TITLE: A Phase 1/2 Double Blind, Placebo-Controlled, Dose Escalation, Safety, and Pharmacokinetic Study in Very Low Birth Weight Neonates of Pagibaximab (BSYX-A110), an Anti-Staphylococcal Monoclonal Antibody for the Prevention of Staphylococcal Bloodstream Infections

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ABSTRACT

Background: Staphylococcal sepsis is a major cause of morbidity and mortality in very low birth weight (VLBW) infants. A human chimeric monoclonal antibody, pagibaximab, was developed against staphylococcal lipoteichoic acid (LTA). We evaluated the safety, tolerability, and pharmacokinetics of pagibaximab in VLBW neonates. Methods: A phase 1/2, randomized, double blind, placebo-controlled, dose escalation study was conducted in VLBW infants (700–1300 grams) 3 to 7 days old. Patients received two doses 14 days apart of intravenous pagibaximab (10, 30, 60, or 90 mg/kg) or placebo in a 2:1 ratio. Blood and urine samples were obtained pre- and post-infusion for analysis of safety and pharmacokinetics, and data gathered on adverse events. Staphylococcal organisms causing sepsis were collected and evaluated. Results: Fifty-three patients received at least one dose of pagibaximab or placebo. The average gestational age was 27.6 weeks; average birth weight was 1003 grams. All serious adverse events were deemed unrelated or probably not drug related. Morbidities and mortality were similar across treatment groups. No evidence of immunogenicity of pagibaximab was detected. Pharmacokinetics was linear. Mean clearance, volume of distribution, and elimination half-life of pagibaximab were independent of dose. The serum half-life was 20.5 ± 6.8 days. Pagibaximab enhanced serum opsonophagocytic activity. All staphylococci causing sepsis were opsonizable by pagibaximab. Conclusion: Two infusions of pagibaximab, administered 2 weeks apart to high-risk neonates appeared safe and tolerable, and pharmacokinetics were linear. Evaluation of more frequent doses, at the highest doses tested, in neonates at high-risk of staphylococcal sepsis, is warranted.
INTRODUCTION

Very low birth weight (VLBW) neonates (<1500 grams birth weight) are at high risk for late-onset (>72 hours of life) hospital-acquired sepsis. Such infections are a major cause of morbidity, prolong time in the hospital and intensive care unit, increase the need for antibiotics, and further increase the substantial cost of medical care for these infants.

Staphylococci, including coagulase-negative staphylococci (CONS) and Staphylococcus aureus, are responsible for between 56 to over 75% of hospital-acquired, late-onset neonatal sepsis. Recent reports show continuing increases in resistance of staphylococci to antimicrobial agents. Frequent and prolonged exposures to antimicrobials have been demonstrated to increase the risk of developing infections with resistant organisms.

Therapeutic products and strategies that could prevent infections would minimize the need for antimicrobial products.

Lipoteichoic acid (LTA) is a highly conserved epitope in the staphylococcal cell wall that inhibits phagocytosis of bacteria in vitro, induces the cytokine cascade through stimulation of toll-like receptors, and may be necessary for staphylococcal survival. An anti-LTA murine/human chimeric monoclonal antibody, pagibaximab, was developed by recombinant DNA technology and activity confirmed in vitro and in animal studies against CONS and S. aureus. Based on preclinical pagibaximab bactericidal activity against a number of clinical isolates in vitro and in staphylococcal sepsis models in suckling animals, we have selected 500 ug/ml as the putative protective level of this antibody. In summary, we found that pagibaximab bound 24 different strains of CONS and S. aureus, and demonstrated increased bacterial killing in vitro against all of these strains. There was a clear dose response curve with 400ug/ml being required to
show the maximum killing activity on all of the strains tested and lower doses being less bactericidal. In a suckling rat model of CONS sepsis, pagibaximab\(^R\) significantly increased survival at 80 mg/kg/dose (p=0.0007) and the effect of 40mg/kg was significantly lower. This was associated with suckling rat serum concentrations of approximately 400-500ug/ml. In a lethal suckling rat model of \textit{S. aureus} sepsis pagibaximab\(^R\) significantly increased survival at 80 mg/kg/dose (p=0.02) and protection was lower at doses of 40mg/kg. This also was associated with suckling rat serum concentrations of 400-500 ug/ml. In view of the fact that VLBW infants have compromised innate immunity we hypothesized that we needed to have antibody excess to ensure bactericidal activity under conditions in which the effector system might be compromised as occurs in the VLBW infant. For this reason we selected 500ug/ml of antibody as the level which we hypothesized would be protective. It has also been hypothesized that pagibaximab could potentially prevent staphylococcal shock syndrome\(^15\). Thus, pagibaximab appears a promising option in preventing staphylococcal sepsis and its sequelae.

Pagibaximab has been studied in healthy human adults as a single intravenous (IV) dose at 3 or 10 milligrams per kilogram (mg/kg) and appeared to be safe and tolerable.\(^38\) The current clinical study, the first study of pagibaximab in VLBW neonates, was intended to evaluate the safety, tolerability, and pharmacokinetics of pagibaximab in this high-risk patient population.

