmacokinetic (PK) measurements will be collected from all patients in both dalbavancin arms (single dose and two-dose regimen), at 30 minutes (end of infusion), at 2 hours after start of the infusion (Day 1), at 48-72 hours (Day 3-4), at 168 ± 24 hours (Day 8), at 312 ± 48 hours (Day 14 ± 2), and at premature discontinuation (if occurring prior to Day 14). Heel sticks may be used for blood collection in Cohort 5. Details regarding PK blood collection tubes, PK sample collection, labeling, processing, storage, and shipment instructions will be provided in the laboratory manual.

7.1.4 Clinically Significant Laboratory Tests

Clinical laboratory tests may be repeated during the study if deemed necessary as part of routine practice based on investigator judgment. All clinically significant abnormal

laboratory test results occurring post-baseline are recommended to be repeated at appropriate intervals per standard of care until they return either to baseline or to a level deemed acceptable by the investigator.

For any subject who meets the potential Hy's law criteria (Section 8.13.2), frequency of liver function tests should be increased to daily monitoring, if appropriate (using local laboratory data and recorded as unscheduled visits) until the liver function tests return to the level at baseline or stabilize.

7.2 Microbiology

Blood cultures: Data for any peripheral blood cultures obtained per standard of care, during screening and during the study, will be collected. It is recommended that blood cultures should not be obtained through an existing intravascular line.

If the baseline blood culture reveal*s* a Gram-positive pathogen, data for any repeat blood cultures obtained as per standard of care will be collected. If blood cultures are positive for the same pathogen on 3 consecutive sampling dates, the patient should be withdrawn from the study drug.

If the baseline blood culture reveal*s* a Gram-negative pathogen, the patient should be removed from study drug immediately and treated with an appropriate antibacterial agent.

Once an organism has been isolated and identified, the local laboratory must send a viable isolate to the central laboratory for confirmation of identification and susceptibility testing.

Infection site cultures: If an exudate/aspirate/pus sample can be obtained at Baseline per Appendix 3 (before administration of study drug), it should be sent for Gram stain and culture to the local laboratory, which should also conduct organism identification and antibiotic susceptibility testing.

7.3 Efficacy

7.3.1 Clinical

7.3.1.1 Evidence of Systemic Inflammation

Temperature, as a physical sign consistent with systemic inflammation, will be collected as either a core, oral, rectal or tympanic (ear) temperature at Baseline, Day 1, 48-72 hours post randomization, Day 8 (± 1 day), Day 14 (± 2 days), Day 28 (± 2 days), and Day 54 (± 7 days), and premature discontinuation.

Laboratory measurements as markers of systemic infection, if available will be collected and recorded on the CRF, including: hs-CRP, WBC count and manual differential.

7.3.1.2 Infection Site Assessment

For Cohorts 1-4 and ABSSSI patients in Cohort 5: Infection site assessment includes the following: purulence/drainage, erythema, heat/localized warmth, pain/tenderness to palpation, fluctuance and swelling/induration at Baseline (within four hours prior to the first dose of study drug), 48-72 hours post randomization, Day 8 (± 1 day), Day 14 (± 2 days), and Day 28 (± 2 days). Ruler measurements of the area of erythema will be obtained at Baseline (within four hours prior to the first dose of study drug), and at 48-72 hours post randomization (in Cohorts 1 – 4 and ABSSSI patients in Cohort 5). Length of the area of erythema will be measured as the longest length. Width will be measured as the widest width perpendicular to the longest length.

Other Assessments:

Clinical Status as defined in Section 2.1.2.

The Investigator's Assessment of Outcome as defined in Section 2.1.2.

Resource utilization will be collected at Day 14 (± 2 days) and Day 28 (± 2 days), as well as other data available (e.g., length of hospitalization, or need for additional outpatient visits including Emergency Department visits, tests and procedures).

Patient and parent/guardian satisfaction with therapy will be assessed using the "Skin and Soft Tissue Infection" (SSTI) Convenience questionnaire at Day 14 (± 2 days), and premature discontinuation (Appendix 6).

8 ADVERSE EVENT REPORTING

8.1 Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE (SAE) requiring immediate notification to Sponsor. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The

investigator is required to assess causality. All AEs will be followed-up by the investigator until the event or its sequel resolve or stabilize at a level acceptable to the investigator, and The Sponsor concurs with that assessment.

8.2 Reporting Period

Adverse events will be collected from the time informed consent is signed through Final Visit.

For SAEs, the reporting period to Sponsor begins from the time informed consent is signed, which is obtained prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through the Final Visit. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

All AEs should be recorded on the CRF if they occur from the time informed consent is signed through Final Visit.

8.3 Definition of an AE

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device, unless the event is captured in the study endpoint, as defined below; the event need not necessarily have a causal relationship with the treatment or usage.

An event would be considered as adequately captured in the study endpoint if it is accurately and fully represented by a protocol-defined reason for clinical failure (other than mortality) or relapse. Such an event should not be reported as an adverse event. Events represented by the study endpoints include all of the following, if related to the primary ABSSSI under study:

- Local signs of fluctuance and localized heat/warmth have not resolved
- Local signs of tenderness to palpation and swelling/induration are worse than mild
- For patients with a wound infection the severity of purulent drainage is worse than baseline
- Persistence of one or more local or systemic signs and symptoms of ABSSSI such that new systemic antibacterial treatment was given
- The patient had a temperature of > 37.6°C (by any measurement method) due to the ABSSSI

- There is relapse/recurrence of ABSSSI (i.e., new or worsened signs or symptoms of the ABSSSI).

Except for circumstances as defined above, examples of AEs include but are not limited to:

- Abnormal test findings (see Section 8.4);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Extravasation of study drug;
- Exposure during Pregnancy.

8.4 Abnormal Test Findings

An abnormal objective test finding (e.g., an abnormal liver function test result) should be reported as an AE if the following conditions apply:

- Test result is associated with accompanying symptoms and/or signs, constituting a clinical syndrome (e.g., abnormal liver function test results, jaundice, and hepatic tenderness suggesting a diagnosis of hepatitis), and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or withdrawal from the study, significant additional concomitant drug treatment, or other therapy.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not define the abnormal objective test finding as an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE. Additional diagnostic testing or medical/surgical interventions that occur as a result of an adverse event due to an abnormal laboratory test finding should be noted in the CRF.

8.5 SAEs

An SAE or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect;
- Is assessed as being a medically important event based on medical and scientific judgment. Such medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the above outcomes. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.6 Hospitalization

Adverse events associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);

- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (e.g., patient has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery). Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as an AE. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

8.7 Important Medical Event

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.8 Severity Assessment

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

- MILD: Does not interfere with the patient's usual function.
- MODERATE: Interferes to some extent with the patient's usual function.
- SEVERE: Interferes significantly with the patient's usual function.

