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ANTI-PCR_V ANTIBODY IN CYSTIC FIBROSIS: A NOVEL APPROACH TARGETING *PSEUDOMONAS AERUGINOSA* AIRWAY INFECTION

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SUMMARY

Pseudomonas aeruginosa (*Pa*) airway infection is associated with increased morbidity and mortality in cystic fibrosis (CF). The type III secretion system is one of the factors responsible for the increased virulence and pro-inflammatory effects of *Pa*. KB001 is a PEGylated, recombinant, anti-*Pseudomonas*-PcrV antibody Fab' fragment that blocks the function of *Pa* TTSS. We studied the safety, pharmacokinetic (PK), and pharmacodynamic properties of KB001 in CF subjects with chronic *Pa* infection. Twenty-seven eligible CF subjects (12 years of age, FEV₁ 40% of predicted, and sputum *Pa* density >10⁵ CFU/gm) received a single intravenous dose of KB001 (3 mg/kg or 10 mg/kg) or placebo. Safety, PK, *Pa* density, clinical outcomes and inflammatory markers were assessed. KB001 had an acceptable safety profile and a mean serum half-life of 11.9 days. All subjects had *Pa* TTSS expression in sputum. There were no significant differences between KB001 and placebo for changes in *Pa* density, symptoms, or spirometry after a single dose. However, compared to baseline, at Day 28 there was a trend towards a dose-dependent reduction in sputum myeloperoxidase, IL-1, and IL-8, and there were significant overall differences in change in sputum neutrophil elastase and neutrophil counts favoring the KB001 10 mg/kg group versus placebo (−0.61 log¹⁰ and −0.63 log¹⁰ respectively; p<0.05). These results support targeting *Pa* TTSS with KB001 as a non-antibiotic strategy to reduce airway inflammation and damage in CF patients with chronic *Pa* infection. Repeat-dosing studies are necessary to evaluate the durability of the anti-inflammatory effects and how that may translate into clinical benefit. (NCT00638365)

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Keywords

Cystic fibrosis; *Pseudomonas aeruginosa*; type III secretion system; inflammation; elastase

INTRODUCTION

Advances in the care for cystic fibrosis (CF) have improved survival over the past several years, but >80% of people with CF still die as either a direct or indirect result of loss of lung function [1] due to a vicious cycle of airway obstruction, polymicrobial lung infection, and exuberant inflammation with destruction of the lung tissue [2].

Despite recognition that many different microbial strains and species can co-exist in the CF airway [3], it is well established that some bacterial species may contribute more profoundly to CF lung disease progression than others. Evidence for an important pathogenic role for *Pseudomonas aeruginosa* (*Pa*) has been recognized for decades [4]. Chronic suppressive therapy targeting *Pa* infection has been shown to provide substantial benefit in lung function [5–6], quality of life [7–8], incidence of exacerbations [5,8–9], and survival [10]. However, it is also well recognized that despite the use of effective antibiotic therapies, chronic *Pa* infection is not eradicated and often leads to emergence of resistant strains. A strategy that targets *Pa* without the risk of developing resistance to treatment is clearly desirable.

The notable effect on CF lung disease progression associated with chronic *Pa* infections compared to infection with other bacterial species such as *S. maltophilia* [11] suggests that some specific attributes of *Pa* may be responsible for increased virulence and an associated elevation of inflammatory response in CF infections. One factor associated with increased *Pa* virulence is the type III secretion system (TTSS), a protein complex that allows injection of bacterial exotoxins into host cells and release into the extracellular space [12–13]. TTSS exotoxins contribute to the cytotoxicity of *Pa* toward eukaryotic host cells including epithelial cells, neutrophils and macrophages. TTSS Exotoxin S (ExoS) induces proinflammatory cytokine secretion through the activation of NFκB [14], and *Pa* strains infecting CF subjects often express ExoS [15].

Further evidence that TTSS is important to *Pa* virulence is derived from studies of neutralizing antibodies targeted at *Pa* PcrV, a structural component near the tip of the needle-like TTSS, where binding and inactivation of PcrV was shown to be protective in animal models of acute *Pa* infection [16–18]. Ventilator-associated pneumonia is a human correlate of acute *Pa* infection, for which *Pa* TTSS has been implicated as playing a role in pathogenesis [19–20]. As for chronic *Pa* airway infections, a murine model demonstrated significantly reduced airway inflammation following treatment with anti-PcrV [21].