**METHODS**

**Study Design**

This was a phase 1/2, randomized, double blind, placebo-controlled, dose escalation study assessing the safety and pharmacokinetic profile of four dose levels of pagibaximab. Based on previous studies of a neonatal monoclonal antibody to prevent infection\(^33\), monoclonal

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\(2\) less bactericidal. In a suckling rat model of CONS sepsis, pagibaximab\(^R\) significantly increased

\(3\) survival at 80 mg/kg/dose (p=0.0007) and the effect of 40mg/kg was significantly lower. This

\(4\) was associated with suckling rat serum concentrations of approximately 400-500ug/ml. In a

\(5\) lethal suckling rat model of \textit{S. aureus} sepsis pagibaximab\(^R\) significantly increased survival at 80

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\(18\)

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\(20\) **Study Design**

\(21\) This was a phase 1/2, randomized, double blind, placebo-controlled, dose escalation

\(22\) study assessing the safety and pharmacokinetic profile of four dose levels of pagibaximab. Based

\(23\) on previous studies of a neonatal monoclonal antibody to prevent infection\(^33\), monoclonal
antibodies to treat infection \(^1\), \(^{11}\), pagibaximab in animal models \(^{37}\), (Mond JJ unpublished data, Weisman LE unpublished data), neonatal suckling rat toxicity studies (Mond JJ unpublished data), and a pagibaximab study in adults \(^{38}\), the 4 dose levels of pagibaximab chosen for the present study were 10, 30, 60, and 90 mg/kg. Based on these in-vitro and animal studies, serum levels of 500 µg/mL of pagibaximab were anticipated to provide protection against the broadest spectrum of CONS and S. aureus sepsis in VLBW neonates. The study was conducted from October 2001 through May 2003 at two medical centers in three NICUs in the United States.

**Study Entry Criteria**

Eligible patients were infants with a birth weight of 700 to 1300 g, 3 to 7 days of age (inclusive), inpatients in the Neonatal Intensive Care Unit (NICU) with IV access, and expected to live at least 1 week following infusion. Patients with any of the following conditions were excluded from eligibility: clinically overt systemic infection; life-threatening hemodynamic instability; severe congenital anomaly or genetic disorder; known or suspected hepatic or renal insufficiency; persistent seizure disorder; immunodeficiency other than due to prematurity; a history of immune globulin administration prior to first study drug infusion; any history (patient or mother) of a hypersensitivity or severe vasomotor reaction to immunoglobulin G (IgG) or blood products; abnormal laboratory findings including liver function tests, blood urea nitrogen (BUN), bilirubin, complete blood count (CBC); concomitant or recent receipt of other investigational agents; expectation that the patient would not be able to be followed for the duration of the study; mother with serology positive for hepatitis B surface antigen or neonate’s receipt of hepatitis B immune globulin since birth. The Institutional Review Board at each center approved the study.

**Evaluation of Patients**
After obtaining informed consent from the infant’s parents or legal guardian, a baseline evaluation of medical history, physical examination, and laboratory testing was performed. Laboratory evaluations included standard hematology, blood chemistry, liver function, renal function, and urinalysis testing.

Fifteen minutes before study drug administration, vital signs, oxygen saturation, and physical examination were obtained. The randomized dose of study drug (pagibaximab or placebo) was administered as an IV infusion at 0.01 milliliters per kilogram per minute (mL/kg/min). The infusion rate was slowly increased to 0.02, 0.05, 0.1, and 0.125 mL/kg/min every 15 minutes if there was no physical evidence of adverse events (AEs) including changes in oxygen saturation, heart rate, blood pressure, temperature, and respirations. Additional vital signs and clinical assessment data were collected every 15 minutes until the infusion was complete and 30 and 60 minutes post-infusion.

On day 14, patients were re-screened for eligibility for the second dose. Eligible patients had a similar pre-dose evaluation. Administration of the second dose of study drug occurred at the patient’s previous randomized dose based on the original treatment assignment and infusion followed the same procedures described for the initial infusion.

On days 3 and 7 patients were assessed for safety, medical history, vital signs, and physical examination. On days 14, 28, and 42 patients were assessed for safety, medical history, vital signs, physical examination, and the following were obtained: urinalysis, CBC with differential and platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine. If available, data on bilirubin, electrolytes, and glucose were also collected. Additionally, on day 42, blood was drawn for human antimurine antibody/human antichimeric antibody (HAMA/HACA) analysis. On day 56, if still
hospitalized, patients were assessed for safety, medical history, vital signs, physical examination, and urinalysis was obtained. If a patient was released from the hospital prior to Day 56, the patient’s parent or legal guardian was contacted by telephone and asked about the patient’s health since hospital discharge. Blood was drawn for anti-LTA antibody levels on days 0 (1 hour after infusion), 3, 7, 14 (prior to second infusion), 14 (1 hr after second infusion), 28, 42, and 56 (if still hospitalized). Patients were followed for a total of 8 weeks after the start of the first study drug infusion.

Throughout the study, patients were closely monitored for signs of infection. If the attending physician deemed it necessary to evaluate a patient for sepsis, meningitis, or other infection, a work-up was performed. The work-up included CBC with differential, platelet count, blood culture from a peripheral vein (although physicians were encouraged to collect 2 samples, a single sample was considered acceptable), cerebrospinal fluid (CSF) examination including gram stain, cell count, and culture, urine culture by bladder tap or sterile catheterization, and culture from other sterile sources as indicated. Samples of all staphylococcal bacteria isolated from blood, CSF, and other sterile sites were sent to a central laboratory for analyses.

**Randomization and Dose Escalation**

Eligible VLBW infants were randomized at a ratio of 2:1 to receive IV pagibaximab at 10, 30, 60, and 90 mg/kg or an equal volume of placebo (saline) on Days 0 and 14. Two birth weight groups (700–1000 g and 1001–1300 g) accrued independently, with each dose and birth weight group consisting of 4 patients receiving pagibaximab and 2 patients receiving placebo. Dose escalation to the next higher level occurred within each birth weight group only after the last patient in the previous dose and weight group was followed for at least 14 days.
from the first dose by the Safety Monitoring Committee. This committee was composed of the two Principal Investigators, the independent Medical Monitor, and three physicians from the study sponsor.

