related, most commonly injection site thrombosis and pyrexia, which were reported as drug-related events in <2% of patients in both drug exposure groups. In this SOC drug-related events of severe intensity were reported in 2/265 (<1%) patients in the daptomycin group and included pyrexia and weakness. The only drug-related event in the SOC Infections and Infestations reported in >1% of patients was fungal vaginosis, which was reported as drug-related in 5/265 (1.9%) of patients in both the daptomycin and comparator groups. The only severe drug-related event in this SOC was a fungal skin infection reported in one patient (<1%) in the daptomycin group. Drug-related events in the SOC Skin and Subcutaneous Tissue Disorders were reported more frequently in the comparator group (19/265; 7.2%) than in the daptomycin group (4/265; 1.5%). Drug-related pruritus and dermatitis were reported in 2 to 3% of patients in the comparator group and in 1% of patients in the daptomycin group. Only one patient in each treatment group (<1% each) experienced a drug-related event within the Respiratory System Disorders SOC. Drug-related dyspnea of moderate intensity was reported in one patient in the daptomycin group and drug-related dyspnea of moderate intensity and epistaxis of severe intensity were reported in one patient in the comparator group. Musculoskeletal, connective tissue and bone disorders assessed as drug-related were noted in 3/265 (1.1%) patients in the daptomycin group. Two of these drug-related events, arthralgia aggravated in one patient and myalgia in another were assessed by the investigator as severe in intensity. Drug-related events within the Metabolism and Nutrition Disorders SOC were reported in approximately 1% of patients in both drug exposure groups. Less than 1% of patients in the daptomycin group and 1.9% of patients in the comparator group experienced drug-related vascular disorders. One patient in the comparator group experienced hypotension of severe intensity that was assessed as possibly drug related.

Table 37: Treatment-Emergent Drug-Related AEs Occurring in ≥1% of Patients by System Organ Class and Preferred Term in Study DAP-SST-9801 (Population: Safety)

System Organ Class Preferred Term	Daptomycin N = 265	Comparator N = 265
Total Number of Patients with Drug-Related AEs	64 (24.2%)	90 (34.0%)
Gastrointestinal Disorders	21 (7.9%)	30 (11.3%)
Nausea	9 (3.4%)	15 (5.7%)
Diarrhea NOS	7 (2.6%)	10 (3.8%)
Vomiting NOS	7 (2.6%)	6 (2.3%)
Constipation	5 (1.9%)	7 (2.6%)
Diarrhea Aggravated	3 (1.1%)	2 (<1%)
Loose Stools	1 (<1%)	3 (1.1%)
Investigations	21 (7.9%)	18 (6.8%)
Blood Creatine Phosphokinase Increased	6 (2.3%)	5 (1.9%)
Blood Creatinine Increased	4 (1.5%)	5 (1.9%)
Liver Function Tests NOS Abnormal	4 (1.5%)	3 (1.1%)
Blood Alkaline Phosphatase Increased	4 (1.5%)	2 (<1%)
Aspartate Aminotransferase Increased	3 (1.1%)	2 (<1%)
Alanine Aminotransferase Increased	3 (1.1%)	2 (<1%)
General Disorders/Administration Site Conditions	13 (4.9%)	18 (6.8%)
Injection Site Thrombosis	3 (1.1%)	4 (1.5%)
Pyrexia	2 (<1%)	5 (1.9%)
Injection Site Phlebitis	3 (1.1%)	2 (<1%)
Injection Site Burning	1 (<1%)	3 (1.1%)
Weakness	3 (1.1%)	1 (<1%)
Skin & Subcutaneous Tissue Disorders	4 (1.5%)	19 (7.2%)
Pruritus NOS	3 (1.1%)	7 (2.6%)
Dermatitis NOS	3 (1.1%)	6 (2.3%)
Infections and Infestations	5 (1.9%)	12 (4.5%)
Vaginosis Fungal NOS	5 (1.9%)	5 (1.9%)
Nervous System Disorders	9 (3.4%)	7 (2.6%)
Dizziness (Excl Vertigo)	3 (1.1%)	4 (1.5%)
Headache NOS	3 (1.1%)	3 (1.1%)
Vascular Disorders	2 (<1%)	5 (1.9%)
Flushing	1 (<1%)	3 (1.1%)
Metabolism and Nutrition Disorders	3 (1.1%)	3 (1.1%)
Blood and Lymphatic System Disorders	3 (1.1%)	2 (<1%)
Musculoskeletal, Connective Tissue and Bone Disorders	3 (1.1%)	0

