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Pharmacokinetics and Safety Profile of the Human Anti-*Pseudomonas aeruginosa* Serotype O11 Immunoglobulin M Monoclonal Antibody KBPA-101 in Healthy Volunteers▽

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KBPA-101 is a human monoclonal antibody of the immunoglobulin M isotype, which is directed against the O-polysaccharide moiety of *Pseudomonas aeruginosa* serotype O11. This double-blind, dose escalation study evaluated the safety and pharmacokinetics of KBPA-101 in 32 healthy volunteers aged 19 to 46 years. Each subject received a single intravenous infusion of KBPA-101 at a dose of 0.1, 0.4, 1.2, or 4 mg/kg of body weight or placebo infused over 2 h. Plasma samples for pharmacokinetic assessments were taken before infusion as well as 0.25, 0.5, 1, 2, 2.5, 4, 6, 8, 12, 24, 36, and 48 h and 4, 7, 10, and 14 days after start of dosing. Plasma concentrations of KBPA-101 were detected with mean maximum concentrations of drug in plasma of 1,877, 7,571, 24,923, and 83,197 ng/ml following doses of 0.1, 0.4, 1.2, and 4.0 mg/kg body weight, respectively. The mean elimination half-life was between 70 and 95 h. The mean volume of distribution was between 4.76 and 5.47 liters. Clearance ranged between 0.039 and 0.120 liters/h. At the highest dose of 4.0 mg/kg, plasma KBPA-101 levels were greater than 5,000 ng/ml for 14 days. KBPA-101 exhibited linear kinetics across all doses. No anti-KBPA-101 antibodies were detected after dosing in any subject. Overall, the human monoclonal antibody KBPA-101 was well tolerated over the entire dose range in healthy volunteers, and no serious adverse events have been reported.

Hospital-acquired (nosocomial) infections are responsible for an increasing number of serious secondary illnesses in the hospital environment. Immunocompromised individuals including burn victims, incubated patients in the intensive care unit, cancer and AIDS patients, as well as patients undergoing organ transplantation are at particularly high risk of contracting nosocomial infections. *Pseudomonas aeruginosa*, along with *Staphylococcus aureus* and *Enterococcus* spp., is one of the most common pathogens responsible for nosocomial infections (6, 13).

P. aeruginosa expresses a variety of membrane-bound virulence factors such as lipopolysaccharide (LPS), pili, flagella, as well as secreted compounds, such as exoenzyme S and exotoxin A, that interfere with host defense systems (2, 14). LPS in particular is responsible for the development of septic shock, a condition associated with extremely poor outcomes. Considerable amounts of LPS can be released from the bacterial membrane during antibiotic treatment and can aggravate the systemic inflammatory response.

The treatment of *P. aeruginosa* infections is a challenge due mainly to its poor outer membrane permeability and/or efflux that results in intrinsic resistance to many antimicrobial agents. In addition, *P. aeruginosa* often harbors chromosomal and/or plasmid-mediated genes that encode antimicrobial resistance mechanisms, enabling it to acquire resistance to almost every class of antimicrobial agent available (3, 7).

The major defense mechanisms counteracting gram-negative bacterial infections are complement-activated killing and complement-mediated opsonophagocytosis. Polysaccharides such as LPS are T-cell-independent antigens that trigger the innate immune system via the stimulation of pattern recognition receptors (e.g., Toll-like receptor 4). Antibodies induced in response to them are mostly of the immunoglobulin M (IgM) isotype. IgM antibodies have several favorable properties that support their use as therapeutic tools: their pentameric form provides 10 antigen binding sites, they bind antigens with high avidity, and IgM antibodies are very effective complement activators (18).

Passive immunotherapy has long been recognized as a valuable addition to standard therapy against infectious diseases. The use of monoclonal antibodies (MAbs) has been established in several therapeutic areas and might represent an alternative or complement to antibiotic therapy. Combined treatment with MAbs and antibiotics may lead to a more rapid resolution of infections, resulting in shorter stays in intensive care units as well as reductions of morbidity, mortality, and health care costs.

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Currently, MAbs are derived from mice and genetically modified to improve tolerability in humans. Nevertheless, these so-called humanized antibodies possess remainders of potentially antigenic sequences and differ in glycosylation patterns from human antibodies. These differences can affect half-life and long-term tolerability. Therefore, a technique to utilize human B cells for the production of therapeutic MAbs has been developed.