**Blinding**

This was a double blind study. The only persons to whom patient treatment assignments were unblinded were the statisticians at the contract research organization overseeing the study, who were responsible for assignment of patient identification numbers and study drug allocation, and the pharmacists at the study sites, who were responsible for preparing the infusion.

**Safety Analyses**

For the purpose of this study, an AE was defined as any adverse change from the patient’s baseline condition that occurred following the first administration of the study drug through the end of the study period. Changes from the patient’s baseline condition known to be normal physiologic changes associated with the development of premature infants were not considered to be AEs. A protocol-defined toxicity table was used to grade the severity of each AE on a scale of 1-4.

A serious adverse event (SAE) was defined as any event that resulted in any of the following outcomes: 1) death; 2) a life-threatening adverse event; 3) inpatient hospitalization or prolongation of hospitalization; 4) persistent or significant disability or incapacity; 5) an important medical event that required intervention in order to prevent any of the other serious outcomes. All grade 4 AEs, as defined in the toxicity table, were considered SAEs. The investigator assessed each SAE for severity and relationship to study drug in a blinded manner.

**Assessment of Immunogenicity**
HAMA/HACA levels were determined by radiometric human anti-Hu96-110 HACA assay. Hu96-110, a human/murine chimeric monoclonal antibody (IgG1κ), is the active ingredient of pagibaximab. Polystyrene beads were coated with Hu96-110. Test serum, normal human serum, and goat anti-human IgG (positive control), were added to borosilicate glass culture tubes. A single Hu96-110 coated bead was added to each tube. Each bead was washed. 125I-Hu96-110 was added to all tubes. Each bead was washed again. The beads were transferred to clean tubes and particle emissions were counted to determine the amount of 125I-Hu96-110 bound to each bead. The assay result was calculated from the bound 125I-Hu96-110 and known concentration of 125I-Hu96-110. The results were expressed as nanograms per milliliter (ng/mL) of Hu96-110. During validation of the assay, the mean and standard deviation of the response in 27 normal human serum samples was 25.4 ± 8.7 ng/mL (mean±SD). The upper limit of the normal was defined as the mean plus three standard deviations or 52 ng/mL. A positive sample would have a value that exceeds the upper limit and or was twice as high as the pre-infusion sample. 38

Pharmacokinetic Analyses

The pharmacokinetic profile of pagibaximab was assessed using an antigen capture enzyme-linked immunosorbent assay measuring the serum concentration of anti-LTA antibodies. In brief, S. aureus LTA was coated onto the bottom of 96-well microtiter plates. After washing off unbound LTA, test sera diluted in phosphate-buffered saline with tween 20 and immunoglobulin-depleted human serum was incubated in the wells. The bound anti-LTA antibody was detected by incubation with a horseradish peroxidase labeled anti-human immunoglobulin antibody and a colorimetric reagent (TMB). The amount of anti-LTA antibody in serum was determined by comparison to a pagibaximab standard of known amount 38. Nonn-
compartmental analysis was used to estimate clearance (CL), volume of distribution (Vz), and half-life (t_{1/2})...

**Opsonophagocytic Activity**

The opsonophagocytic (bacterial killing) activity of pagibaximab in serum was determined using a modified standard assay. Specifically, the following components were used: *Staphylococcus epidermidis (S. epidermidis)* American Type Culture Collection (ATCC) strain 55133 (for measurement of patient serum activity) or clinical isolates (for measurement of pagibaximab activity) as the source of bacteria, HL60 cells (human acute promyelocytic leukemia cell line) as a source of human polymorphonuclear cells (PMNs), and C1q as a source of complement. In brief, patient serum (diluted 1:90) or pagibaximab (at various concentrations), PMNs, and diluted complement were mixed with a suspension of bacteria and incubated in a 96-well plate. Bacterial killing was measured by comparing the number of bacteria present at the time of initial mixing and after 2 hours of incubation. Bacteria were enumerated by performing colony counts on tryptic agar plates with 5% sheep blood. Controls included PMNs alone, complement alone, and PMNs plus complement. Using the formula: 

\[
\frac{\text{number of bacteria (time 0 – 2 h)}}{\text{number of bacteria at time 0}} \times 100
\]

the percent bacterial killing was calculated.

**Bacterial Analysis**

Frozen stocks of staphylococcal isolates were shipped to a central laboratory for species identification. Clinical isolates of CONS from blood cultures were analyzed. The isolates were thawed and streaked for isolation on blood agar (Remel, Lenexa, KS) to confirm culture purity and presence of staphylococci. Species was determined by API STAPH IDENT system (BioMerieux, Hazelwood, MO). Briefly, isolated staphylococcal colonies were tested in...
various biochemical assays as per the manufacturers instructions. Two ATCC reference isolates, ATCC 49521 and ATCC 35984 were used as control organisms for *S. aureus* and *S. epidermidis* respectively. Those staphylococcal isolates for which an unequivocal species could not be determined by Api Staph Strip, were sent to Accugenix (Newark, DE) for 16S 500bp sequence identification.

The same isolates were evaluated for genetic relatedness by performing pulse field gel electrophoresis (PFGE) following published procedures. Briefly, chromosomal DNA was isolated from the various staphylococcal isolates, digested in agarose with Smal, and then subjected to PFGE using a CHEF system (BioRad, Hecules, CA). Dendrograms were generated based on the genetic relatedness of the digestion patterns.