KB001 is a Humaneered® PEGylated, recombinant, anti-*Pseudomonas*-PcrV antibody Fab' fragment that inhibits the function of *Pa* TTSS. The Humaneered® process generates high-affinity monoclonal antibodies that are close to human germ-line in sequence to eliminate immunogenicity. PEGylation extends serum half life and also protects against inactivation in the lung. Because KB001-A is a Fab' antibody fragment lacking the IgG Fc region, it does not activate immune cells and exacerbate inflammation. Also, KB001 is directed against a

bacterial protein; there is no cross-reactivity with mammalian cells, further reducing the likelihood of side effects known to occur with other monoclonal antibodies. (data on file, KaloBios) We hypothesized that the inhibition of PcrV function could represent a novel therapeutic strategy for treating chronic *Pa* airway infection and the associated inflammation in CF. We conducted a clinical trial with the primary objective of assessing the safety and tolerability of a single intravenous (IV) dose of KB001 in CF subjects with chronic *Pa* airway infections. Secondary objectives included KB001 serum pharmacokinetics (PK), sputum concentrations, and immunogenicity, as well as the effects of KB001 on lung function, sputum bacterial density, and inflammatory markers up to 56 days post-infusion.

METHODS

Study Design and Subjects

This was a randomized, double-blind, placebo-controlled, sequential-cohort, single-dose, dose-escalation study, performed at 10 CF Care Centers in the U.S. The study protocol was reviewed by the Protocol Review Committee of the CF Foundation Therapeutics Development Network (TDN), and was approved by the Institutional Review Board for each participating center. All participants and/or legal guardians provided written informed consent/assent.

Entry criteria included diagnosis of CF, age 12 years and older, forced expiratory volume in 1 second (FEV₁) of 40 percent of predicted and a quantitative *Pa* culture with 1×10^5 colony forming units (CFU)/gm sputum at screening. Stable regimens of CF respiratory medications and treatments were required for at least 2 weeks prior to study, and for 4 weeks prior to screening subjects had to be free from signs of a pulmonary exacerbation, and had not received systemic corticosteroids and/or systemic antibiotics (other than chronic azithromycin). Subjects treated with cycled maintenance inhaled antibiotics during screening were to have received at least 3 cycles of the antibiotic (i.e. 12 weeks of dosing) over the 6 months prior to study. These subjects were screened during the last half of their “on” cycle with the objective of administering study treatment (Day 0) within 14 days of completing their inhaled antibiotic cycle (no inhaled antibiotics allowed from Day 0 – 28, Figure 1). Subjects with a history of chronic inhaled antibiotic use were to resume their next inhaled antibiotic cycle on Day 29, with the same antibiotic received during screening. Subjects were excluded if they required continuous daily inhaled antibiotics, could not produce sputum, or had a history of *Burkholderia cepacia* complex infection.

Two cohorts of 12 subjects were planned: each randomized 2:1 to receive a single intravenous (IV) infusion of KB001 or placebo. Subjects randomized to receive KB001 received 3 mg/kg in the first cohort and 10 mg/kg in the second cohort. The TDN Data Monitoring Committee (DMC) reviewed the safety data after the first cohort and allowed the enrollment of the second cohort to proceed. Placebo infusions were 0.9% sodium chloride and matched the appearance and volume of study drug. Unblinded pharmacists prepared the infusions, and the label on the infusion bags maintained the blind for the subjects and research teams. Study drug was administered by IV infusion over 1 hour. Following screening, subjects received study drug on Day 0, and returned on Days 14, 28, and 56 for

evaluations (solid circles in Figure 1). In addition, a brief assessment by telephone was conducted on Day 7 (open circle in Figure 1).

Safety Assessments

Safety was evaluated by physical examination, assessment of vital signs, hematology and serum chemistry at study visits. Adverse events (AEs) and serious adverse events (SAEs) were collected through Day 56.

Pharmacokinetics, TTSS detection, and Immunogenicity

Serum for PK assessment of KB001 was obtained pre-infusion and at intervals post-infusion on Day 0, and then on Days 14, 28, and 56. Induced sputum was collected and analyzed in accordance with the TDN Coordinating Center's standard operating procedures (SOP) for sputum induction and analysis [22–23]. Induced sputum for determination of KB001 concentrations was collected at Days 0 (pre-dose), 14, 28, and 56. Detection and quantification of KB001 was performed by antigen-binding ELISA, with the lower limit of quantification (LLQ) of 20 ng/mL for serum and 800 ng/mL for processed sputum. Induced sputum was also analyzed for the presence of the *Pa* TTSS (PcrV expression by reverse transcriptase PCR, and genotyping for ExoS and ExoU). Immunogenicity of KB001 was evaluated by collecting serum to assay for anti-KB001 antibody from all patients pre-infusion and at Day 56.