8.9 Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE. If the investigator does not know whether or not study drug caused the event, then the event will be handled as "related to study drug" for reporting purposes, as defined by the Sponsor (see Section 8.13 on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to study drug", this should be clearly documented on study records. Specifically, the investigator will choose whether the AE is unrelated, unlikely related, possibly related or probably related to dalbavancin or any of the comparators used by the patient.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

The Investigator will assess causality of the event in relation to dalbavancin based on the following defined criteria:

- UNRELATED: No relationship between the event and medicinal product
- UNLIKELY, Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible); Disease or other drugs provide plausible explanations

- POSSIBLY, Event or laboratory test abnormality, with reasonable time relationship to drug intake; Could also be explained by disease or other drugs; Information on drug withdrawal may be lacking or unclear
- PROBABLY, Event or laboratory test abnormality, with reasonable time relationship to drug intake; Unlikely to be attributed to disease or other drugs; Response to withdrawal clinically reasonable; rechallenge not required

8.10 Exposure during Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero) occurs if a female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure).

If any study patient becomes or is found to be pregnant during the study patient's treatment with the investigational product, no further study drug should be given and the investigator must submit this information to Sponsor on a Pregnancy Form. In addition, the investigator must submit information regarding environmental exposure to dalbavancin in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to dalbavancin by spillage) using the Pregnancy Form. This reporting must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all Pregnancy reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (i.e., induced abortion) and then notify the Sponsor of the outcome. The investigator will provide this information as a follow up to the initial Pregnancy Form. The reason(s) for an induced abortion should be specified. A Pregnancy report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, an SAE case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the investigator should follow the procedures for reporting SAEs.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (i.e., no minimum follow-up period of a presumably normal infant is required before a Pregnancy Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the investigator assesses as possibly related to the exposure during pregnancy to the investigational medication should be reported.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

8.11 Discontinuation from Study Drug Due to AEs (See also Patient Withdrawal, Section 6.3)

Patients will be advised they are free to withdraw from study drug administration and/or from the study at any time. Over the course of the study, the Investigator(s) and/or the Sponsor may discontinue administration of study drug to a patient in the case of unnecessary risk, adverse drug events, or noncompliance. When a patient withdraws or is withdrawn from the study medication, all safety data normally required at the end of the study will be obtained, if possible.

Discontinuation from study drug due to an AE should be distinguished from discontinuation due to insufficient response, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient discontinues study drug due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.12 Eliciting AE Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient through the Final Visit. In addition, each study patient will be questioned about the occurrence of any AEs.

8.13 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs that is considered by the investigator or the Company to be at least possibly related to dalbavancin, expedited reporting will follow local and international regulations, as appropriate.

8.13.1 SAE Reporting Requirements

If an SAE or exposure during pregnancy occurs, the Sponsor is to be notified within 24 hours of awareness of the event by the investigator on an SAE form or Pregnancy form. If the SAE is fatal or life-threatening, notification to the Sponsor must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of Pregnancy cases.

In the rare instance that the investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs and pregnancies, the investigator is obligated to pursue and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the SAE form. In general, this information may include hospital discharge summary, laboratory test, etc. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor. The information should be reported on an SAE/Pregnancy form and sent to:

US AbbVie PharmacoVigilance group

SAE Form fax number: [+1-714-796-9504; Backup: +1-714-246-5295]

OR

Email SAE/Pregnancy Forms to: IR-Clinical-SAE@abbvie.com

The Sponsor will acknowledge receipt of all SAE information within 1 working day of their receipt of the information. If an acknowledgement is not received please email the Sponsor to ensure their receipt of the SAE or SAE follow-up information.

8.13.2 Adverse Events of Special Interest

Criteria for potential Hy's law cases are as follows:

- ALT or AST ≥ 3 × ULN AND
- Total bilirubin ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

Study site personnel must report every participant who meets these potential criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the participant signs the ICF for the study until the Final Visit.

For sites using a local laboratory, the investigator will need to assess if any of the above criteria have been met. A potential Hy's law case must be reported to the sponsor on the AE of Interest Abnormal Liver Function Reporting Form as soon as possible (within 24 hours of learning of the potential Hy's law case) via the SAE/Pregnancy fax number or email address listed above in Section 8.13.1, even if no AE has occurred. The CRF for potential Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. Frequency of liver function tests should be increased to daily monitoring, if appropriate (using local laboratory data and recorded as unscheduled visits) until the liver function tests return to the level at baseline or stabilize.

8.13.3 Non-SAE Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. Please note that while all AEs are reported on the AE page of the CRF, there is an additional form used for collection of SAE information, as described in Section 8.13.1, which is not the same as the AE CRF. When the same data are collected, the two forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection

of SAE information. The information on the AE CRF and the SAE form must be the same and will be reconciled at defined period throughout the study to ensure that they do.

8.13.4 Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including reporting of suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations. Death and life-threatening Suspected, Unexpected Serious Adverse Reactions (SUSARs) are subject to expedited reporting within a timeframe of 7 calendar days (life-threatening and fatal) or 15 calendar days (all other SUSARs).

8.14 Removal of Patients from the Trial or Study Drug

The investigator may withdraw a patient from the clinical trial for any of the following reasons:

- A protocol deviation occurs,
- A serious or intolerable adverse event occurs,
- A clinically significant change in a laboratory parameter occurs,
- The sponsor or investigator terminates the study, or
- The patient requests to be discontinued from the study.

A patient should be withdrawn from the trial treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient or the parent/guardian of the patient.

Early withdrawal of a patient from study is defined as withdrawal at any time prior to the day 54 study visit. If a patient is withdrawn from the study, the study monitor should be notified as soon as possible.

Patients who terminate therapy due to an adverse event will be followed clinically and with appropriate laboratory tests until the adverse event resolves. The frequency of follow-up will be determined by the investigator. Any laboratory tests showing significant changes from screening values should be repeated until the values return to normal or baseline. An explanation of why the patient was withdrawn from the study will be recorded.

If, in the opinion of the Investigators, Sponsor, or the IRB, the incidence and severity of AEs outweighs the benefit of continuing the study, the study may be terminated. In the event this course of action is to be pursued, the Investigators will make every attempt to communicate

with the Sponsor prior to the decision to develop a complete plan of action and to assess outcomes.

9 DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

The study is designed to determine the safety and descriptive efficacy of dalbavancin for the treatment of ABSSSI known or suspected to be caused by susceptible Gram-positive organisms, including MRSA. Since the study is primarily a safety study, the sample size was not calculated based on a power calculation for a hypothesis test.

The study will enroll approximately 188 patients from birth (inclusive) old (such that 188 patients will be included in the Safety Population). Patients 3 months and older will be randomized to receive dalbavancin or comparator, in a 3:3:1 randomization scheme: 76 patients will be randomized to dalbavancin (single-dose IV), 76 patients will be randomized to dalbavancin (2 doses once weekly IV therapy), and 26 patients will be randomized to comparator (IV vancomycin or IV oxacillin or flucloxacillin). The randomization scheme will not include the youngest age cohort (birth to < 3 months of age), as all 10 patients in this cohort will receive the single-dose regimen of dalbavancin, bringing the total number of patients enrolled in the study to approximately 188 patients. No patient in Cohort 5 (birth to < 3 months) will be randomized to the comparator arm.