**Analysis of Sepsis Episodes**

For all patients who had sepsis evaluations, analyses of sepsis caused by CONS were divided into four categories. Each category included signs and symptoms consistent with clinical sepsis. In addition if: 1) two or more peripheral blood cultures grew CONS, this was categorized as definite sepsis; 2) one peripheral blood culture grew CONS when only one peripheral blood culture was drawn, this was categorized as probable sepsis; 3) one peripheral blood culture grew CONS when more than one peripheral blood culture was drawn, this was categorized as possible sepsis; 4) one or more central venous line blood cultures grew CONS in the absence of positive peripheral cultures, this was categorized as line sepsis.

**Statistical Methods**

The statistical analyses were essentially descriptive. Safety analyses were performed on the Intent-to-Treat (ITT) population, defined as all randomized patients who received at least 1 dose of study drug. Continuous variables were summarized by the mean, standard deviation,
median, and range. Categorical variables were summarized by the frequency and percentage.  

There was no formal hypothesis testing planned for primary objectives. However, if differences were observed, appropriate formal hypothesis testing for primary and/or secondary outcomes was performed at the significance level of $\alpha=0.05$ (2-sided).

RESULTS

Patient Population

Fifty-five patients were randomized into the study. Of these, two patients never received the study drug; consent for one patient was withdrawn prior to the first study drug infusion and the other was excluded due to low hemoglobin. These 53 patients (46 from Baylor College of Medicine, and 6 from Weill Medical College) were considered the intent to treat population that formed the basis of our analysis. Fifty-three patients received at least one dose of study drug and 44 (83%) of 53 received two doses. Nine patients (17%) did not receive the second dose because they met one or more exclusion criteria for the second dose.

Patient Baseline Characteristics

Demographics and other baseline characteristics of study patients were generally comparable across the treatment groups (Table 1). The mean gestational age for patients was 27.6 weeks (ranging from 25.0 to 33.0 weeks), and mean birth weight 1003 g (ranging from 702 to 1300 g).

Pharmacokinetics

Mean patient pre-infusion (endogenous) plasma anti-LTA concentrations were low and ranged from 3.49 to 9.44 µg/mL across the dose groups. Mean plasma anti-LTA concentrations increased in a dose-related manner (Figure 1). In the 60 mg/kg and 90 mg/kg dose groups,
following the second infusion of pagibaximab, an extrapolation of the serum levels suggests that a sustained mean anti-LTA level over 500 µg/mL was observed for a period of approximately 6 and 12 days, respectively (Figure 1). Six (85.7%) of 8 patients in the 60 mg/kg dose group and 8 (100%) of 8 patients in the 90 mg/kg dose group had plasma anti-LTA concentrations over 500 µg/mL immediately after the Day 14 pagibaximab infusion. In the 10 mg/kg and 30 mg/kg dose groups, no patient and 1 (12.5%) of 8 patients, respectively, had an antibody concentration over 500 µg/mL immediately after the Day 14 infusion. One patient in the 90 mg/kg dose group had an antibody concentration over 500 µg/mL on Day 28.

Following IV infusion of pagibaximab, mean pharmacokinetic values across dose groups were independent of dose. Total plasma clearance (Cl) ranged from 0.32 to 0.43 milliliters per hour (mL/h), mean volume of distribution (Vz) ranged from 182 to 285 mL, and mean $t_{1/2}$ ranged from 369 to 599 hours (h) or 19 to 25 days. The pharmacokinetics of pagibaximab in premature infants therefore appeared linear at doses ranging from 10 to 90 mg/kg.

Examination of the mean plasma anti-LTA over time profile (Figure 1) revealed that the decay after the first dose appeared to be similar to that after the second dose. However, this evaluation was limited by the time points available. Blood sampling for pharmacokinetic analysis was restricted by the small volume of blood available from the neonates.

Dose proportionality analysis showed that the linear regression of the log area under the plasma concentration-time curve (AUC) versus the log total dose suggested that for these data doses were proportional with the estimated slope of 0.92, the 95% confidence interval of 0.78 to 1.06, and a p-value of <0.0001.

One patient in the 90 mg/kg dose group received only the first dose of pagibaximab, but blood samples were collected for the entire 56-day period. This patient’s pharmacokinetic
parameters for CL (0.347 mL/h), Vz (241 mL), and t\(_{1/2}\) (481 h) were consistent with the rest of the 90 mg/kg group, suggesting that the pharmacokinetics of pagibaximab were consistent after 1 or 2 doses.

**Safety Analyses**

All safety data were reviewed throughout the study by an independent Medical Monitor, the Safety Monitoring Committee, and an external Data Safety Monitoring Board and there were no safety concerns.

**Adverse Events**

Fifty-two (98%) of the 53 patients in the ITT population experienced at least one AE during the study. Adverse events experienced by patients in this study were consistent with events known to occur with prematurity and in low birth weight neonates. The AEs most commonly reported in study patients were anemia and hyperkalemia, with 38 (71.7%) and 29 (54.7%) of 53 patients, respectively, experiencing at least one episode. The percentage of patients experiencing the most common AEs was generally similar between the treatment groups (Table 2). There was no trend toward increased frequency of clinical or laboratory AE with increased pagibaximab dose.

One AE, moderate oxygen supplementation, was assessed by the investigator as probably related to study drug infusion. This event, experienced by a patient in the 90 mg/kg pagibaximab group, occurred immediately after the second study drug infusion and resolved in 1 hour. All other AEs were considered by the investigators as either unrelated or probably not related to study drug.

