PROTOCOL TITLE: Linezolid vs Vancomycin/Cefazolin in the Treatment of Hemodialysis Patients With Catheter-Related Gram-Positive Bloodstream Infections

Study Objectives:
Primary Objective:
 Microbiological efficacy of linezolid compared to vancomycin/cefazolin in the treatment of hemodialysis subjects with Gram-positive catheter-related bloodstream infections.

Secondary Objectives:
 Clinical efficacy of linezolid compared to vancomycin/cefazolin.
 Incidence of metastatic sequelae associated with Gram-positive infections in subjects treated with linezolid or vancomycin/cefazolin.
 Pathogen eradication.
 Eradication of Staphylococcus (S) aureus nasal colonization.
 Safety and tolerance.

METHODS
Study Design: This was an open-label, multicenter, randomized (1:1), comparator-controlled study of linezolid versus (vs) vancomycin/cefazolin in the treatment of subjects with known or suspected catheter-related Gram-positive bloodstream infections. Subjects with end-stage renal disease who were 18 years of age or older and weighing 40 kg or more with known or suspected Gram-positive bloodstream infections resulting from tunneled or non-tunneled catheters were eligible for enrollment. Subjects who received dialysis through a fistula or venous graft were eligible to enroll as long as they had a central vascular catheter that was suspected or known to be the cause of the bloodstream infection. Subjects with acute renal failure undergoing hemodialysis and subjects undergoing peritoneal dialysis were not eligible to enroll in the study.

Prior to receiving the first dose of study medication, Investigators had to obtain one set of blood cultures through the hemodialysis catheter and all other indwelling intravascular catheters. Another set of blood cultures had to be obtained through a peripheral percutaneous site (venous or arterial access). If a catheter had more than 1 port, blood was to be collected from all ports. After obtaining blood for cultures, all intravascular catheters were to be removed. Catheter tips were to be sent to the local laboratory for semiquantitative (Maki method) or quantitative (Brun-Buisson method) cultures. Any exudates present at the catheter access site were to have a qualitative culture by an exit site swab or pus collection. If there was evidence of an abscess, the site was to be aspirated and the aspirate sent for culture to the local laboratory.

A Gram-positive bacterial pathogen had to be cultured from the required baseline blood cultures for the subject to remain eligible to participate in the study. If the Gram-positive

isolate was S aureus, it was to be cultured from at least 1 culture bottle from either the peripheral set or the catheter set of culture bottles. For all other Gram-positive pathogens (eg, coagulase-negative staphylococci), isolates were to be cultured from at least 2 culture bottles of which one had to be from the peripheral set.

Subjects eligible to remain in the study due to the isolation of a Gram-positive bacterial blood pathogen were required to have peripheral percutaneous blood cultures (venous or arterial access) repeated 24 to 48 hours after the initiation of treatment. If the repeat blood culture was positive (identical Gram-positive pathogen as compared to baseline), the peripheral percutaneous blood culture was to be redrawn within 24 to 48 hours of the culture results being received. If the blood culture remained positive and it was drawn after 96 hours of treatment, the subject was to be considered a treatment failure and withdrawn from the study. Subjects with poor vascular access were permitted to have the repeat blood draws obtained through a newly inserted intravascular catheter or matured fistula. In the absence of repeat peripheral blood culture results, subjects who remained febrile for 96 hours or greater were to be considered treatment failures and withdrawn from the study.

An end-of-treatment (EOT) visit was to occur within 72 hours after the last dose of study medication. A short-term follow-up (STFU) visit for test of cure (TOC) was occurred 2-3 weeks after the last dose of study medication. A long-term follow-up (LTFU) visit was required 6-8 weeks after the last dose of study medication. Schedule of events is summarized in Table 1.

Number of Subjects (Planned and Analyzed): One hundred and sixty six (166) subjects per treatment group were planned; 61 subjects received treatment and were analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects were to be males and females, 18 years of age or older, weighing 40 kg or more with end-stage renal disease. Subjects were to be on hemodialysis and had: 1) signs and symptoms of a localized catheter-related infection (eg, tenderness and/or pain, erythema, swelling, purulent exudates within 2 cm of entry site); 2) a body temperature of 38oC or higher or less than 36o C (oral equivalent); or 3) a blood culture positive for a Gram-positive pathogen. If the Gram-positive isolate was S aureus, it had to be cultured from at least 1 culture bottle from either the peripheral set or the catheter set of culture bottles. For all other Gram-positive pathogens (eg, coagulase-negative staphylococci), isolates were to be cultured from at least 2 culture bottles, of which 1 had to be from the peripheral set. There was to be no other obvious source of the bacteremia. Subjects were to have at least one of the following systemic signs of infection (obtained up to 24 hours prior to baseline): 1) hypotension, defined as systolic blood pressure of 90 mm Hg or lower or its reduction by 40 mm Hg or greater from the subject's baseline, in the absence of other causes for hypotension; 2) tachycardia defined as a pulse rate greater than 100 beats per minute; 3) tachypnea defined as a respiratory rate >20 breaths per minute or partial pressure of carbon dioxide (PACO2)