The enrollment target for Cohort 5 includes at least 5 patients ≤ 28 days (including pre-term neonates).

There will be 5 age cohorts:

- Cohort 1 –12 years to 17 years old, inclusive,
- Cohort 2 – 6 years to <12 years old,
- Cohort 3 – 2 years to < 6 years old,
- Cohort 4 – 3 months to < 2 years old, and
- Cohort 5 – birth to < 3 months of age (including pre-term neonates with gestational age ≥ 32 weeks).

With the exception of Cohort 5, patients will be randomized 3:3:1 to each of the three treatment groups. In Cohorts 3 and 4 (enrolled patients aged 2 years to < 6 years old and

3 months to < 2 years old, respectively), there will be approximately 15 patients in each dalbavancin arm, and 5 patients in each comparator arm. In Cohorts 1 and 2 (enrolling patients 12 years to 17 years old, inclusive and 6 years to < 12 years old, respectively), there will be approximately 23 patients in each dalbavancin arm, and 8 patients in each comparator arm.

9.2 Definition of Analysis Populations

Intent-to-Treat (ITT): All randomized patients regardless of whether or not they received study drug.

Safety: All patients in the ITT population who received at least 1 dose of study drug.

Modified Intent-to-Treat (mITT): All randomized patients who received at least one dose of study drug and had a diagnosis of ABSSSI (or a suspected or confirmed sepsis for Cohort 5) not known to be caused exclusively by a Gram-negative organism.

Clinically Evaluable (CE): Four CE populations will be defined based on the timing of the outcome assessment, CE-48-72 hours (post randomization), CE-EOT, CE-TOC, and CE-Follow-up visit. Patients who meet all of the following criteria will be considered to be clinically evaluable at the respective visit:

- Fulfilled inclusion/exclusion criteria such that the clinical response is not confounded (if a patient is subsequently found to have violated an enrollment criteria, even if not noted at the baseline visit, the patient will not be included in the clinical evaluable population);
- For patients randomized to dalbavancin, received at least 1 dose of active study medication. For patients randomized to comparator, received at least 5 days of study drug therapy;
- For Cohorts 1-4: received no more than one dose of another systemic antibacterial therapy (with the exception of systemic aztreonam, oral or IV metronidazole or oral vancomycin) with documented activity against the causative organism from study drug initiation until the outcome assessment (visit) for a non-ABSSSI indication. [Note: Patients receiving a new non-study systemic antibacterial treatment (with the exception of aztreonam or metronidazole) for treatment of the ABSSSI from initiation of study drug through the outcome assessment (visit) will be assessed as Evaluable Failures];

Note: Cohort 5 are permitted to receive allowed concomitant antibacterials, as outlined in Section 5.4.3.

- Had an outcome assessment at which a clinical response could be evaluated for the time point specified;
- Received appropriate adjunctive antibacterial coverage if the patient had a culture-documented mixed ABSSSI (one or more Gram-positive pathogens with one or more Gram-negative aerobic or anaerobic organisms).

Microbiological ITT (microITT):

This population will consist of all patients in the ITT population who had at least 1 Gram-positive pathogen isolated at Baseline (see Appendix 2).

Microbiologically Evaluable (ME):

This population will consist of patients who meet all of the criteria for the CE population and microITT population.

9.3 General Statistical Considerations

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Safety results and adverse events will be tabulated by separate treatment regimens, including those who did and did not receive additional agents (aztreonam and/or metronidazole), in order to analyze safety in these respective groups.

Summary of efficacy variables will be done by age and treatment group for all patients. A comprehensive Statistical Analysis Plan (SAP) will be finalized prior to closure of the database.

9.4 Patient Characteristics

Enrollment, protocol deviations, discontinuations from the study drug and withdrawal from the study will be summarized by treatment group. Demographics (age, race, sex), medical and surgical history, description of the ABSSSI (or suspected or known sepsis for Cohort 5), baseline assessment of the local and systemic signs, microbiological assessment of the primary infection site and blood, and study drug administration will also be summarized.

9.5 Safety and Efficacy Analyses

For all safety analyses, patient data will be analyzed in the treatment group based on the actual study drug received (Safety Population). For all efficacy analyses, patient data will be analyzed based on the study arm to which they were randomized.

9.5.1 Analysis of Primary Outcome Measures (Safety)

The study is designed to determine the safety and descriptive efficacy of dalbavancin for the treatment of ABSSSI known or suspected to be caused by susceptible Gram-positive organisms, including MRSA.

The primary outcome measure is the safety of dalbavancin for the treatment of ABSSSI in children, including the following:

- Audiologic testing will be conducted in at least 20 children < 12 years old (in selected centers), of which at least 9 children will be < 2 years old. Audiologic testing will be performed at Baseline and repeated at Day 28 (± 2 days). Testing (as specified in the protocol) performed within 7 days prior to study drug administration can be used as the Baseline assessment.
- The impact of dalbavancin on **bowel flora**, to be evaluated in all patients from birth to < 2 years, by performing PCR for *Clostridium difficile* (C diff) and culture for vancomycin-resistant enterococci (VRE) on a stool specimen or rectal swab at Baseline and Day 28 (± 2 days). The testing of bowel flora in this age group will be done in all three study arms.

9.5.2 Analysis of Secondary Outcome Measures

The number and percentage of patients with a clinical outcome, as defined below, will be determined in each treatment group in the mITT, CE-EOT, CE-TOC and CE-Follow-up visit populations:

Clinical response at 48-72 hours post randomization is defined as ≥ 20% reduction in lesion size compared to baseline, measured in patients who did not receive rescue therapy and are alive (Cohorts 1-4). In Cohort 5 (birth to < 3 months), clinical response in patients with ABSSSI at 48-72 hours post-randomization is defined as cessation of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions. In patients diagnosed with sepsis in Cohort 5, clinical response at 48-72 hours post-randomization is defined as improvement of at least one abnormal clinical and laboratory parameter related to sepsis. Clinical response, in each of the 5 cohorts, will be assessed in patients who did not receive rescue therapy and are alive. As per this protocol, any anti-infective medication started after at least 48 hours of start of study treatment will be considered rescue medication (in Cohort 5, rescue therapy is defined as additional antibiotic therapy initiated after at least 48 hours of start of study treatment).

Clinical response at remaining time-points will be based primarily on the global clinical assessment of the patient made by the investigator at that evaluation time-point.

Clinical response at the EOT visit (14 ± 2 days) is defined as Cure, Improvement, Failure, or Unknown.