**Serious Adverse Events**
Twenty-three (43%) of 53 patients in the ITT population experienced at least one SAE during the study. Cholestasis was the most common SAE, with 10 patients (18.9%) reporting at least one episode. Other SAEs occurring in ≥5% of patients in the ITT population included necrotizing enterocolitis (NEC) and sepsis due to an identified organism (7 patients, or 13.2%, each), hyperkalemia and thrombocytopenia (3 patients, or 5.7%, each).

The SAEs experienced by patients in this study were generally similar across treatment groups. No trend toward increased frequency of SAEs with increasing pagibaximab dose was observed. All SAEs reported for patients in this study were recognized co-morbidities associated with prematurity, and all were assessed by the investigators as either unrelated or probably not related to study drug.

**Significant Clinical Outcomes**

In order to assess any potential adverse effect of pagibaximab on clinical events known to occur at high frequency in low birth weight neonates, the frequency of patients experiencing NEC (Bell’s stage 2 or greater) \(^7\), bronchopulmonary dysplasia (oxygen dependency at 36 weeks postmenstrual age) (BPD) \(^6\), severe intraventricular hemorrhage (Papille’s grade 3 or 4) (IVH) \(^25\), retinopathy of prematurity requiring surgery (ROP) and death were summarized by treatment group. The percentage of patients in the pagibaximab and placebo treatment groups experiencing significant clinical outcomes was generally similar for BPD (57.6% vs 66.6%, respectively), NEC (15.2% vs 11.1%, respectively), ROP (3.0% vs 10.0%, respectively), and death (9.1% vs 5.0% respectively). Severe IVH was experienced by 3.0% of patients in the pagibaximab group, 20% of patients in the placebo group (p=0.061). The number of patients experiencing significant clinical outcomes in the individual treatment groups was small,
however, no trend toward increased frequency of any significant clinical event with increased pagibaximab dose was observed.

Deaths

Four (7.5%) of the 53 patients in the ITT population died during the study, including three (9.1%) of 33 patients receiving pagibaximab and one (5.0%) of 20 patients receiving placebo (p=1.00). A second patient in the placebo group died 7 months after completing the study follow-up period.

One patient in the pagibaximab treatment group died on study Day 21 due to NEC and sepsis. This infant received the first dose of pagibaximab 10 mg/kg on study Day 0 and did not receive the second dose because of failing to fulfill the eligibility criteria. A second patient in the pagibaximab treatment group died on study Day 5 due to severe hyaline membrane disease and subsequent NEC and no organism was identified. This infant received the first dose of pagibaximab 10 mg/kg on study Day 0 and died prior to receiving the second dose. A third patient in the pagibaximab treatment group died on study Day 11 from sepsis. This infant received the first dose of pagibaximab 60 mg/kg on study Day 0 and died prior to administration of the second dose.

One patient in the placebo group died on study Day 36 from sepsis, necrotizing enterocolitis, and prematurity resulting in multiple organ failure. This infant received the first dose of placebo (as part of the 10 mg/kg dose group) on study Day 0 and did not receive the second dose because of failing to fulfill the eligibility criteria. A second patient in the placebo group died 7 months after completing the study follow-up period. The immediate cause of death was cardiopulmonary failure secondary to multiple organ system insufficiency and extreme prematurity.
None of these deaths was considered by the investigators to be attributable to study drug. All of the events resulting in death are known to be associated with premature infants with very low birth weight.

HAMA/HACA Analysis
Concentrations of HAMA/HACA were relatively unchanged for all patients across treatment groups throughout the study, and remained well below the upper normal limit (52 ng/mL) from pre-dose to post-dose.

Vital Signs, Physical Examinations, and Clinical Chemistry/Hematology/Urinalysis
In all treatment groups, patient infusion vital signs showed normal variability. Non-infusion vital signs showed no indication of a dose response effect. Systolic and diastolic pressures increased with age, as expected for this population, and were similar across treatment groups. Heart rate and respiratory rate showed normal variability for all treatment groups. Temperature was stable over time for all treatment groups. Median body weight increased from approximately 1000 to 2140 g over the study period; all dose groups showed the same tendency. Variability in all laboratory results over time was consistent with premature newborn parameters.

Opsonophagocytic Activity
Pagibaximab enhanced the opsonophagocytic (bacterial killing) activity in serum (Table 3). An increase in opsonophagocytic activity was demonstrated at the lowest dose level (10 mg/kg), and was increased at the higher dose levels. There did not appear to be a significant difference in activity between the 30, 60, and 90 mg/kg group, however only a single serum dilution of these samples were tested. Differences may have been observed at higher dilutions, but not enough serum was available for testing. In contrast, minimal or no opsonophagocytic activity was observed in placebo patients.
Clinical Signs and Symptoms Leading to Evaluation of Sepsis

Sepsis evaluations were performed in 51 of the 53 patients in the ITT population. The most common signs and symptoms leading to evaluation for sepsis were similar across treatment groups. The most common clinical signs and symptoms leading to evaluation of sepsis were similar for patients in the pagibaximab and placebo groups, with apnea/bradycardia accounting for 23.7% and 26.2% of events, respectively, and cyanosis accounting for 18.3% and 18.5% of events, respectively. Overall, no dose response effect upon the frequency of signs and symptoms leading to evaluation of sepsis was observed.