KBPA-101 is a human MAb obtained from a volunteer immunized with a *P. aeruginosa* O-polysaccharide toxin A conjugate vaccine (10, 11). It is of IgM/κ isotype and directed against the LPS O-polysaccharide moiety of *P. aeruginosa* serotype IATS O11. Preclinical tests with KBPA-101 included systemic infections in a murine burn wound sepsis model, where full protection of animals against lethal challenges with *P. aeruginosa* was achieved at very low doses of <5 μg/animal. Also, an acute lung infection model using mice showed protection against local respiratory infections.

Although KBPA-101 is derived from a human donor, there are potential safety concerns associated with the use of MAbs, including immunological and hypersensitivity reactions. Since KBPA-101 is selected for its species-specific effector function and the targeted antigen is not expressed endogenously in humans, no crossover reactivity with autoantigens is expected.

The aim of this single-center, double-blind, dose escalation phase I study was to evaluate the safety and pharmacokinetic profile of single, intravenous doses of KBPA-101 in healthy adults.

MATERIALS AND METHODS

Patients. Healthy men and sterilized, hysterectomized, or postmenopausal women between 19 and 46 years of age were eligible to participate if they signed an informed consent, had a body mass index of 18 to 30, had a negative urine drug screen, and had negative blood screening results for hepatitis B surface antigen, hepatitis C antibody, parvovirus B-19 antibody, and human immunodeficiency virus antibody. Subjects were excluded if they had a history of serious adverse reactions or hypersensitivity to any drug, had a presence or history of allergies requiring acute or chronic treatment (except seasonal allergic rhinitis), or had a history of drug abuse in the last 5 years or if there were abnormal physical findings of clinical significance at the screening examination or at baseline that interfered with the objectives of the study. Also, subjects with any surgical or medical condition that interfered with the distribution, metabolism, or excretion of the drug, including impaired renal or hepatic function, diabetes mellitus, cardiovascular abnormalities, chronic symptoms of pronounced constipation or diarrhea, or conditions associated with total or partial obstruction of the urinary tract, were excluded. Subjects with clinically significant abnormal laboratory values at the screening evaluation, symptoms of a significant somatic or mental illness in the 4-week period preceding drug administration, or a history of cardiovascular dysfunction/deregulation were also excluded.

Subjects were prohibited from receiving any prescription medication within 14 days prior to the administration of the drug and/or nonprescription medication within 7 days of the administration of the drug. Subjects were further prohibited from receiving any investigational drug or donating blood (500 ml or more) during the 3-month period prior to the study. Consumption of alcoholic beverages was prohibited during 48 h prior to the first and last drug administration and 72 h thereafter.

The protocol and informed consent form were approved by the local ethics committee and Swiss authorities before the study was initiated. The study was conducted at Swiss Pharma Contract, Allschwil, Switzerland, and carried out in accordance with good clinical practice regulations, the 2000 version of the Declaration of Helsinki, Swiss Federal Law on Medicinal Products, and the U.S. Code of Federal Regulations dealing with clinical studies.

Randomization. Thirty-two subjects were sequentially assigned to one of four escalating-dose cohorts (0.1, 0.4, 1.2, or 4 mg of KBPA-101 per kg of body weight). For each cohort (comprising eight subjects), six subjects were randomized to receive KBPA-101, and two subjects were randomized to receive placebo.

Dose calculation. The highest dose tested in animal studies was 12 mg/kg body weight in mice. According to FDA guidelines on maximum safe starting doses in healthy volunteers (http://www.fda.gov/CDER/guidance/5541fnl.pdf), this value was divided by 12.3 to get the human-equivalent dose and then further divided by 10, the safety factor, to arrive at a dose of 0.1 mg/kg. Further doses were calculated based on an escalation factor of approximately 3.

Study drug. KBPA-101 for injection was supplied as a sterile, nonpyrogenic, phosphate-buffered solution at a concentration of 1.4 mg/ml (Sanquin Pharmaceutical Services, Amsterdam, The Netherlands). Each subject received a single dose by intravenous infusion over 2 h through a 0.22-μm-pore-size, low-protein-binding, in-line filter. Subjects were closely monitored, and the infusion would have been discontinued at the first sign of anaphylaxis. The KBPA-101-producing clone was obtained by the fusion of lymphocytes from a healthy individual actively immunized with a *P. aeruginosa* O-polysaccharide–toxin A conjugate vaccine (10, 11) and the mouse-human heteromyeloma cell line LA55.