Clinical response at the TOC visit (28 ± 2 days) and at the follow-up visit (54 ± 7 days) isdefined as Cure, Failure or Unknown.

Patients with missing data or who are lost to follow-up are considered failures and by definition, are not included in the CE-EOT population.

Microbiological outcomes: Clinical **response** will also be determined **by baseline pathogen** at 48-72 hours post randomization, EOT, TOC, and last follow-up visit as described above in the microITT Population. Direct demonstration of eradication or persistence of the causative organism must be attempted, if feasible, in all patients where it is considered standard practice. However, this must be done in all patients who are considered treatment failures.

All-cause mortality: For Cohort 5 only (birth to < 3 months), all-cause mortality will be determined at test of cure visit (28 ± 2 days after start of therapy).

Pharmacokinetic outcome: Concentration of dalbavancin in plasma. The population PK profile of dalbavancin will be assessed using a sparse sampling approach and will be reported separately.

9.5.3 Analysis of Additional Efficacy Outcome Measure

Infection site assessment includes the following: purulence/drainage, erythema, heat/localized warmth, pain/tenderness to palpation, fluctuance and swelling/induration.

Resource utilization will be collected at Day 14 (± 2 days) and Day 28 (± 2 days), as well as other data available (e.g., length of hospitalization, or need for additional outpatient visits including Emergency Department visits, tests and procedures).

Patient and parent/guardian **satisfaction** with therapy will be assessed using the SSTI-Convenience questionnaire at Day 14 (± 2 days).

Additional analyses will be conducted for the following:

- The proportion of patients with clinical success or failure at EOT in the microITT and ME populations.
- The proportion of patients with a success or relapse/recurrence at the Follow-up visit in the CE-Follow-up visit population. Only patients who were a clinical success at the TOC visit will be included in this analysis.
- The proportion of patients with a clinical success by baseline pathogen in the microITT and ME populations at the EOT Visit
- Concordance analysis of clinical response at 48-72 hours post randomization and clinical status at EOT in the mITT population.

Descriptive summaries of the local signs including a summary of the percentage of patients with resolution (defined as the local sign is absent) of the local sign, ABSSSI lesion measurements (absolute and percent reduction from baseline), by study visit and treatment group will be presented.

For patients in Cohort 5 with sepsis, descriptive summaries of the local signs of sepsis along with laboratory parameters will be presented by study visit.

9.6 Safety Analyses

Safety will be assessed through summaries of AEs, physical examinations, vital signs and clinical laboratory results. All safety analyses will be based on the Safety population and will

be summarized by treatment group. Patients who receive the wrong regimen of study drug for their entire course of treatment will be analyzed in the group based on the regimen received.

Summary tables of treatment-emergent AEs (TEAEs) will be provided. A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to study drug discontinuation, withdrawal from the study or an SAE will be provided. AEs occurring prior to the first dose of study drug (AEs are recorded from the time of informed consent) will be provided in a listing.

Descriptive statistics summarizing laboratory data (hematology and chemistry) will be presented for all study visits. The change from baseline to each post-baseline visit will also be summarized by treatment group. Laboratory values will be classified as of potential clinical concern and the number and percentage of patients with a lab value of potential clinical concern will be summarized by visit and treatment group. Descriptive statistics of the vital signs will be presented by treatment group and study visit, as well as the change from baseline at each study visit. The percentage of abnormalities based on the physical exam will be presented by treatment group and study visit.

9.7 Pharmacokinetic Analysis

The PK data acquisition and analysis strategy in this study entails the use of a sparse PK sampling schedule. Pharmacokinetic sample handling and shipping procedures are described in the PK Sample Handling and Shipping Manual (or Lab Manual).

Plasma concentrations of dalbavancin will be listed by age cohort. Dalbavancin plasma concentration data, along with other information including demographic data, will be combined with appropriate data from other clinical studies and analyzed using a population PK approach and reported separately.

9.8 Interim Analysis

Not applicable

9.9 Handling of Missing Data

Missing values will not be imputed except as detailed in the SAP for missing dates and times. Additional sensitivity analyses for handling missing data will be detailed in the SAP. For the secondary outcome measure of clinical status at EOT, if any component of the outcome

measure, for example, assessment of the local signs, is missing, the patient will be considered a failure. By definition, patients with missing data are excluded from the CE population.

10 QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow the Sponsor monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by the Sponsor, or companies working with or on behalf of the Sponsor, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11 DATA HANDLING AND RECORD KEEPING

11.1 Case Report Forms / Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

The investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs and source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital’s or the physician’s patient chart. In these cases, data collected on the CRFs must match the data in those charts.

11.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or The Sponsor, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone call reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH) guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), The Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to The Sponsor, such as another investigator, another institution, or to The Sponsor. The investigator must obtain The Sponsor's written permission before disposing of any records, even if retention requirements have been met.

12 ETHICS

12.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to The Sponsor.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and The Sponsor in writing immediately after the implementation.

12.2 Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Patients, adopted by the General Assembly of the World Medical Association (2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on Good Clinical Practice (GCP), and applicable local regulatory requirements and laws.

12.3 Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, The Sponsor will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and The Sponsor before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each signed consent form. Depending on the age of the child and local IRB requirements, an assent form may also be required. The investigator will retain the original of each signed consent/assent forms.

12.4 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, The Sponsor should be informed immediately.

In addition, the investigator will inform The Sponsor immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate

hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13 DEFINITION OF END OF STUDY

13.1 End of Study in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and have completed the study as stated in the regulatory application (i.e., Clinical Trial Application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2 End of Study in all Participating Countries

End of Study in all participating countries is defined as the last patient's Final Visit.

14 SPONSOR STUDY TERMINATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of The Sponsor. In addition, The Sponsor retains the right to discontinue development of dalbavancin at any time.

If a study is prematurely terminated, The Sponsor will promptly notify the investigator and the investigator must also inform the IRB/IEC. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 90 days. Investigator must also inform the IRB/IEC. As directed by The Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible.

15 PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

15.1 Communication of Results by The Sponsor

The Sponsor fulfills its commitment to publicly disclose the results of studies through registration and posting of the results of this study on clinicaltrials.gov and EudraCT.

If posting of study results to clinicaltrials.gov jeopardizes a planned publication of the study results, a Pending Full Publication notice is substituted for the synopsis until the study results publication has been issued or 2 years have elapsed, whichever occurs first.

15.2 Publications by Investigators

The Sponsor has no objection to publication by the Investigator of any information collected or generated by the Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, the Investigator will provide The Sponsor an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to The Sponsor at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The Investigator will, on request, remove any previously undisclosed Confidential Information (other than the study results themselves) before disclosure.