Sepsis

Twenty-seven (50.9%) of the 53 patients, including 16 of 33 (48.5%) patients in the pagibaximab group and 11 of 19 (55%) patients in the placebo group, experienced at least one sepsis episode. Three patients each in the pagibaximab group (9.1%) and the placebo group (15%) experienced a second episode of sepsis. Four patients each in the pagibaximab group (12.1%) and the placebo group (20%) experienced sepsis with multiple organisms. Coagulase-negative staphylococcus (CONS) was the most common organism (40.5%) isolated from blood cultures in patients with sepsis in both the pagibaximab and placebo groups, and only one patient in the 60 mg/kg pagibaximab group experienced Staphylococcus aureus (2.4%) sepsis as part of a mixed infection with CONS (see Figure 1). Sixteen non-staphylococcal sepsis events occurred in both the pagibaximab (n=7, 21.2%) and placebo (n=9, 45%) groups (p=0.12). The organisms isolated from these blood cultures were Enterococcus (14.3%), Candida (7.1%), Escherichia coli (7.1%), Klebsiella (7.1%), Pseudomonas (7.1%), Enterobacter (4.8%), Serratia (4.8%), Acinetobacter (2.4%), and Streptococcus agalactiae (2.4%), and did not differ significantly between groups.
Sepsis caused by CONS

Sixteen (31%) of 53 patients experienced sepsis caused by CONS, including 11 (33.3%) of 33 patients receiving pagibaximab and five (25%) of 20 patients receiving placebo (p=0.76). One patient in the 30 mg/kg pagibaximab group (9.1%) experienced a second episode of CONS sepsis. Although analysis by pagibaximab dose level showed a slightly greater proportion of patients in the 90 mg/kg pagibaximab group experiencing sepsis caused by CONS (4 of 9 patients, 44%) compared with those in the other treatment groups, statistical testing using Fisher’s exact test showed no overall difference between dose groups (p-value = 0.9).

Of the 16 patients with CONS sepsis, 15 experienced definite (10 patients, 63%) or probable (5 patients, 31.3%) sepsis. No patient experienced possible sepsis caused by CONS. One patient receiving pagibaximab at the 90 mg/kg dose level experienced line sepsis caused by CONS. In all cases, estimated or observed plasma anti-LTA levels were below the putative protective level of 500 µg/mL at the time of CONS diagnosis. Speciation of the isolates in the 16 patients with CONS sepsis revealed substantial variation with sepsis caused by *S. epidermidis* in eleven patients, and in one patient each by *S. simulans, S. caprae*, mixed infection of *S. epidermidis* and *S. hominus*, mixed infection of *S. epidermidis* and *S. haemolyticus*, and mixed infection of *S. epidermidis* and *S. aureus*.

Age at Diagnosis of First Episode of Sepsis Caused by CONS

The mean age of patients at the diagnosis of the first episode of sepsis caused by CONS ranged from 11.5 to 22.5 days across treatment groups. In the pagibaximab 10 mg/kg treatment group, the mean age at diagnosis of the first episode was 22.5 days, in 30 mg/kg treatment group, 11.5 days, in the 60 mg/kg treatment group, 16.0 days and in the 90 mg/kg treatment group, 16.0 days. In the placebo group, the mean age at first diagnosis of CONS sepsis was 17.8 days.
Opsonizability of CONS by Pagibaximab

Of 25 staphylococcal isolates recovered from the blood cultures of 16 patients with staphylococcal infection, pagibaximab demonstrated bacterial killing (opsonophagocytic assay) against all the isolates. However, there was distinct heterogeneity in the ability of antibody to opsonize the different isolates. Whereas some isolates were opsonized at a concentration of less than 50 ug/ml, others required 400 ug/ml. At pagibaximab concentrations of 400ug/ml 18 (67%) isolates demonstrated > 90% bacterial killing, 21 (78%) isolates demonstrated > 80% bacterial killing, and 24 (89%) isolates demonstrated > 70% bacterial killing.

Dendrogram of CONS

We also analyzed these 25 CONS bacterial isolates for genetic relatedness. The dendrogram (see Figure 2) of these isolates (using a similarity coefficient of 80%) suggests the strains of CONS varied substantially and were generally unrelated between patients who were infected, even in the same hospital (data not shown). There appeared to be two clusters that were closely related: patients # 28, 33, 35, 50, 55, 23, and 10 from the same hospital; patients # 3, 51, and 29 from two different hospitals in New York and Houston. When paired cultures for the same sepsis episode were tested (n=5) all of these pairs appeared to be related. Although one patient (#23) appeared to have two species in each culture, the strains in the two cultures appeared related. The other patient (#10) appeared to have two species in one culture and one species in the other culture, and the species in the two cultures appeared to be related.

DISCUSSION

Mean pre-infusion (endogenous) plasma anti-LTA antibody levels were found to be negligible in the VLBW neonates in this study. This may be because premature infants do not
receive their normal transplacental passage of antibody which occurs predominantly in the final
weeks of pregnancy, or the immaturity of the premature neonatal immune system makes it
unlikely that they would mount a significant antibody response following exposure in-utero or in
the first few days of life. A direct correlation between low serum levels of IgG and an
increased risk of late-onset neonatal sepsis has been shown. Thus, VLBW neonates are
unlikely to possess functional opsonophagocytic activity to staphylococci at birth or during
hospitalization, making them a population at high risk of staphylococcal sepsis. Therefore,
passive immunization with pagibaximab could be a potentially important step in preventing all
neonatal staphylococcal infection. This may be especially important in methicillin resistant
(community and hospital acquired) and methicillin sensitive S. aureus infections, though less
frequent result in greater morbidity and mortality than CONS in the premature infant.