Pharmacodynamics

The PD of KB001 was assessed in part by analyzing induced sputum for inflammatory cytology and biomarkers, including cell count and differential, free neutrophil elastase (NE), matrix metalloproteinase 9 (MMP-9), myeloperoxidase (MPO), interleukin 8 (IL-8), IL-1 β , IL-6, IL-17, and tumor necrosis factor alpha (TNF α). Induced sputum was also analyzed for quantitative sputum cultures (for *Pa* and *S. aureus*). Blood absolute neutrophil counts (ANC) and C-reactive protein were measured to assess changes in systemic inflammation. Clinical outcomes including patient questionnaires (Cystic Fibrosis Questionnaire-Revised, CFQ-R) [24] and spirometry were performed at the visits.

The primary evaluation of PD markers was at Day 28 (at least 4 weeks off inhaled antibiotics) to allow for assessment of KB001 as a single agent. The Day 56 evaluation allowed for the assessment of the potential additive effects of KB001 with a cycled inhaled antibiotic.

Statistical Analysis

All subjects who were randomized and received any study medication were included in the Safety Population. For PD ("efficacy") endpoints, patients were considered evaluable if they met the eligibility criteria, received study medication, did not receive any excluded medications, and provided adequate sputum samples for *Pa* quantitative culture and inflammatory markers at baseline and Day 28. The analytical approach for all endpoints focused on comparisons between KB001 and placebo as well as change from baseline within a treatment group. For the assessment of the PD of KB001, comparisons between KB001 and placebo within each cohort were descriptive in nature, and without adjustment for

multiple comparisons. After pooling placebo patients from both cohorts, the Wilcoxon Rank-Sum test was conducted to test for difference between KB001 (3 mg/kg or 10 mg/kg) and placebo, and to evaluate group change from Day 0 (baseline) to each follow-up time point. Statistical significance was considered when p-values were < 0.05.

RESULTS

Of 46 subjects screened, 27 satisfied inclusion criteria and were enrolled in the study; 15 subjects (10 active, 5 placebo) were enrolled in Cohort 1 and 12 subjects (8 active, 4 placebo) were enrolled in Cohort 2. All subjects completed the study and were included in the safety population (Figure 2). Pharmacodynamic evaluations were based on an Evaluable Population of 22 subjects. As detailed in figure 2, 5 subjects were excluded from the analysis (2 did not receive a full dose due to infusion reactions, and 3 received prohibited medications).

The population demographics and baseline characteristics are summarized in Table 1. The subjects in each group had a high *Pa* burden and were similar in most of the other characteristics, and although subjects in the KB001 10 mg/kg group had a higher use of inhaled antibiotics in the 6 months prior and chronic use of azithromycin, the difference was not statistically significant.

Safety

The administration of a single infusion of KB001 in CF subjects with chronic *Pa* airway infections revealed a favorable safety profile. There were no deaths or life-threatening adverse events, with most AEs and SAEs being consistent with underlying CF. Infusion-related AEs occurred in 2 subjects receiving KB001 (one from each cohort) who developed non-serious, mild-to-moderate reactions that resolved quickly after stopping the infusion and without additional treatment. Symptoms in one or both of these subjects included flushing, pruritis, tachycardia, elevated blood pressure, rash, nausea, and chest tightness. After evaluating further lab tests, an independent expert review of these subjects by the DMC concluded that these reactions were not anaphylactic, IgE-mediated, or complement-mediated in nature. Two subjects were hospitalized for acute illnesses that were deemed non-drug related; one for sinusitis (placebo group) and one for bronchitis (3 mg/kg KB001 group). By Day 56 for the Safety Population, CF exacerbations were reported for 2 subjects in the placebo group, 1 subject in the KB001 3 mg/kg group, and none in the KB001 10 mg/kg group. There were no clinically relevant changes in physical examinations, vital signs, or safety labs.