If the study is part of a multi-center study, the Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 18 months of completion or termination of the study at all participating sites, the Investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the Institution will comply with recognized ethical standards concerning publications and authorship, including Section II – “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between The Sponsor and the Institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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17 APPENDICES

Appendix 1 Schedule of Activities

Protocol Activity	Baseline Pre-Dose (Day -1 to 1)[a]	Study Day[b]						Premature Discontinuation[d]
		1[b]	48-72 hours	8 ± 1	14 ± 2 (EOT Visit)[c]	28 ± 2 (TOC Visit)[c]	54 ± 7 (Follow-up Visit)[c]	
Informed Consent/Assent	X							
Access IWRS for PID	X							
Medical History and Demographics	X							
Complete Physical Examination	X							
Targeted Examination of Infection Site[e]	X[f]		X[f]	X	X	X	X	X
Vital Signs[g]	X	X	X	X	X	X	X	X
Eligibility Labs[h]	X[h]							
Pregnancy testing[i]	X[h]					X		X
Whole blood for pathogen diagnosis[j] (in children ≥ 2 years old **and** ≥ 12 kg)	X							
Estimate CrCL with Schwartz "bedside" equation (3 months to 17 years inclusive)	X							
Urine output (birth to < 3 months only)	X							
Infection site specimen collection[k]	X							
Audiology[l]	X					X		X
Bowel flora testing (C. diff PCR and VRE culture)[m]	X					X		X
Previous Drug and Non-drug Treatments	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Concomitant Non-drug Adjunctive Therapy	X	X	X	X	X	X	X	X
Randomization		X						
Treatment Administration[n]		[Through at least Day 10]						
Dalbavancin plasma PK sampling[o]		X	X	X	X			X[o]
Investigator Assessment of Clinical Response					X	X	X	X
SSTI-Convenience Questionnaire					X			X
Resource utilization					X	X		X
Record oral dosing (comparator)					X			
Adverse Events	X	X	X	X	X	X	X	X

Abbreviations: ABSSSI: acute bacterial skin and skin structure infections, C. diff: *Clostridium difficile*, CrCL: creatinine clearance, EDTA: Ethylenediaminetetraacetic acid, EOT: end of treatment visit, IV: intravenous, IWRS: interactive web randomization system, MRSA: methicillin resistant Staphylococcus aureus, PCR: polymerization chain reaction, PID: Patient Identification [number], PK: pharmacokinetic, SSTI: Skin and Soft Tissue, TOC: test of cure visit, VRE: vancomycin resistant enterococci

[a] The measurement of temperature to satisfy entry criteria may be a body temperature measured by the patient/caregiver or investigator within 24 hours of first dose.

[b] Study "Day" is calendar day beginning with Day 1, the calendar day the first infusion of study medication is started.

[c] The EOT Visit should be targeted for Day 14 ± 2 days, the TOC Visit should be targeted for Day 28 ± 2 days, and the Follow-up Visit should be targeted for Day 54 ± 7 days.

[d] Obtain specimen or measurement at time of premature discontinuation, if patient discontinues earlier than last scheduled assessment for that particular activity.

[e] Done by reviewing presence or absence of symptoms of ABSSSI. In Cohort 5 (birth to < 3 months), a complete physical examination will be performed at all noted timepoints.

[f] Ruler measurements are to be performed at Baseline (within 4 hours prior to first dose of study drug) and at 48-72 hours post randomization (in Cohorts 1 – 4 and ABSSSI patients in Cohort 5 [birth to < 3 months]).

[g] Vital signs include blood pressure, respiratory rate, heart rate, and temperature (oral, rectal or tympanic). Height and weight will be obtained at baseline only.

[h] Standard of care laboratory tests obtained within 72 hours prior to first dose can be used to determine eligibility. If not already collected per standard of care, at screening, clinical laboratory tests needed to determine eligibility and serum or urine pregnancy testing (for post-menarchal females) will be done locally in order to qualify the patient for the study. All efforts should be made to utilize standard of care clinical laboratory tests if available to minimize blood collection.

[i] Pregnancy test to be performed on post-menarchal female patients only. Serum or urine test is acceptable. Performed at Baseline and Day 28.

[j] At Baseline, a whole blood sample will be obtained to identify the bacteria that cause ABSSSI (EDTA whole blood, frozen) in children ≥2 years old **and** ≥ 12 kg.

[k] If an exudate/aspirate/pus sample can be obtained per Appendix 3, it should be cultured by the local laboratory, which should also conduct organism identification and antibiotic susceptibility testing. In all patients who are considered treatment failures, direct demonstration of eradication or persistence of the causative organism must be done.

[l] Audiologic testing will be conducted in at least 20 children < 12 years old (in selected centers), of which at least 9 children will be less than 2 years old. Audiologic testing to be conducted on infants (<12 months old) will include: evoked otoacoustic emissions testing, acoustic immittance measures (tympanometry and contra and ipsilateral acoustic reflex thresholds) and (optional) threshold auditory brainstem responses. For the older children, testing will include evoked otoacoustic emissions, acoustic immittance measures (tympanometry and contra ipsilateral acoustic reflex thresholds), and age appropriate behavioral audiologic threshold assessment. Testing will be performed at Baseline and repeated at Day 28 (± 2 days). Testing (as specified in the protocol) performed within 7 days prior to study drug administration can be used as the Baseline assessment. If the audiologic assessment at Day 28 shows an abnormality that exceeds by a clinically significant margin any abnormality observed in the pre-study assessment, follow-up assessments will be performed at 3 months and 6 months post-dose, as needed or until returned to baseline. If necessary, the patient will be referred to an otolaryngologist or other hearing specialist for further testing.

[m] PCR for C diff and culture for VRE on stool specimen or rectal swab will be done only in all patients aged birth to < 2 years.

[n] First dose should be administered within 4 hours after randomization. In the comparator arm, after at least 72 hours of IV oxacillin or flucloxacillin, patients may be switched to oral cefadroxil if criteria for oral therapy are met; if on IV vancomycin, they may be switched to oral clindamycin if MRSA is documented and if criteria for oral therapy are met, as noted in protocol.

[o] Plasma PK samples (0.25 mL of blood per sample) will be collected from all patients on dalbavancin (single-dose arm and two-dose arm), at 30 minutes and at 2 hours (Day 1), at 48-72 hours (Day 3-4), at 168 ± 24 hours (Day 8 ± 1) before the Day 8 dalbavancin dose, at 312 ± 48 hours (Day 14 ± 2), and at Premature Discontinuation (if occurring prior to Day 14).

Appendix 2 Microbiology

Culture and Susceptibility testing

All clinically significant Gram-positive pathogens will be tested locally for vancomycin susceptibility, as appropriate. The central laboratory will test all Gram-positive isolates for both vancomycin and dalbavancin susceptibilities. *Staphylococcus aureus* will also be tested for oxacillin susceptibility as a marker for methicillin resistance by both the central and local laboratories. All clinically significant non-anaerobic Gram-negative isolates (in randomized patients) will be tested for aztreonam susceptibility at the local laboratory, and for aztreonam susceptibility at the central laboratory [21].