Safety monitoring. The first cohort received KBPA-101 at a concentration of 0.1 mg/kg. Enrollment of sequential, dose-escalating cohorts proceeded following a review of the safety data from at least seven of eight patients from the prior cohort. Clinical adverse events (AE) were graded by the treating physician as none, mild, moderate, or severe.

Subjects were monitored during and for 48 h following the infusion of KBPA-101 in a clinical research unit. Continuous electrocardiogram monitoring was performed from 0.5 h before until 5 h after the start of infusion. Subjects returned to the unit for follow-up evaluations on study days 4, 7, 10, and 14, and physical examinations were repeated on day 14.

Pharmacokinetic parameters. Plasma samples for pharmacokinetic assessments were obtained before infusion as well as 0.25, 0.5, 1, 2, 2.5, 4, 6, 8, 12, 24, 36, and 48 h and 4, 7, 10, and 14 days postinfusion. Plasma concentrations of KBPA-101 were determined by enzyme-linked immunosorbent assay using a mouse monoclonal anti-idiotypic antibody against KBPA-101 (MAb 1H9, an in-house preparation) and purified KBPA-101 as a standard. Binding antibodies were detected with an alkaline phosphatase-conjugated anti-mouse IgG antibody (KPL Inc., Gaithersburg, MD).

The pharmacokinetic characteristics of KBPA-101 were assessed across dose levels, and basic pharmacokinetic parameters were calculated (8). Missing values were not accounted for during the evaluation. Values below the limit of quantification were set to zero prior to the time to peak concentration of drug in serum (T_{max}) and set to missing after T_{max}. The KBPA-101 concentrations in plasma were reported at the time points and time intervals specified for each individual for each of the treatments (active/placebo) separately and subjected to descriptive statistics including calculation of median, arithmetic mean, standard deviation, coefficient of variation, 95% confidence interval, and maximum and minimum values. The following noncompartmental pharmacokinetic parameters of KBPA-101 were derived from each individual plasma concentration-versus-time profile using standard methods (8): plasma concentration-time data were used to determine peak concentrations of drug in serum (C_{max}), T_{max}, the elimination half-life ($t_{1/2}$), the area under the plasma concentration-time curve (AUC) from immediately prior to dosing (time zero) until the last sample was taken [$AUC_{(0\rightarrow tn)}$], the percentage of the extrapolated area to time infinity in relation to the total area under the curve [$AUC_{(0\rightarrow inf)}$], volume of distribution associated with the terminal phase (V_z), apparent volume of distribution at steady state (V_{ss}), and systemic clearance (CL).

The pharmacokinetic parameters $AUC_{(0\rightarrow tn)}$, $AUC_{(0\rightarrow inf)}$, C_{max}, and T_{max} were compared for the different treatments. The bioavailabilities were derived from the ratios of the corresponding AUC values. The geometric means of the individual ratios were reported as point estimates for $AUC_{(0\rightarrow tn)}$, $AUC_{(0\rightarrow inf)}$, and C_{max}. Analysis was performed by statistical general linear model procedures of the pharmacokinetic parameters in SAS (SAS Institute Inc., Cary, NC).

Immunogenicity. Analysis of circulating anti-idiotypic antibodies to KBPA-101 at screening and on days 7 and 14 was performed using an enzyme-linked immunosorbent assay with KBPA-101-coated microtiter plates. Sera from patients were serially diluted with phosphate-buffered saline (pH 7.4), and binding antibodies were detected using an anti-human IgG alkaline phosphatase-conjugated antibody (Sigma-Aldrich, Buchs, Switzerland). Purified mouse anti-KBPA-101 anti-idiotypic MAb 1H9 was used as a positive control detected with an anti-mouse IgG alkaline phosphatase-conjugated antibody (KPL Inc., Gaithersburg, MD). Absolute quantification of anti-KBPA-101 antibodies was not possible, as the positive control was not of human origin. Thus, the assay delivered relative values for each subject. Relative concentrations below the detection limit of 62.5 ng/ml were set to zero. If not indicated differently, all listed chemicals were from Fluka Chemie AG (Buchs, Switzerland).