The pharmacokinetics of pagibaximab in premature neonates was dose proportional over
doses ranging from 10 to 90 mg/kg. The mean t\textsubscript{1/2} ranged from 19 to 25 days across the dose
groups and is consistent with previous reports of IgG infusions in neonates. This is also
consistent with results from previous study of pagibaximab in human healthy adults, with
other studies of human/mouse chimeric or full human IgG1 antibodies administered IV in adults
and commercially available intravenous immunoglobulin (IVIG) in neonates. Moreover, after the second infusion of pagibaximab at 60 or 90 mg/kg, mean anti-LTA levels
greater then 500 µg/mL, the putative protection level for staphylococcal sepsis, were observed.
With the 90 mg/kg dose achieving more sustained levels greater then 500 ug/ml, it suggests that
higher or more frequent doses of pagibaximab may be appropriate for further study.

Human antimurine antibody/human antichimeric antibody levels remained low in the
neonates receiving IV pagibaximab at 10, 30, 60, and 90 mg/kg at study days 0 and 42,
suggesting that pagibaximab did not elicit an antibody response to itself even after repeated
doses. In addition, the AEs, SAEs, and clinical outcomes across study groups were not
significantly different. This is also similar to previous reports of IgG safety and tolerability in
neonates.\textsuperscript{35,36} This study suggests that the first use of pagibaximab in VLBW neonates at 10, 30,
60 and 90 mg/kg IV administered twice two weeks apart appeared safe and well tolerated.
CONS was the most common cause of sepsis in the VLBW neonates in this study, with
an incidence of 30.2\% across treatment groups and less than 2 \% of patients developed \textit{S. aureus}
sepsis. These findings are consistent with the results of previous larger studies of late-onset
sepsis in VLBW infants\textsuperscript{3,10,31} that demonstrated CONS in 14 to 23\% of patients and \textit{S. aureus} in
1.6 to 5\% of patients. The majority (63\%) of sepsis cases caused by CONS in this study were
confirmed by two or more peripheral blood cultures growing CONS. There was no significant
difference in incidence rates of sepsis caused by CONS across dose levels of pagibaximab and
placebo, overall or by category of infection. Given the small number of patients in each
treatment group in this study, no definitive conclusions can be reached regarding the effect of
pagibaximab. Larger studies of pagibaximab in VLBW neonates are needed to demonstrate any
potential effect for prevention of staphylococcal sepsis in the target population.

Patients receiving 60 or 90 mg/kg of pagibaximab were observed to have sustained
plasma anti-LTA levels above the putative protection level of 500 µg/mL following the second
dose, so further evaluation of the product with larger and or more frequent doses should be
considered. However, at the time of diagnosis of sepsis caused by CONS, all affected patients
had estimated or observed plasma anti-LTA levels below 500 µg/mL. Thus, further evaluation of
pagibaximab should focus on dosing regimens that can produce plasma anti-LTA levels over 500
µg/mL, for the potential prevention of staphylococcal sepsis.
ACKNOWLEDGEMENTS:

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REFERENCES


Table 1. Patient Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>10 mg/kg (N=8)</th>
<th>30 mg/kg (N=8)</th>
<th>60 mg/kg (N=8)</th>
<th>90 mg/kg (N=9)</th>
<th>Placebo (N=20)</th>
<th>Total (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age, wk</td>
<td>27.4 ± 1.7</td>
<td>27.5 ± 1.4</td>
<td>27.0 ± 1.5</td>
<td>28.3 ± 2.2</td>
<td>27.6 ± 2.4</td>
<td>27.6 ± 2.0</td>
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<tr>
<td>Birth Weight, gm</td>
<td>990 ± 170</td>
<td>1030 ± 172</td>
<td>1015 ± 168</td>
<td>1015 ± 209</td>
<td>987 ± 159</td>
<td>1003 ± 167</td>
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<tr>
<td>Gender, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>37.5</td>
<td>50.0</td>
<td>25.0</td>
<td>44.4</td>
<td>45.0</td>
<td>41.5</td>
</tr>
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<td>Race, %</td>
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<td></td>
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<tr>
<td>Black</td>
<td>25.0</td>
<td>25.0</td>
<td>12.5</td>
<td>11.1</td>
<td>35.0</td>
<td>24.5</td>
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<tr>
<td>Hispanic</td>
<td>37.5</td>
<td>62.5</td>
<td>62.5</td>
<td>11.1</td>
<td>25.0</td>
<td>35.8</td>
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<tr>
<td>White</td>
<td>25.0</td>
<td>12.5</td>
<td>25.0</td>
<td>66.7</td>
<td>30.0</td>
<td>32.1</td>
</tr>
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<td>APGAR (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Minute</td>
<td>5.4 ± 2.0</td>
<td>5.6 ± 2.9</td>
<td>5.5 ± 1.9</td>
<td>5.4 ± 1.9</td>
<td>4.9 ± 2.1</td>
<td>5.3 ± 2.1</td>
</tr>
<tr>
<td>5 Minute</td>
<td>7.4 ± 1.4</td>
<td>7.3 ± 2.1</td>
<td>7.6 ± 1.1</td>
<td>7.3 ± 1.3</td>
<td>7.0 ± 2.0</td>
<td>7.3 ± 1.6</td>
</tr>
</tbody>
</table>

* N indicates number of patients in the treatment group; SD indicates standard deviation
Table 2. Adverse Events Occurring in ≥10% of Patients in the Intent to Treat Population, by Treatment Group