Adverse events leading to discontinuation of treatment - Study DAP-SST-9801

A total of 21 patients were discontinued from study treatment due to AEs, including 9/265 (3.4%) patients in the daptomycin group and 12/265 (4.5%) patients in the comparator group. The events leading to discontinuation were reported as possibly or probably related to study treatment for 4/265 (1.5%) patients in the daptomycin group and 9/265 (3.4%) patients in the comparator group. In the daptomycin group, the SAEs that resulted in discontinuation of study treatment and were assessed as drug-related included hypersensitivity reaction, anemia and thrombocytopenia, worsening of abdominal and joint pain in

a patient with sickle cell disease, and elevated serum CPK. In the comparator group, SAEs that resulted in discontinuation of study treatment and were assessed as drug-related included nausea, vomiting and rigors; elevated vancomycin levels and pruritic rash; drug fever; hypersensitivity reaction with elevations in ALT and AST; rash; nausea and vomiting; drug rash; peripheral swelling; and urticaria.

Medical Officer Comment

The Medical Officer reviewed the CRFs and patient narratives of all patients in study DAP-SST-9801 who discontinued study drug treatment due to AEs. As described below under "Serious adverse events", the Medical Officer believes that one of the patients (0070100041) with two AEs assessed by the investigator as possibly related are actually not related to study drug treatment (abdominal pain and arthralgias in a patient with sickle cell crisis). The AEs resulting in discontinuation of study drug treatment are consistent with the known AE profile of the drugs. The Medical Officer agrees with the other assessments of causality in both the comparator and daptomycin groups with the following two exceptions:

- Patient 0118100050 was a 78 year old male treated with vancomycin for 3 days for a wound infection of the left great toe. Study medication was discontinued due to severe nausea and vomiting. Deep swab of the wound grew multiple Gram-positive and Gram-negative organisms, including methicillin-sensitive *S. aureus* (MSSA). The investigator assessed the nausea and vomiting as not related to study drug; the Medical Officer considers it to be possibly related.
- Patient 0163100041 was a 43 year old female who received one dose of vancomycin for a wound infection of the right ankle which grew (methicillin-resistant *S. aureus* (MRSA). She developed urticaria after the first dose of vancomycin, and the study was discontinued. The investigator considered the urticaria to be possibly related to study drug. However, the patient received a course of vancomycin therapy after the study was discontinued without further urticaria; therefore, the Medical Officer considers this AE to be not related to study drug.

The following patient who was discontinued from the study due to AEs in the daptomycin arm of study DAP-SST-9801 is presented to demonstrate a severe allergic reaction to daptomycin.

- Patient 0053100064 was a 40 year old female with a post-operative MSSA infection of the left hip who received 5 doses of daptomycin. After the fourth dose she developed an allergic reaction consisting of fever, chills, and shortness of breath. She received the fifth dose of daptomycin the following day; at the end of the infusion, she developed tachycardia, fever to 106°F, and hypoxia, and the study drug was discontinued. The investigator considered this AE to be probably related to study drug treatment, and the Medical Officer agrees.

Serious adverse events - Study DAP-SST-9801

Table 38 below presents treatment-emergent SAEs by MedDRA SOC. A total of 64 patients, 32/265 (12.1%) in each drug exposure group, experienced 1 or more SAEs. There was no difference between the drug exposure groups for the overall incidence of any SAE. The only SAEs with reported incidence of ≥1% of patients were cellulitis and urosepsis, occurring in 4/265 (1.5%) patients and 3/265 (1.1%) patients, respectively, in the daptomycin group. All other serious events were reported in <1% of patients in both drug exposure groups. Four patients, including 2/265 (<1%) patients in each arm, experienced serious drug-related events. These included a hypersensitivity reaction and diarrhea (aggravated) in the daptomycin group; and hypersensitivity reaction and pruritic rash in the comparator group. For about one-third of the patients who experienced SAEs, at least one SAE started while on treatment. For approximately one-half of the patients in each drug exposure group who experienced SAEs, all SAE(s) started more than five days after the end of treatment.