TABLE 1. Summary of demographic data for the study population

Demographic parameter	Result for all subjects ($n = 32$)[a]
Mean age (yr) (min–max)	34.0 (19.0–46.0)
Mean ht (cm) (min–max)	175.2 (161.0–190.0)
Mean wt (kg) (min–max)	70.8 (56.6–79.0)
Mean body mass index (kg/m^2) (min–max)	23.1 (18.5–26.2)
No. (%) of patients	
Gender	
Male	30 (93.8)
Female	2 (6.8)
Ethnic origin	
Caucasian	30 (93.8)
Hispanic	1 (3.1)
Oriental/Asian	1 (3.1)
With smoking history of:	
Smoker (14-70 cigarettes/wk)	5 (15.6)
Ex-smoker	5 (15.6)
Nonsmoker	22 (68.8)
Occasional alcohol consumption	21 (65.6)
Caffeine consumption	23 (71.9)

[a] Descriptive statistics (mean, minimum, and maximum).

RESULTS

Enrollment. Thirty-two healthy subjects, 2 females (6.3%) and 30 males (93.8%) ranging in age from 19 to 46 years (mean, 34 years), entered the study (Table 1). Thirty subjects were of Caucasian origin, one was of Hispanic origin, and one was of Oriental/Asian origin. The mean body mass index was 23.1. All subjects completed the study according to the protocol. The study inclusion criteria for female subjects were quite strict. Therefore, the protocol did not contain any specifications regarding gender balance, which resulted in a higher percentage of males than females.

Safety results. All infusions of the study drug were well tolerated and completed without interruption. No serious AE was observed, and none of the subjects discontinued the study due to an AE. Eight subjects (25.0%) reported a total of nine AE (seven mild and two moderate AE) (Table 2). Seven of these subjects received KBPA-101 and experienced six mild and one moderate AE. One subject that received placebo experienced one mild and one moderate AE. Three subjects (9.4%) reported an AE related to KBPA-101 administration. All AE resolved without sequelae. There was no correlation between the incidence of AE and increased dose. Four of the six subjects (66.7%) receiving 0.4 mg/kg KBPA-101 experienced a total of four AE. In the other KBPA-101 dose-level groups (0.1 mg/kg, 1.2 mg/kg, and 4.0 mg/kg), one subject per group (16.7%) experienced one AE. One of the eight subjects (12.5%) who received placebo experienced two AE. This subject belonged to the 0.4 mg/kg placebo group ($n = 2$).

Pharmacokinetic evaluation. In general, the maximum plasma concentration was observed at the end of infusion or shortly thereafter. Plasma concentrations of KBPA-101 were detected in all subjects receiving the study drug immediately after dosing (0.25 h, first postdose collection) and were detectable throughout the study period of 14 days. For each dose, the mean plasma concentration reached a maximum 2 to 4 h after infusion and gradually decreased throughout the sampling interval (Fig. 1).

The C_{max} and AUC increased proportionally with KBPA-101 doses of 0.1, 0.4, 1.2, and 4 mg/kg, but the values for CL and volume of distribution were similar across all doses (Table 3).

Following each infusion, the dose proportionality was investigated by normalizing the AUC, $AUC_{(0\rightarrow tn)}$, and C_{max} with the amount of KBPA-101 actually administered (Table 3). Statistical analysis using analysis of variance of dose-normalized parameters and regression analysis of non-dose-normalized parameters confirmed the assumption of linear pharmacokinetics.

The mean $t_{1/2}$ was between 70 and 95 h and did not show any tendency to change with increasing dose. The mean volume of

TABLE 2. AE and relationship to KBPA-101

Dose for cohort (mg/kg)	Group (no. of patients)	AE	No. of AE with intensity and relationship[a]								Total R and UR
			Mild		Moderate		Severe		Total		
			UR	R	UR	R	UR	R	UR	R	
0.1	KBPA-101 (6)	Pressure on heart site	0	1	0	0	0	0	0	1	1
0.4	KBPA-101 (6)	Dizziness	1	0	0	0	0	0	1	0	1
		Feeling of pressure in the head	0	1	0	0	0	0	0	1	1
		Rhinitis	0	0	1	0	0	0	1	0	1
		Sore throat	1	0	0	0	0	0	1	0	1
	Placebo (2)[b]	Common cold	1	0	0	0	0	0	1	0	1
		Nausea	0	0	0	1	0	0	0	1	1
1.2	KBPA-101 (6)	Muscle ache	1	0	0	0	0	0	1	0	1
4.0	KBPA-101 (6)	Headache	0	1	0	0	0	0	0	1	1

[a] UR, unrelated or unlikely; R, possible, probable, or related.
[b] This is the only placebo group with AE.