Study Treatment: Subjects in the linezolid arm received empiric treatment of intravenous (IV) or oral (PO) linezolid (600 mg) every 12 hours along with IV gentamicin (2 mg/kg body weight loading dose and subsequent doses targeted to keep serum peak levels between 6-8 μg/mL and trough levels less than 1 μg/mL). Once it was known that the baseline pathogen was Gram-positive, gentamicin therapy was discontinued, and subjects were to continue with either IV or PO linezolid (600 mg every 12 hours) alone.

Subjects in the comparator-treatment arm received empiric treatment of IV vancomycin (15 mg/kg body weight loading dose and subsequent doses targeted to keep serum trough levels between 10-15 μg/mL) along with IV gentamicin (2 mg/kg body weight loading dose and subsequent doses targeted to keep serum peak levels between 6-8 μg/mL and trough levels less than 1 μg/mL). Once it was known that the baseline pathogen was Gram-positive, gentamicin therapy was to be stopped. Subjects with a methicillin-resistant Gram-positive pathogen were to continue with IV vancomycin alone and subjects with a methicillin-susceptible Gram-positive pathogen and not allergic to penicillin could be switched to IV cefazolin (1 g every 24 hours) alone.

If the identification of the Gram-positive pathogen was known at study enrollment, subjects were initiated on linezolid or vancomycin without gentamicin. Also, a subject randomized to the comparator arm could be initiated on IV cefazolin without gentamicin if it was known at study enrollment that the pathogen was methicillin-susceptible and the subject was not allergic to penicillin. Sites could use aztreonam instead of gentamicin for the initial empiric Gram-negative coverage for catheter-related bloodstream infections if there was a high likelihood of gentamicin resistant Gram-negative bacteria at the site.

Both treatment groups could use aztreonam (supplied by the investigative site) to treat Gram-negative bacterial infections that developed after the Baseline visit. If a scheduled antibiotic treatment occurred close to a hemodialysis treatment session, antibiotic therapy was to be given after the hemodialysis treatment session. Subjects could be treated on an inpatient basis at the discretion of the Investigator based on the subjects' medical condition. Subjects with bacteremia were to receive a minimum of 7 days of therapy up to a maximum of 28 days of therapy. Twenty one (21) days of therapy were recommended.

Linezolid (IV and PO), vancomycin (IV), cefazolin (IV), and gentamicin (IV) were supplied by the Sponsor as open-label supplies. Ancillary supplies (0.9% sodium chloride for injection, 5% dextrose for injection, and sterile water for injection) were supplied by the study sites. Aztreonam could be used for coverage of concomitant Gram-negative infections that developed during the study. In such cases, the drug was provided by the study site.

Linezolid for IV use was provided as a ready-to-use sterile solution containing 600 mg of active

medication. IV infusion bags of 300 mL each contained 2 mg of active medication for every 1 mL of diluent (2 mg/mL), plus dextrose, sodium citrate, citric acid, and water for injection (final pH adjusted at time of manufacturing using 10% hydrochloric acid or 10% sodium hydroxide). Linezolid tablets for oral administration were provided as 600 mg film-coated compressed tablets. Vancomycin (sterile vancomycin hydrochloride United States Pharmacopeia [USP]) was supplied in vials containing 500 mg or 1 g of active ingredient. Cefazolin (sterile cefazolin sodium USP) was supplied in vials containing 1 g of active ingredient. Gentamicin (sterile gentamicin sulfate USP) was supplied in 1 mL vials containing 20 mg/mL or 2 mL vials containing 40 mg/mL of active ingredient.

Efficacy and Safety Endpoints: Primary Endpoint:
- To assess the primary objective was subject microbiologic outcome at the Test of Cure (TOC) visit.

Secondary Endpoints:
- Clinical efficacy was measured by clinical outcome of treatment.
- Incidence of complications during the study, such as metastatic infection, was measured at the LTFU.
- Pathogen eradication was measured by eradication rates of individual pathogens at the TOC visit.
- Eradication of S aureus nasal colonization was measured by nasal carriage rate at the follow-up visits.
- Safety and tolerance was measured by laboratory assay results and adverse event (AE) findings, including mortality.

Safety Evaluations: Safety assessments were to be based on the disposition of subjects with regards to AEs, vital signs, safety laboratory assessments, physical examinations, incidence of metastatic infections, and concomitant (non-investigational) medication.