The local laboratory should retain all isolates until the end of the study, if possible, or until confirmation of a viable organism is received from the central laboratory. Back-up cultures will be requested when the central laboratory does not receive a viable culture, or recovers an organism different from the one recorded by the local laboratory.

Gram-staining of material from the site of infection

One slide for Gram-stain is to be prepared from each specimen obtained from the infected site. The slide is to be stained and read by the local laboratory and then sent to the central laboratory for rereading and confirmation. A review of each slide should note the presence or absence of organisms and as well as squamous and polymorphonuclear cells.

A Gram-stain of material obtained from the site of a skin infection provides supportive information that may help interpret the results of a culture obtained from that site. Every effort should be made, prior to culture, to perform a Gram-stain of the material obtained from a needle aspiration, deep swab performed under sterile conditions, or from biopsy material. A supportive Gram-stain documents the presence of the organism of interest as well as local inflammation as defined by the presence of inflammatory cells such as polymorphonuclear leukocytes. Note that a positive culture for a targeted pathogen without a supporting Gram-stain could still be considered microbiologic evidence of infection and a Gram-stain identifying a target organism and inflammation may not necessarily provide evidence of infection without additional positive results obtained through culture.

Organisms considered as pathogens

The following organisms will always be considered a pathogen when isolated from an acceptable ABSSSI specimen:

- Monomicrobial infections caused by:
    - Staphylococcus aureus
    - Group A (Streptococcus pyogenes)
    - Group B (Streptococcus agalactiae)
    - Group C β–hemolytic streptococci
    - Streptococcus anginosus-milleri Group (e.g., Streptococcus anginosus, Streptococcus intermedius, Streptococcus constellatus)
    - Enterococcus faecalis
    - Enterococcus faecium
    - Gram-positive anaerobes
- Polymicrobial infection caused by:
    - any combination of *S. aureus*, Group A, B or C β-hemolytic streptococci, *Streptococcus anginosus-milleri* Group*, E. faecalis, E. faecium*, and Gram-positive anaerobes

Even if the organism was isolated from an acceptable ABSSSI specimen, the following are never a pathogen:

- S. saprophyticus
- Corynebacterium spp.
- S. epidermidis
- Bacillus spp.
- Diphtheroids
- Micrococcus spp.
- Lactobacillus spp.
- Candida spp., Aspergillus spp., or other fungi

All isolates not defined above will be assessed on a case-by-case basis via manual review by the Sponsor. If needed, patient clinical (e.g., type of infection, type of specimen, patient underlying conditions, etc.) and microbiological information (e.g., Gram-stain) will be used to assist in determining if the isolate is a pathogen. All organisms isolated from a blood culture and all Gram-negative organisms will be reviewed by the Sponsor to determine if the organism is a pathogen.

Based on the results of *in vitro* testing, animal studies, PK/PD modeling, surveillance programs and clinical trial data, the U.S. breakpoint for susceptibility of dalbavancin to Gram-positive organisms, including methicillin-sensitive and methicillin-resistant *S. aureus*, is ≤ 0.25 µg/mL. Disc diffusion interpretive criteria are not available for dalbavancin. A detailed description of the relevant microbiology data is available in the investigator brochure.

Appendix 3 Acceptable Methods for Infection Specimen Collection

Subtype of Infection	Source of Material	Method of Collection*
Cellulitis	• Aspirate • Punch biopsy	• After cleansing the skin at the leading edge of erythema, non-bacteriostatic sterile saline is injected and aspirated or a punch biopsy can be performed, as medically appropriate
Abscess	• Purulent fluid • Biopsy material	• Aseptic aspiration of purulent material/fluid (aspiration alone does not define the lesion as an abscess). • Biopsy material obtained from I&D under sterile conditions; only appropriate for the initial I&D or for worsening of the infection requiring discontinuation of study drug
Traumatic wound	• Scrapings from wound base • Biopsy material from wound base	• After cleansing (with non-bacteriostatic saline) and debriding the wound bed, and using sterile techniques, scrape ulcer/wound base with sterile dermal curette or scalpel to obtain tissue • After following above procedure, biopsy tissue at the base of the lesion • Any procedure performed after baseline should only be performed for worsening of the infection requiring discontinuation of study drug
Surgical site infection	• Scrapings from base of wound • Biopsy material from base of surgical site	• After cleansing (with non-bacteriostatic saline) and debriding the surgical site, and using sterile techniques, scrape the base of the lesion with sterile dermal curette or scalpel to obtain tissue • After following above procedure, biopsy tissue at the base of the lesion • Any procedure performed after baseline should only be performed for worsening of the infection requiring discontinuation of study drug

* Prior to collection of ABSSSI site specimen(s), the ABSSSI site is to be prepared by a standard of care surgical site skin preparation method with the appropriate application of an antiseptic agent such as: an iodophor (e.g. 5% povidone-iodine); an alcohol-containing product (e.g. 70% ethyl alcohol, 70% isopropyl alcohol); chlorhexidine gluconate; a combination product (e.g. 5% povidone iodine solution in 70% ethanol; or, >0.5% chlorhexidine with alcohol)

Appendix 4 Method for determination of creatinine clearance

Creatinine clearance will be calculated for ages 3 months to 17 yrs (inclusive) using the Schwartz "bedside" equation:

$$\text{CrCl (mL/min/1.73 m}^2\text{)} = \frac{0.413 \times \text{Height (length) (cm)}}{\text{Serum creatinine (mg/dL)}}$$

Appendix 5 Infection Site Assessment

Please refer to the Infection Site Assessment and Measurement Manual for full instructions.

Infection site assessments include the following as described in the Infection Site Assessment and Measurement Manual:

1. Physical examination of the infection site
2. Measurement of infection site erythema

Infection site assessments are to be performed at Baseline (within four hours prior to the first dose of study drug), 48-72 hours post randomization, Day 8 (± 1 day), Day 14 (± 2 days), Day 28 (± 2 days), and Day 54 (± 7 days). Ruler measurements are to be performed at Baseline (within four hours prior to first dose of study drug) and at 48-72 hours post randomization in Cohorts 1 – 4 and ABSSSI patients in Cohort 5.

Appendix 6 SSTI-Convenience Questionnaire

CONVENIENCE QUESTIONNAIRE – GENERAL

Patient Identification No.:		Visit Description:
|___|___| |___|___|___| |___|___|___|		Day 14 (± 2 days)

Date Questionnaire Administered: |__|__| |__|__|__| |__|__|__|__|

dd mmm yyyy

FEELINGS RELATED TO THE OVERALL ANTIBIOTIC TREATMENT				
1. How often were you (or your child) concerned about receiving the antibiotic treatment?				
None of the time 1 □	A little of the time 2 □	Some of the time 3 □	Most of the time 4 □	All of the time 5 □

OUTPATIENT TREATMENT CONVENIENCE

Are you (or your child) currently hospitalized?

1 □ Yes ' *Please go directly to question* 4

0 □ No ' *Please answer all remaining questions*.