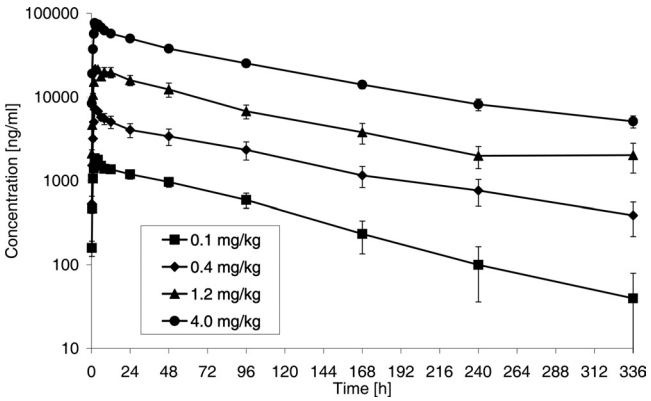

FIG. 1. Logarithmic representation of the plasma concentration of KBPA-101 (mean ± standard error) versus time following single ascending intravenous infusions of KBPA-101 to four cohorts of healthy subjects representing four dose regimens (0.1, 0.4, 1.2, and 4 mg/kg) measured over 336 h (14 days). For each cohort (comprising eight subjects), six subjects were randomized to receive KBPA-101, and two subjects were randomized to receive placebo.

distribution was between 4.76 and 5.47 liters. This is consistent with a principal distribution of KBPA-101 in the central compartment and typical for compounds of high molecular weight (15).

Immunogenicity. There was no tendency toward a change or systematic increase in the concentration of anti-KBPA-101 antibodies with dose or over time (up to 14 days after the start of infusion). All median data were within the baseline variation between all the groups. Therefore, the data indicate that single ascending intravenous infusions of KBPA-101 did not induce an antibody response in healthy subjects.

DISCUSSION

In this paper, we report the first clinical evaluation of a new fully human MAb against O-polysaccharide of *P. aeruginosa* IATS serotype O11. KBPA-101 was well tolerated following the administration of single intravenous doses of 0.1, 0.4, 1.2, and 4 mg/kg of body weight to healthy adults. None of the subjects experienced dose-limiting toxicity; therefore, the maximum tolerated dose of KBPA-101 was not established in this study.

Biological/biotechnology-derived proteins can induce an unintended immune response that can comprise antibody formation, T-cell activation, or the activation of the innate immune system. Therefore, the absence of antibodies against KBPA-101, up to 14 days following infusion, is an important finding. Other fully human therapeutic proteins were previously found to elicit an immunogenic reaction with direct consequences for the therapeutic dosing regimen (1, 5, 19).

No subject of the trial reported here experienced a serious AE during the study, and no clinically significant abnormalities were observed in clinical laboratory tests.

This finding is in line with the safety profile of the trials reported previously by Harrison et al. and Saravolatz et al. (9, 17). In both studies, IgM preparations were demonstrated to be safe and well tolerated, and no severe AE related to the application of the drug were found. In both clinical trials, those investigators paid special attention to complement activation and the potential of excessive complement activation through the infused antibodies. Saravolatz et al. monitored serum complement activity (C3, C4, and CH50) and observed no indication of acute complement consumption after the infusion of MAb. Harrison et al. reported equally favorable results. There was no evidence that the infusions of IgM evoked acute complement consumption. Similarly, the infusion of up to 8 mg/kg body weight of a human pan-anti-LPS IgM antibody did not elicit AE in a clinical trial with neutropenic patients (4). Furthermore, no clinical or laboratory evidence of treatment-related toxicity has been observed at any dose level.

Dose-proportional increases in C_{max} and $AUC_{(0\rightarrow inf)}$ were observed following the administration of doses of 0.1, 0.4, 1.2, and 4.0 mg/kg, but systemic CL, V_{ss}, and V_z values were similar across all doses. These results indicate that KBPA-101 exhibited linear pharmacokinetics across the dose range of 0.1 to 4 mg/kg, thus greatly facilitating therapy planning and further development.

The mean $t_{1/2}$ of KBPA-101 ranged between 70 and 95 h.