Pharmacokinetics, TTSS Detection, and Immunogenicity

The PK parameters were comparable between the 3 mg/kg and 10 mg/kg treatment groups (Table 2), and there were no gender differences observed. The KB001 mean serum half-life was 11.9 days following a single IV infusion. In the placebo group, 6 of 9 subjects tested positive for anti-PcrV antibody as did 3 subjects in each of the treated groups prior to infusion. These predose serum titers were less than 1.8% of the corresponding maximal serum concentrations (C_{max}) following KB001 dosing. People with CF are known to form

antibodies to TTSS of *Pa*, some of which may bind to the PcrV protein and give a signal in the KB001 assay [25]. Sputum KB001 concentrations were all below the LLQ at all time points with the exception of 3 subjects in whom the concentration of KB001 in sputum was 1.7% to 4.9% of that in serum at Day 14; only one of these subjects had KB001 still detectable in sputum at Day 28 (4.0% of serum value).

Evidence of TTSS was present in all subjects. PcrV expression was detected in sputum samples from all but one subject in each dose group including placebo. In the PcrV negative samples there was no detection of *Pa* using a probe for a constitutively expressed control gene, suggesting that the *Pa* titer or the mRNA recovery in these samples was low. The ExoS gene was detected in the sputum of all but one subject, in whom the ExoU gene was detected.

No serum samples were found to be positive for human anti-KB001 antibodies.

Pharmacodynamics

There was a tendency for the concentrations of many of the inflammatory biomarkers to decrease in the KB001 groups and increase in the placebo group. Thus, while there were no significant changes in biomarkers from baseline within subject groups, there was a consistent trend towards a KB001 dose-dependent reduction in sputum MPO, IL-8, IL-1 β and NE (Figure 3 and online supplement). Significant reductions compared to placebo were observed at Day 14 for IL-1 β and NE (KB001 3 mg/kg group, $p < 0.05$). At Day 28 there was a median increase of NE in the placebo group ($n=8$) of $0.38 \log_{10}$ and a median decrease in the KB001 10 mg/kg group ($n=6$) of $0.23 \log_{10}$ ($p=0.039$). There was a significant median percent reduction from baseline compared to placebo for sputum macrophages at Day 28 for the KB001 3 mg/kg group ($p=0.024$) and at Day 56 for the 10 mg/kg group ($p=0.023$). Also at day 28 there was a median increase in neutrophils per gram of sputum of $0.25 \log_{10}$ in the placebo group, a decrease of $0.03 \log_{10}$ in the KB001 3 mg/kg group ($p=0.073$), and a decrease of $0.38 \log_{10}$ in the KB001 10 mg/kg group ($p<0.05$ compared to placebo). For the other measured biomarkers, no significant differences were noted between groups.

Baseline *Pa* burden was similar across the treatment groups. At Day 28 there was a numerical reduction from baseline in median mucoid *Pa* density in the KB001 10 mg/kg group ($-0.4 \log_{10}$) compared to placebo ($+0.8 \log_{10}$). However, these changes were not statistically significant, and this trend was not seen in non-mucoid or total *Pa* density over 28 or 56 days (see Figure, online supplement). The proportion of subjects with *S. aureus* was greatest in the 10 mg/kg group and lowest in the placebo group (Table 1). There were too few subjects with *S. aureus* to evaluate for significant changes in burden.

There were no significant differences between active treatment and placebo groups for ANC, C-reactive protein, CFQ-R Respiratory domain scores, or spirometric parameters (FEV₁, FEF₂₅₋₇₅, or FVC) at any time point.

DISCUSSION

In this study we report the results of administration of a single intravenous infusion of KB001 in CF subjects with chronic *Pa* lung infection. The treatment appears to have been safe and generally well-tolerated, with dose-proportional serum PK demonstrated. Our inability to detect KB001 in the induced sputum of all but three treated patients is likely a function of 1) the high LLQ of the sputum KB001 assay, 2) the time point of the first sample was not until 2 weeks after dosing, and 3) the antigen-binding ELISA assay only detects unbound KB001, and not the antibody already bound to PcrV in the sputum. Analysis of the induced sputum samples provided support for the ability of KB001 to modulate inflammation in the airways.

Chronic *Pa* infection is an important contributor to CF lung disease progression and mortality, encouraging efforts to use antibiotic prophylaxis in CF patients to prevent initial infection [26–27], aggressively treat “early” infection to convert to patients to culture negativity [28], and chronically suppress established infections [29]. Despite these efforts, a majority of CF adults today are chronically infected with *Pa* [1], and the organism remains a significant risk factor for accelerated lung function decline [30–31], increased probability of treatment for exacerbation [32–33], and mortality [34–35].