2. Did receiving the antibiotic treatment interfere with your (or your child's) usual daily activities?

Significantly	Moderately	Slightly	Not at all
1 □	2 □	3 □	4 □

3. Were you (or your child) easily able to modify your schedule to take the antibiotic treatment?

Yes	No
1 □	2 □

TREATMENT REGIMEN SATISFACTION AND PREFERENCE

4. Overall, how satisfied were you (or your child) with the antibiotic treatment?

Extremely satisfied 1 □	Very satisfied 2 □	Moderately satisfied 3 □	Slightly satisfied 4 □	Not at all satisfied 5 □

5. In terms of your experience with your (or your child's) antibiotic treatment, would you recommend for yourself (or your child) or others the same antibiotic treatment again?

Definitely Yes 1 □	Probably 2 □	Maybe 3 □	Probably No 4 □	Definitely Not 5 □

6. If you had the choice between the following antibiotic treatments for yourself (or your child), which one would you prefer?

One 30-minute infusion once 1 □	One 3-hour infusion once 2 □	One 30-minute infusion once a week for two weeks 3 □	Two 1-hour infusions per day for a whole week 4 □	A few days of two 60-minute infusions per day and then 1 pill 3-4 times per day the rest of the week 5 □

FEELINGS RELATED TO THE OVERALL ANTIBIOTIC TREATMENT

7. Overall, how satisfied were you with the care you (or your child) received?

Very satisfied 1 □	Neutral 2 □	Very or quite dissatisfied 3 □

8. Were you satisfied with the effect of the IV antibiotic on your (or your child's) infection?

Very satisfied 1 □	Neutral 2 □	Very or quite dissatisfied 3 □

9. Overall how satisfied are you (or your child) with the location of care received (hospital, outpatient or both)?

Very satisfied 1 □	Neutral 2 □	Very or quite dissatisfied 3 □

10. Where do you think it is preferable to receive the kind of care provided (for yourself or your child)?		
In the hospital 1 □	In the community (as an outpatient) 2 □	No preference 3 □

Appendix 7 Investigator's Signature

Study Title:	A Phase 3, Multicenter, Open-Label, Randomized, Comparator Controlled Trial of the Safety and Efficacy of Dalbavancin versus Active Comparator in Pediatric Subjects with Acute Bacterial Skin and Skin Structure Infections
Study Number:	DUR001-306
Original Protocol Date:	23 December 2014
Amendment 1 Date:	26 February 2015
Amendment 2 Date:	02 March 2016
Amendment 3 Date:	13 June 2016
Amendment 4 Date:	09 March 2017
Amendment 5 Date:	27 June 2017
Amendment 6 Date:	26 April 2018
Amendment 7 Date:	29 March 2022
Amendment 8 Date:	18 November 2022

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol. I understand the study protocol and will conduct the study according to the procedures therein and according to the principles of good clinical practice.

Name: _____

Signature: _____ **Date:** _____

Appendix 8 Protocol Amendment Summary

Title: A Phase 3, Multicenter, Open-Label, Randomized, Comparator Controlled Trial of the Safety and Efficacy of Dalbavancin versus Active Comparator in Pediatric Subjects with Acute Bacterial Skin and Skin Structure Infections

Protocol Amendment: DUR001-306 Amendment #8

Date of Amendment: 18 November 2022

Amendment Summary

A summary of changes to the protocol recorded in Amendment 8 are outlined in the table below.

Briefly, the main change is that safety laboratory testing after eligibility and the peripheral blood culture are no longer required by protocol. Data from clinical laboratory tests and peripheral blood cultures performed as standard of care during the study will be collected. Any minor formatting changes and correction of typographical errors are not summarized in the table below. Please note that in May 2020, Allergan plc. was acquired by AbbVie (Allergan Sales, LLC and Allergan Ltd is a wholly owned subsidiary of AbbVie Inc.). In April 2022, AbbVie became the Sponsor of study.

Section	Revision	Rationale
• Title Page	• Text was edited as follows (altered text in bold): Sponsor: ~~Allergan Sales, LLC (a subsidiary of AbbVie)~~ ~~5 Giralda Farms~~ ~~Madison, NJ 07940~~ ~~USA~~ ~~(formerly~~ ~~Allergan Sales, LLC~~ ~~185 Hudson Street~~ ~~Harborside 5, Suite 1900~~ ~~Jersey City, NJ 07311~~ ~~USA)~~ ~~Allergan Ltd., (a subsidiary of AbbVie)~~ ~~1st Floor, Marlow International, The Parkway, Marlow Buckinghamshire, SL7 1YL United Kingdom~~ **AbbVie Inc.** **1 North Waukegan RoadNorth Chicago, IL 60064** **USA** **AbbVie Deutschland GmbH & Co. KG** **Knollstrasse 50** **Ludwigshafen** **67061 Germany**	Updated Sponsor information.
• Throughout the document	Changed Allergan to **AbbVie Inc. and AbbVie Deutschland GmbH & Co. KG**	Updated Sponsor information.

Section	Revision	Rationale
• Synopsis and Section 4.2 - Exclusion criteria	• Text was edited as follows (altered text in bold): Clinically significant hepatic impairment, defined as serum bilirubin or alkaline phosphatase > 2X ULN for age, and/or serum AST or ALT > 3X ULN for age **(neonates with elevated total bilirubin can participate if conjugated or direct bilirubin were normal per age)**.	Clarified to include neonate participation per the criteria.
• Synopsis-Primary Analysis	• Text was edited as follows (altered text in bold): Clinical laboratory tests **needed to determine eligibility** will be ~~**obtained**~~ **collected during screening, if not already collected as standard of care. Data from clinical laboratory tests performed as standard of care during the study will be collected**. ~~**at Baseline and at Day 14 (± 2 days), or at premature discontinuation.**~~	Aligned clinical laboratory tests with standard of care.

Section	Revision	Rationale
• Section 6.1 (Baseline [Day -1 to 1] - Within 24 Hours Prior to First Dose)	• Text was edited as follows (altered text in bold): Blood for laboratory testing: ~~**hematology, serum chemistry, and hs-CRP (high sensitivity C-reactive protein) levels will be collected for the central laboratory or the site's local laboratory (whichever laboratory the site plans to use for hematology, serum chemistry, and hs-CRP testing for the remainder of the study).**~~ **Standard of care laboratory tests obtained within 72 hours prior to first dose can be used to determine eligibility.** ~~**lFor eligibility, i**~~ If not already collected per standard of care, ~~at Baseline~~ **during screening, clinical laboratory tests needed to determine eligibility** ~~**hematology, serum chemistry**~~, and serum or urine pregnancy testing (for post-menarchal females) will be done locally in order to qualify the patient for the study. **All efforts should be made to utilize standard of care clinical laboratory tests if available to minimize blood collection. Data from clinical laboratory tests performed as standard of care during the study will be collected**. ~~**Peripheral blood culture (1 aerobic bottle) done locally prior to study drug treatment: not through an existing intravascular line**~~	Aligned clinical laboratory tests and peripheral blood culture with standard of care. Clarified timing of standard of care laboratory tests used to determine eligibility.
• Section 6.2 Treatment Period	• Text was edited as follows (altered text in bold) ~~**Peripheral blood cultures, if positive in the previous 48 to 72 hours**~~ ~~**For Cohort 5 (birth to < 3 months) only: Blood for laboratory testing of hematology, serum chemistry, and hs-CRP**~~ ~~**Blood for laboratory testing, including: hematology and serum chemistry; For Cohort 5 only, laboratory testing will also include hs-CRP**~~	Aligned clinical laboratory tests and peripheral blood culture with standard of care.