TABLE 3. Pharmacokinetic parameters of KBPA-101 following single ascending intravenous infusions

Parameter	Mean result ± SD for KBPA-101 dose of[a]:			
	0.1 mg/kg	0.4 mg/kg	1.2 mg/kg	4.0 mg/kg
AUC (h/μg/ml)[b]	160.4 ± 75.8	657.5 ± 389.9	2,282.9 ± 1,177.4	7,432 ± 1,746.9
$AUC_{(0\rightarrow tn)}$ (h/μg/ml)[b]	141.9 ± 67.2	584.5 ± 312	1,966.4 ± 903.4	6,695.7 ± 1,431.6
% AUC	18.9 ± 8.9	9.7 ± 5.7	11.1 ± 7.4	9.4 ± 3.6
C_{max} (ng/ml)[b]	1,877 ± 333.6	7,571.5 ± 714.6	24,922.8 ± 4,218	83,197 ± 10,661.6
T_{max} (h) (median)[c]	2.2 ± 0.3 (2.0)	3.2 ± 2.3 (2.5)	3.8 ± 4 (2.25)	2.8 ± 0.9 (2.5)
CL (liters/h)	0.054 ± 0.022	0.120 ± 0.195	0.053 ± 0.040	0.039 ± 0.010
V_{ss} (liters)	4.8 ± 0.9	4.9 ± 0.7	4.9 ± 0.6	5 ± 0.6
V_z (liters)	4.86 ± 0.99	5.47 ± 0.99	4.76 ± 1.07	5.13 ± 0.87
$t_{1/2}$ (h)	69.9 ± 24.3	85.8 ± 51.4	85.9 ± 41.2	95.2 ± 20.2
AUC dose, normalized[d]	22.1 ± 10.5	22.7 ± 12.9	26.6 ± 13.7	27.3 ± 7.4
$AUC_{(0\rightarrow tn)}$ dose, normalized[d]	19.5 ± 9.3	20.2 ± 10.3	22.9 ± 10.5	24.6 ± 5.8
C_{max} dose, normalized[d]	259.2 ± 48.3	263.6 ± 37.5	288.6 ± 48.7	307.6 ± 57

[a] $n = 6$ for each dose.
[b] Regression analysis of non-dose-normalized parameters revealed no statistically significant difference of the intercept from zero.
[c] Median values are in parentheses.
[d] Analysis of variance statistical analysis did not identify any difference between dose-normalized mean values.

This roughly coincides with the reported half-life of 5 days for IgM MAbs (12).

Pharmacokinetic data for human IgM MAbs directed against *P. aeruginosa* were reported previously; however, the data were obtained from studies with infected patients (4, 9, 16). Saravolatz et al. previously found a $t_{1/2}$ of 52.3 to 99.1 h (range of means) for five human anti-*P. aeruginosa* IgM MAbs that were manufactured with a technology comparable to that used for KBPA-101. Those IgMs were administered to 12 patients who were thought to be at high risk for developing *P. aeruginosa* infection but not presently infected (17). Although those patients were not healthy volunteers, as in our case, the main features of that study are comparable to ours and show comparable results for a number of measured parameters.

C_{max} values of 1.87 to 83.2 μg/ml of KBPA-101 following doses of 0.1 to 4.0 mg/kg body weight are comparable to C_{max} ranges of 16.0 to 24.2 μg/ml following a single-dose IgM infusion of 0.6 mg/kg body weight in noninfected patients reported previously by Saravolatz (17). Doubling the dose in the same group of noninfected patients resulted in plasma concentrations between 20.8 and 34.9 μg/ml Thus, the pharmacokinetic parameters observed previously by Saravolatz et al. are in the same range of magnitude as those reported here.

Preclinical studies of a murine burn wound sepsis model suggested 3 μg/ml KBPA-101 to be the minimal protective serum concentration. A pharmacokinetic computer simulation of single-dose data for healthy volunteers based on dose intervals of 2, 3, and 4 days and $t_{1/2}$ values of 30 and 90 h predicted that a dose regimen of 1.2 mg/kg administered every third day will result in trough plasma concentrations over 3 μg/ml for at least 9.6 days.

In summary, the increased incidence of antibiotic-resistant strains of *P. aeruginosa* in both nosocomial and community-acquired infections and the associated morbidity and mortality highlight the need for novel therapies to augment present antimicrobial approaches (3, 7). The present study demonstrates the safety of KBPA-101, a human MAb against *P. aeruginosa*, in healthy volunteers. These results warrant further testing of KBPA-101 with *P. aeruginosa*-infected patients in order to confirm the therapeutic potential of this compound.

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Hedvika Lazar and Christophe Hammer are employed by Kenta Biotech AG and hold stocks in the company. All other authors are not affiliated with Kenta Biotech AG and do not hold stocks in Kenta Biotech AG.

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