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Pagibaximab (N=33)</th>
<th>Placebo (N=20)</th>
<th>Total (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>24 (72.7)</td>
<td>14 (70.0)</td>
<td>38 (71.7)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>17 (51.5)</td>
<td>12 (60.0)</td>
<td>29 (54.7)</td>
</tr>
<tr>
<td>Apnea</td>
<td>12 (36.4)</td>
<td>5 (25.0)</td>
<td>17 (32.1)</td>
</tr>
<tr>
<td>Serum Alkaline Phosphatase Increased</td>
<td>6 (18.2)</td>
<td>9 (45.0)</td>
<td>15 (28.3)</td>
</tr>
<tr>
<td>Respiratory Distress</td>
<td>11 (33.3)</td>
<td>4 (20.0)</td>
<td>15 (28.3)</td>
</tr>
<tr>
<td>Intraventricular Haemorrhage</td>
<td>6 (18.2)</td>
<td>7 (35.0)</td>
<td>13 (24.5)</td>
</tr>
<tr>
<td>Conjugated Hyperbilirubin Increased</td>
<td>7 (21.2)</td>
<td>5 (25.0)</td>
<td>12 (22.6)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8 (24.2)</td>
<td>4 (20.0)</td>
<td>12 (22.6)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>5 (15.2)</td>
<td>5 (25.0)</td>
<td>10 (18.9)</td>
</tr>
<tr>
<td>Unconjugated Hyperbilirubinemia</td>
<td>5 (15.2)</td>
<td>3 (15.0)</td>
<td>8 (15.1)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6 (18.2)</td>
<td>2 (10.0)</td>
<td>8 (15.1)</td>
</tr>
<tr>
<td>Oxygen Desaturation</td>
<td>5 (15.2)</td>
<td>3 (15.0)</td>
<td>8 (15.1)</td>
</tr>
<tr>
<td>Blood Urea Nitrogen Increased</td>
<td>2 (6.1)</td>
<td>4 (20.0)</td>
<td>6 (11.3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (15.2)</td>
<td>1 (5.0)</td>
<td>6 (11.3)</td>
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</table>

N indicates number of patients; n indicates number of patients who experienced the adverse event.
Table 3. Opsonophagocytic activity (per cent bacterial killing) in serum of neonates over time against *S. epidermidis* ATCC strain 55133.

<table>
<thead>
<tr>
<th>Day of Study</th>
<th>0</th>
<th>0</th>
<th>14</th>
<th>14</th>
<th>28</th>
<th>42</th>
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<tbody>
<tr>
<td>Relation to Infusion</td>
<td>Prior</td>
<td>1 Hour After</td>
<td>Prior</td>
<td>One Hour After</td>
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<td></td>
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<tr>
<td>Infusion Number</td>
<td>One</td>
<td>One</td>
<td>Two</td>
<td>Two</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg/kg/dose</td>
<td>26.7 (24.7)</td>
<td>37.2 (18.2)</td>
<td>24.1 (7.3)</td>
<td>46.9 (14.1)</td>
<td>29.4 (9.1)</td>
<td>20.9 (6.2)</td>
</tr>
<tr>
<td>30 mg/kg/dose</td>
<td>0 (0)</td>
<td>69.4 (7.9)</td>
<td>42.1 (10.5)</td>
<td>68.4 (10.6)</td>
<td>48.5 (10)</td>
<td>35.3 (7.7)</td>
</tr>
<tr>
<td>60 mg/kg/dose</td>
<td>0 (0)</td>
<td>60 (11.5)</td>
<td>44.8 (9.1)</td>
<td>56.7 (13.2)</td>
<td>50.1 (10.7)</td>
<td>38.6 (7.9)</td>
</tr>
<tr>
<td>90 mg/kg/dose</td>
<td>12 (12)</td>
<td>71.1 (9.2)</td>
<td>46.4 (9.4)</td>
<td>51.7 (14.5)</td>
<td>49.3 (11.1)</td>
<td>45.4 (9)</td>
</tr>
</tbody>
</table>

Mean (+) Standard Error of the Mean
LEGENDS

Figure 1: Mean ± standard deviation plasma anti-LTA antibody concentrations over time by pagibaximab dose group on a semi-logarithmic axes. Error bars represent 1 standard deviation. There were: seven patients in the 10 mg/kg dose group with data for 6 patients included on Day 56; eight patients in the 30 mg/kg dose group with data for 7 patients included on Day 42 and data for 5 patients included on Day 56; eight patients in the 60 mg/kg dose group with data for 7 patients included on Day 14, Day 28 and Day 42 and data for 6 patients included on Day 56; eight patients in the 90 mg/kg dose group with data for 6 patients included on Day 56. The individual symbols represent positive staphylococcal blood cultures and are plotted as serum concentration of pagibaximab (as determined by direct measurement by ELISA) versus the time in days when the positive blood culture was drawn: ●-placebo, ▼-10 mg/kg, ▲-30 mg/kg, ▭-60 mg/kg, ●-90 mg/kg dosing group. All placebo symbols lie on the X axis since there were no measurable serum antibody concentrations in this group. All staphylococcal infections occurred at an estimated serum ant-LTA concentrations of < 500 ug/ml.

Figure 2: PFGE patterns for genetic relatedness of the 25 CONS isolates. In the far right-side columns, the patient identification (ID) number and bacterial species identification for each Staphylococci were listed for each isolate’s dendrogram.
Figure 2

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Bacterial ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td><em>S. simulans</em></td>
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<tr>
<td>48</td>
<td><em>S. epidermidis</em></td>
</tr>
<tr>
<td>27</td>
<td><em>S. caprae</em></td>
</tr>
<tr>
<td>27</td>
<td><em>S. caprae</em></td>
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<td><em>S. epidermidis</em></td>
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<td><em>S. epidermidis</em></td>
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<td><em>S. epidermidis</em></td>
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<td><em>S. epidermidis</em></td>
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<td><em>S. epidermidis</em></td>
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<td><em>S. epidermidis</em></td>
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<td><em>S. epidermidis</em></td>
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<td><em>S. haemolyticus</em></td>
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<td><em>S. hominis</em></td>
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