Section	Revision	Rationale
• Section 6.2.7 Premature Discontinuation Visit	• Text was edited as follows (altered text in bold): ~~**Blood for laboratory testing, including hematology, and serum chemistry**~~ • Obtain plasma PK measurement on patients on dalbavancin arm (single dose and two-dose) **only if premature discontinuation visit occurs prior to Day 14**.	Aligned clinical laboratory tests with standard of care. Clarified timing of PK sample collection.

• Section 7.1.3 (Clinical Laboratory Assays)	• Text was edited as follows (altered text in bold): Patients will be in a seated or supine position during **protocol required** blood collection. ~~**The following laboratory parameters will be measured:**~~ ~~**Hematology: Complete blood count (CBC): hemoglobin, hematocrit, platelets, white blood cell (WBC) and differential counts: at Baseline, Day 14 (± 2 days), and at time of premature discontinuation. Additionally, for Cohort 5 only (birth to < 3 months), at 48 – 72 hours.**~~ ~~**Serum Chemistry: total bilirubin, direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), GGT, BUN, creatinine, glucose (random), total protein, albumin, LDH, amylase, sodium, potassium, bicarbonate, chloride: at Baseline and Day 14 (± 2 days). Additionally, for Cohort 5 only (birth to < 3 months), at 48 – 72 hours.**~~ ~~**Hs-CRP: at Baseline only. Additionally, for Cohort 5 only (birth to < 3 months) at 48-72 hours and at Day 14 ± 2 days.**~~ **Standard of care laboratory** tests **obtained within 72 hours prior to first dose can be used to determine eligibility. Clinical laboratory tests needed to determine eligibility will be collected during screening, if not already collected as standard of care. All efforts should be made to utilize standard of care clinical laboratory tests if available to minimize blood collection.** **Data from clinical laboratory tests performed as standard of care during the study will be collected.** **Data from any** peripheral blood cultures **performed as standard of care during the study will be collected.** ~~**(1 aerobic bottle): At Baseline (prior to study drug treatment) not through an existing intravascular line. Blood cultures should be repeated upon knowledge of a positive result at Baseline until sterilization**	Aligned clinical laboratory tests and peripheral blood culture with standard of care. Clarified timing of standard of care laboratory tests used to determine eligibility. Clarified timing and volume of PK sample collection.

Section	Revision	Rationale
	~~**is confirmed. If clinically indicated, a blood culture should be collected at time of treatment discontinuation or for determination of treatment failure.**~~ ~~**Pre-dose laboratory assessments will not be performed if the screening period occurs within 24 hours prior to dosing unless clinically indicated. If multiple laboratory tests are obtained within 24 hours of study drug administration, record test results closest to administration study drug.**~~ Plasma samples **(0.25 mL of blood per sample)** for pharmacokinetic (PK) measurements will be collected from all patients in both dalbavancin arms (single dose and two-dose regimen), at 30 minutes (end of infusion), at 2 hours after start of the infusion (Day 1), at 48-72 hours (Day 3-4), at 168 ± 24 hours (Day 8), at 312 ± 48 hours (Day 14 ± 2), and at premature discontinuation **(if occurring prior to Day 14).** ~~**Collection of PK samples on Day 14 should be timed with collection of samples for serum chemistry and hematology.**~~ Heel sticks may be used for blood collection in Cohort 5. ~~Blood collection tubes for PK sampling will be provided by the central laboratory.~~ **Details regarding PK blood collection tubes,** PK sample collection, labeling, processing, storage, and shipment instructions will be provided in the laboratory manual.	
• Section 7.1.4 (Clinically Significant Laboratory Tests)	• Text was edited as follows (altered text in bold): All clinically significant abnormal laboratory test results occurring post-baseline **are recommended to** ~~**will**~~ be repeated at appropriate intervals **per standard of care** until they return either to baseline or to a level deemed acceptable by the investigator ~~**and the Sponsor Medical Safety Physician**~~.	Aligned clinical laboratory tests with standard of care.

Section	Revision	Rationale
• Section 7.2 (Microbiology)	• Text was edited as follows (altered text in bold): **Data for any peripheral blood cultures ~~If not already collected~~ obtained** per standard of care, **~~at Baseline~~ during screening and during the study, will be collected.~~~~, before administration of study drug, a peripheral blood culture (1 aerobic bottle) for identification and susceptibility testing will be drawn.~~ It is recommended that ~~B~~**blood cultures should not be obtained through an existing intravascular line. If the baseline blood culture reveal**s** a Gram-positive pathogen, **data for any repeat** blood cultures obtained **~~should be repeated~~ as per standard of care will be collected**.~~upon knowledge of the positive result, until sterilization is confirmed.~~	Aligned peripheral blood culture with standard of care.
• Section 7.3 (Efficacy)	• Text was edited as follows (altered text in bold): Laboratory measurements as markers of systemic infection, **if available** will be collected **on the CRF**, including: hs-CRP, WBC count and manual differential.	Clarified to include data from laboratory tests are collected in the CRF if available.

Section	Revision	Rationale
• Section 8.13.2 (Adverse Events of Special Interest)	• Text was edited as follows (altered text in bold): Criteria for potential Hy's law cases are as follows: • ALT or AST ≥ 3 × ULN AND • Total bilirubin ≥ 2 × ULN AND • Alkaline phosphatase < 2 × ULN Study site personnel must report every participant who meets these potential criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the participant signs the ICF for the study until the Final Visit. ~~**A central laboratory alert for potential Hy's law cases will be in place, and the central laboratory must notify investigators and the sponsor immediately when the above criteria have been met**~~. For sites using a local laboratory, the investigator will need to assess if any of the above criteria have been met. A potential Hy's law case must be reported to the sponsor on the AE of Interest Abnormal Liver Function Reporting Form as soon as possible (within 24 hours of learning of the potential Hy's law case) via the SAE/Pregnancy fax number or email address listed above in Section 8.13.1, even if no AE has occurred.	Aligned clinical laboratory tests with standard of care.
• Section 17 (Appendix 1)	Updated schedule of activities and aligned footnotes accordingly.	Clarified for readability.