The TTSS is a well-characterized contributor to the virulence of planktonic *Pa* infections [12–13,36], but the role for TTSS in the acceleration of lung disease among CF patients with chronic *Pa* infections is unclear. In animal models of acute *Pa* infection, anti-PcrV antibodies increase survival by protection of the animal’s immune cells from being killed by the TTSS, which in turn allows a more robust host immune response to better clear the infection [16–18]. However, acute infection models may not be relevant to the complex, polymicrobial chronic infections in the CF lung: patients may survive for decades without clearing *Pa* lung infections [37]. In addition, studies to characterize the extent of *Pa* TTSS expression in CF lung infections have suggested that even though TTSS may be a key factor in the establishment of chronic infection, it is one of many virulence factors that appear to be down-regulated as chronic CF lung infections mature [38–39]. However, our findings suggest that TTSS expression is not completely lost and that strains expressing TTSS persist in most subjects with chronic *Pa* infection. Our contrasting results might be in part due to a higher sensitivity of the RT PCR assay of the whole bacterial population present in sputum, as opposed to selecting a few colonies from culture medium as done previously [38]. While not necessarily the most prevalent or dominant strain, the presence of these more virulent strains have significant implications for pathogenicity despite their lower numbers. In addition, it has been recently shown that biofilms are capable of expressing TTSS [40], and that TTSS-expressing *Pa* can be cultured from the lungs of chronically infected CF subjects [19], suggesting that biofilms may play a more important role in virulence than previously suspected. Furthermore, viruses like rhinovirus cause release of planktonic bacteria from biofilms [41] and are associated with CF exacerbations and higher *Pa* density in sputum [42]. Finally, highly-pathogenic, small-colony variants of *Pa* have been isolated from CF sputum and show dramatically elevated TTSS expression [43]. Collectively, these findings provide support to the validity of targeting TTSS as a therapeutic strategy in patients with CF chronically infected with *Pa*.

We observed consistent KB001 dose-proportional trends in reduction of sputum markers of inflammation at Day 28 post-administration, suggesting a role for TTSS in *Pa*-associated lung inflammation in CF. The differences in inflammatory marker changes from baseline to day 28 between placebo and 10 mg/kg KB001 groups were substantial, with statistically significant differences in change of sputum neutrophils and free NE concentrations. In parallel, *Pa* TTSS expression was detected in the sputum of all study subjects, further supporting a role for TTSS in chronic CF infections.

Admittedly, these results were observed in a small sample population, with an increase in local inflammation of subjects receiving placebo contributing to net differences in inflammation between treatment groups. Whether the increase in placebo group inflammation resulted from removal of chronic suppressive inhaled anti-*Pa* antibiotic therapy is difficult to determine, since fewer subjects in the placebo group were receiving inhaled antibiotics. This also made it impossible to evaluate statistically whether restarting inhaled antibiotics on Day 29 had an additive effect on the outcomes, as subgroups were too small.

Free NE is an important inflammatory marker in CF lung disease for several reasons. NE has been shown to directly damage animal lungs [44] and elevated NE concentrations have been associated with reduced ciliary beat frequency [45] and mucociliary clearance [46], impaired opsonophagocytosis [47], as well as increased mucus secretion [48] and IL-8 [49] and leukotriene B₄ [50] production. Elevated NE lung concentrations have been associated with accelerated CF lung disease progression [51], and NE has been identified as the most tractable biomarker for studying the effect of CF anti-inflammatory therapies [52]. It is therefore not surprising that free NE has been identified as a promising CF therapeutic target [53]. In the current study, we observed a 0.5 log difference in change in free sputum NE at day 28 between patients receiving a single infusion of 10 mg/kg KB001 versus placebo, an effect that is comparable with that previously seen for administration of intravenous anti-*Pa* antibiotics to CF subjects during pulmonary exacerbation [54], and substantially greater than that seen in an attempt to directly reduce free NE with alpha-1-antitrypsin in CF subjects [55].

No substantial changes were noted in pulmonary function, CFQ-R or sputum bacterial density across treatment groups. It is not surprising that statistical significance could not be demonstrated for these clinical and microbiologic endpoints after only a single dose of KB001 in a small number of study subjects. It will be of great interest to see if these endpoints will improve with repeated doses of KB001 in a larger and longer-term study.