Statistical Methods: Microbiologically evaluable (ME) subjects were a subset of intent-to-treat (ITT) subjects, where ITT subjects were those who received one or more doses of active study medication. All ITT subjects who had a gram-positive pathogen recovered from a peripheral or catheter blood culture in baseline ITT analysis window were defined as modified intent-to-treat (MITT) subjects. The sample size was determined using a two-sided α=0.05, power of 80%, equivalence between treatments to within 20%, and assuming that each treatment group would yield a 70% microbiological success rate, the number of microbiologically evaluable subjects required per treatment group was 83. Assuming a microbiological evaluability rate of 50%, this translated to a requirement of 166 enrolled subjects per treatment group.

Analyses of primary and secondary efficacy variables were to be done separately using ME,

modified-microbiologically evaluable (MME), and MITT subjects. Comparability of treatment groups at the TOC visit with respect to clinical and microbiological outcomes was to be assessed using 95% confidence intervals on the differences in cure/eradication rates (based on the normal approximation to the binomial distribution) and chi-square tests for homogeneity of proportions. Due to the expected small number of evaluable subjects at each center, terms for Investigator effect and treatment group-by-Investigator interaction were not to be included in the statistical models used for analysis. However, consistency of treatment effects across centers was to be investigated for those centers with appreciable numbers of subjects by pooling all centers within a country. Safety variables were to be analyzed using the ITT population. All statistical tests were two-sided. A p-value of 0.05 or less was considered statistically significant.

RESULTS: Enrollment in the study was suspended as a precautionary measure in light of the mortality imbalance observed in a similar study of catheter-related bloodstream infections. Less than one-third of intended subjects had been enrolled since study initiation. A decision was taken to terminate the study due to factors affecting the timeline to completion, such as the slow enrollment and the inclusion of sufficient evaluable subjects.

Subject Disposition and Demography: Of the 65 subjects screened for the study, 61 received study treatment (30 from the linezolid group and 31 from the comparator group). Nine subjects (30%) from the linezolid group completed the study compared to 14 subjects (45%) from the comparator group. Most of the subjects in both treatment groups discontinued the study due to non-treatment-related reasons categorized as “Other”. These were mostly due to either no pathogen isolated at baseline, pathogen isolated from a source other than peripheral blood, or pathogen isolated concomitantly with Pseudomonas aeruginosa, a Gram-negative bacillus. Three subjects from the linezolid group died while receiving active treatment. The cause of death was reported as being unrelated to study drug treatment (ie, cardiopulmonary failure, endocarditis, and myocardial infarction). One subject was discontinued on Day 9 due to persistently sterile cultures after enrollment and died on Day 15. Table 2 summarizes the subject disposition.

Both treatment groups were comparable with respect to baseline demographics. Subjects ranged in age from 22 to 89 years with a mean age of 54 and 50 years in the linezolid and comparator groups, respectively. There was a higher proportion of subjects 45 years of age or older in the linezolid group (80%) vs the comparator group (52%). The majority of the subjects enrolled in each group were males (57% and 58% in the linezolid and comparator groups, respectively). Both groups were comparable with respect to race. Demographics are summarized in Table 3.

Efficacy Results: Due to the early termination of this study, there were not enough subjects available to perform a meaningful efficacy analysis.

Safety Results: Table 4 summarizes treatment emergent AEs by system organ class and preferred term. Vomiting occurred more frequently in the linezolid group compared to the comparator group (6 vs 1 subjects).

Eight subjects from the linezolid group and 3 subjects from the comparator group had 1 or more SAEs. None of the SAEs were related to study treatment. Four subjects (3 linezolid, 1 comparator) died; the 1 death in the comparator group occurred 6 days after the subject was discontinued from the study due to a persistently sterile culture following enrollment. Table 7 summarizes the SAEs and deaths.

Discontinuation: Four subjects (3 in the linezolid group and 1 in the comparator group) discontinued the study due to non-treatment-related AEs. These events included bronchopneumonia, endocarditis, and duodenal ulcer in the linezolid group, and sepsis in the comparator group. The Investigator considered the bronchopneumonia and duodenal ulcer to be SAEs (Table 7).

Majority of subjects across both treatment arms had Gram-positive infections. Gram-negative infections occurred at a similar rate in both treatment arms. During active treatment, 3 deaths occurred on the linezolid arm while no deaths were observed on the comparator arm (Table 8). Of the 3 subjects who died, all 3 had Gram positive-only infections (S hominis, S aureus, and/or S pyogenes).

Other Safety Parameters: Changes in safety laboratory values were similar between the linezolid and comparator groups and generally consisted of elevations in blood urea nitrogen (BUN) and creatinine and decreases in hemoglobin, hematocrit, and red blood cell counts. These findings were consistent with a population of subjects having impaired renal function and bloodstream infections.

CONCLUSION: There were no new or unexpected safety findings following administration of the study drugs.