Table 38: Treatment-Emergent SAEs by System Organ Class in Study DAP-SST-9801: Safety Population

System Organ Class Preferred Term	Daptomycin N = 265	Comparator N = 265
Total Number of Patients with SAEs	32 (12.1%)	32 (12.1%)
Infections and Infestations	18 (6.8%)	13 (4.9%)
Cellulitis	4 (1.5%)	0
Urosepsis	3 (1.1%)	0
Vascular Disorders	5 (1.9%)	3 (1.1%)
Cardiac Disorders	2 (<1%)	4 (1.5%)
Gastrointestinal Disorders	2 (<1%)	2 (<1%)
Skin & Subcutaneous Tissue Disorders	2 (<1%)	2 (< 1%)
Immune System Disorders	1 (<1%)	2 (<1%)
Metabolism and Nutrition Disorders	1 (<1%)	2 (<1%)
Nervous System Disorders	1 (<1%)	2 (<1%)
Neoplasms Benign and Malignant (including Cysts and Polyps)	2 (<1%)	1 (<1%)
Surgical and Medical Procedures	2 (<1%)	1 (<1%)
General Disorders/Administration Site Conditions	1 (<1%)	1 (<1%)
Renal and Urinary Disorders	1 (<1%)	1 (<1%)
Respiratory, Thoracic and Mediastinal Disorders	1 (<1%)	1 (<1%)
Blood and Lymphatic System Disorders	0	1 (<1%)
Congenital and Familial/Genetic Disorders	1 (<1%)	0

Medical Officer Comment

The Medical Officer reviewed the CRFs and patient narratives of all patients with SAEs. Most of the serious events in the daptomycin arm appeared to be related to the patient's underlying illness or the presenting illness. The investigator considered that three SAEs were possibly related and two AEs were probably related to study drug in the daptomycin arm. Forty-two SAEs were reported by the investigator in 32 patients. The Medical Officer agrees with these assessments with the exception of two SAE's in one patient (0070100041) with a sickle cell crisis; the investigator deemed abdominal pain and arthralgias to be possibly

related to daptomycin, and the Medical Officer considers them to be unrelated. One additional patient had an SAE that the Medical Officer considers to be possibly related to daptomycin, while the investigator assessed the SAE as unrelated; a brief summary of this case follows.

- Patient 0002100045 was a 66 year old male treated with daptomycin for four days for an abdominal wall wound infection caused by *Streptococcus constellatus* and *Streptococcus intermedius*. Serum creatinine rose from a baseline of 2.4 mg/dL to 7.1 mg/dL on d1P. Since no other etiology is evident for the patient's worsening renal insufficiency, the Medical Officer considers this SAE to be possibly related to study drug treatment.

Deaths - Study DAP-SST-9801

A total of 8/265 (3.0%) patients died during study DAP-SST-9801, including 2/265 (<1%) patients in the daptomycin group and 6/265 (2.3%) patients in the comparator group. None of the deaths were judged to be related to study treatment. Table 39 presents a list of the 8 patients who died. Six of eight (75%) patients were male and 6/8 (75%) patients were >70 years old at study entry. The primary site of infection was a wound infection in 6/8 (75%) patients; infected ulcer (not diabetic) and diabetic ulcer infection occurred in one patient each. All 8 of these patients who died had complicating medical conditions, including 4/8 (50%) with DM. One daptomycin-treated patient died of deep venous thrombosis (DVT) and pulmonary embolism, and one died of progressive lung cancer. One comparator-treated patient died of progression of underlying cancer; two died of underlying cardio- or cerebrovascular conditions; and one died of worsening of pre-existing anemia. Two comparator-treated patients died of sepsis more than 3 weeks post-treatment. The duration of study treatment in these 8 patients ranged from 4 to 10 days. Five patients died 3 to 62 days after successfully completing therapy. One patient was on d4 of study treatment at the time of death; one patient had discontinued treatment on d4 due to an AE not associated with the death and died 15 days later; and one patient had discontinued treatment due to clinical failure, was switched to non-study medication, and died 22 days later.

Medical Officer Comment

The Medical Officer reviewed the CRFs and patient narratives of all patient deaths in this study. The sponsor concluded that the causes of death in these eight patients who died during study DAP-SST-9801appeared to be directly related to pre-existing underlying conditions, and the Medical Officer agrees. No death in either group appeared to be directly related to daptomycin or comparator. Of note, however, is the fact that in some instances, documentation of the ultimate cause of death was not included with the submission. Two of these deaths fall in to this category: Patient 0204100080 in the comparator group died of severe anemia (admission hemoglobin = 4 g/dL) predating study drug administration, but no cause for the anemia is given. Patient 0104100041 died of progressive lung cancer on d30P, but no information is given regarding the terminal event.

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