In summary, this study showed that a single dose of KB001 appeared to be safe, and supported the validity of targeting TTSS as a therapeutic strategy in patients with CF chronically infected with *Pa*. If it can be shown that this magnitude of reduction in free NE and other inflammatory markers can be sustained with repeated exposure, KB001 may represent a promising, non-antibiotic, therapeutic strategy for mitigating the significant effects of *Pa* infection on the progression of CF lung disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Schematic of study design

On Day 0 subjects were randomized to receive KB001 or placebo. Filled circles, clinical study visits. Open circle, telephone interview. Filled squares, times of sample collection for safety and efficacy analyses.

Figure 2. Subject disposition

A total of 27 subjects were randomized to one of three study treatments in successive cohorts. Two subjects receiving KB001 withdrew from the study due to infusion-related AEs and no subjects were lost to follow-up. Three subjects who completed the study were excluded from efficacy analyses due to administration of prohibited medications during the study period and one subject was unable to expectorate enough sputum for all analyses on Day 28.

Figure 3. Baseline sputum inflammatory marker concentrations and effects of study drug infusion at Day 28

Baseline mean values (log transformed with 95% confidence intervals) are shown on the left and changes from baseline observed at Day 28 are shown on the right for evaluable subjects (Figure 2). Left and right panel ordinates are not of equivalent scales.

Table 1

Subject Demographics and Baseline Characteristics (Safety Population)

Subject Characteristics	KB001		
	Placebo (n = 9)	3 mg/kg (n = 10)	10 mg/kg (n = 8)
Age, yrs (range)	33.4 (19–55)	29.9 (17–58)	27.8 (20–37)
Male, n (%)	7 (78)	5 (50)	6 (75)
Weight, Kg (SD)	74 (11.8)	64 (10.9)	69 (15.3)
FEV ₁ , % predicted (SD)	67.8 (13.0)	75.2 (21.4)	69.6 (19.7)
CFTR F508del Homozygous (%)	6 (67)	4 (40)	6 (75)
CFTR F508del Heterozygous (%)	3 (33)	6 (60)	2 (25)
CFQ-R Respiratory Symptom Score (SD)	71.6 (15.3)	66.7 (7.4)	75.0 (14.6)
Sputum <i>Pa</i> density, log ₁₀ CFU/g (SD)	7.33 (2.07)	8.00 (1.20)	7.80 (0.73)
<i>S. aureus</i> present in sputum, n (%)	3 (33.3)	5 (50)	6 (75)
Sputum <i>S. aureus</i> density, log ₁₀ CFU/g (SD)	5.50 (3.40)	4.51 (2.17)	6.32 (1.57)
Chronic dornase alfa use, n (%)	6 (66.7)	6 (60.0)	5 (62.5)
Chronic azithromycin use, n (%)	3 (33.3)	5 (50.0)	5 (62.5)
Received inhaled antibiotics in the past 6 months, n (%)			
0 courses	6 (66.7)	5 (50.0)	1 (12.5)
1 course	0	0	0
2 courses*	0 (0.0)	3 (30.0)	1 (12.5)
3 courses	3 (33.3)	2 (20.0)	6 (75.0)
Received inhaled antibiotics in past 2 weeks, n (%)	1 (11)	2 (20)	4 (50)
Received IV antibiotics in the prior 12 mo, n (%)	2 (22)	4 (40)	4 (50)

* These subjects were not taking inhaled antibiotics during screening

Table 2

Serum KB001 PK Parameters Following a Single 1-hour IV Infusion

Pharmacokinetic Parameter	3 mg/kg KB001 (n=7)	10 mg/kg KB001 (n=7)
Geometric Mean Half-life, hrs (SD)	280 (63)	293 (15)
Mean Clearance, mL/hr/kg (SD)	0.147 (0.0369)	0.139 (0.0327)
Mean Steady-State Volume of Distribution, mL/kg (SD)	44.7 (7.02)	43.9 (9.17)
Geometric Mean Residence Time, hrs (SD)	67.8 (13.0)	75.2 (21.4)
Mean Maximum Concentration, µg/mL (SD)	64.62 (25.37) ^a	219.77 (47.54)
Mean Area Under the Curve _(0-∞) , hr × µg/mL(SD)	22,713.53 (5,803.52)	77,817.51 (22,303.37)

^a
(n=9)