Pharmacokinetics and safety of panobacumab: specific adjunctive immunotherapy in critical patients with nosocomial Pseudomonas aeruginosa O11 pneumonia

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Objectives: Nosocomial Pseudomonas aeruginosa pneumonia remains a major concern in critically ill patients. We explored the potential impact of microorganism-targeted adjunctive immunotherapy in such patients.

Patients and methods: This multicentre, open pilot Phase 2a clinical trial (NCT00851435) prospectively evaluated the safety, pharmacokinetics and potential efficacy of three doses of 1.2 mg/kg panobacumab, a fully human monoclonal anti-lipopolysaccharide IgM, given every 72 h in 18 patients developing nosocomial P. aeruginosa (serotype O11) pneumonia.

Results: Seventeen out of 18 patients were included in the pharmacokinetic analysis. In 13 patients receiving three doses, the maximal concentration after the third infusion was 33.9 ± 8.0 mg/mL, total area under the serum concentration–time curve was 5397 ± 1993 mg h/mL and elimination half-life was 102.3 ± 47.8 h. Panobacumab was well tolerated, induced no immunogenicity and was detected in respiratory samples. In contrast to Acute Physiology and Chronic Health Evaluation II (APACHE II) prediction, all 13 patients receiving three doses survived, with a mean clinical resolution in 9.0 ± 2.7 days. Two patients suffered a recurrence at days 17 and 20.

Conclusions: These data suggest that panobacumab is safe, with a pharmacokinetic profile similar to that in healthy volunteers. It was associated with high clinical cure and survival rates in patients developing nosocomial P. aeruginosa O11 pneumonia. We concluded that these promising results warrant further trials.

Keywords: ventilator-associated pneumonia, IgM, monoclonal antibody, pharmacokinetics

Introduction

Pseudomonas aeruginosa pneumonia is one of the most common nosocomial infections in critically ill patients.1–4 The recent emergence and spread of multidrug-resistant strains may explain crude mortality rates as high as 40%–70%.5–7 The membrane-bound virulence factor lipopolysaccharide (LPS) found on P. aeruginosa species elicits an IgM-mediated antibody response, which is a potent activator of the complement cascade and significantly enhances the antibacterial response. The IgM response, however, takes several days to develop fully, a delay that could increase the risk of death. In this context, combination of antibiotics with specific adjunctive immunotherapy is expected to improve the management and outcome of such infections.

Panobacumab is a fully human monoclonal antibody of the IgMκ isotype, which is directed against the LPS O-polysaccharide moiety of P. aeruginosa serotype IATS O11,8,9 which accounts for
Patients and methods

Patients and definitions

Patients ≥ 18 years with nosocomial pneumonia caused by *P. aeruginosa* O11 were screened for eligibility according to clinical and microbiological criteria. Pneumonia was suspected in the presence of a new or progressing pulmonary infiltrate on frontal chest radiography associated with one of the following criteria: temperature > 38°C or < 36°C; white blood count > 10^9/mm³ or < 10^9/mm³; purulent sputum. Diagnosis of ventilator-associated pneumonia (VAP) further required either a non-protected bronchoalveolar lavage (BAL) or mini-BAL positive for *P. aeruginosa* ≥ 10^6 cfu/mL or a protected mini-BAL positive for *P. aeruginosa* ≥ 10^6 cfu/mL. According to recent recommendations, diagnosis of hospital-acquired pneumonia (HAP) further required an endotracheal aspirate (ETA) positive for *P. aeruginosa* ≥ 10^6 cfu/mL and a clinical pulmonary infection score (CPIS) of ≥ 6.

*P. aeruginosa* serotype was determined by specifically developed PCR or by conventional microbiology/serology. Reasons for exclusion included complement deficiency, clinically relevant liver insufficiency, disseminated intravascular coagulation, transplant-related immunosuppressive treatment, HIV infection, septic shock with blood pressure < 90 mmHg despite vasopressors, neutropenia and pregnancy. The study was approved by all local ethics committees. Written informed consent was obtained either from the patient or their next of kin prior to screening or during the screening process according to local ethics requirements.

The study was conducted in full compliance with the principles of the Declaration of Helsinki and in accordance with the ‘International ethical guidelines for biomedical research involving human subjects’ as laid down by the CIOMS in collaboration with the WHO and the GCP guideline CPMP/ICH/135/95. The study protocol was submitted to independent local ethics committees and approved prior to the start of the study. Clinical trial applications were submitted to the regulatory authorities of each country and were approved by these institutions. The study was registered at clinicaltrials.gov under the number NCT00851435.

Procedures

Concentrations of panobacumab in serum were determined by ELISA. Maximal concentrations (C_max) were measured at the end of each infusion and minimal concentrations (C_min) just before the next infusion. The following non-compartmental pharmacokinetic (PK) parameters of panobacumab were derived from each individual serum concentration versus time profile using standard methods. Calculations were performed using WinNonlin (Pharsight Corporation, version 5.2). The total area under the curve including all three doses (AUC_t愁) was calculated with the linear trapezoidal rule for the ascending and the log-linear trapezoidal rule for the descending parts. This was extrapolated to infinity from the last measured concentration of the third dose ([C_l(t)]) and the slope of the terminal phase of the natural logarithm of the serum concentration (lnC) versus time (t) plot (third dose). AUC_t愁 values were estimated from the slope of lnC versus t of the terminal linear phase (third dose), including at least four data points. Total serum clearance (CL) was calculated from the ratio of total dose (D_total) and AUC_t愁, and volume of distribution (V) from the product of CL and t1/2/ln2. Beside these calculations for individual patients, the averaged serum concentration–time curve was fitted with the Solver tool of Excel (MS Office 2003) to both a one- and a two-compartment model, applying a bi- (infusion, elimination) and tri- (infusion, distribution, elimination) exponential function, respectively. Both functions were each the sum of the contributions of all three single doses. The respective concentration contributions of the single doses were considered as follows: Equation 1 describes the infusions over 2 h for both models:

\[ C_{\text{infusion}}(t) = C_s \times (1 - e^{-\lambda_1 \times t}) \text{ for } t \geq t_{\text{start}} \]

where \( C_{\text{infusion}}(t) \) is the concentration at time \( t \) during the infusion, \( C_s \) is the concentration at steady state of a constant infusion, \( \lambda_1 \) is the rate constant of the elimination phase and \( t_{\text{start}} \) is \( t \) at the start of the individual infusion. \( C_{\text{infusion}}(t) \) was only considered for the duration of the infusions. The contribution of each dose after infusion stop was calculated as shown in Equation 2 for the one-compartment model and Equation 3 for the two-compartment model:

\[ C(t) = C_{\text{infusion}}(t_{\text{infusion stop}}) \times e^{-(\lambda_1 + \lambda_2) \times t} + C_1 \times e^{-(\lambda_1 + \lambda_2) \times t} \]

where \( C_{\text{infusion}}(t_{\text{infusion stop}}) \) corresponds to \( C_{\text{infusion}}(t) \) at infusion stop (see Eq. 1) and \( C_1 \) and \( C_2 \) to the single contributions of the fast and terminal phases to \( C_{\text{infusion}} \) at infusion stop, the sum of \( C_2 \) and \( C_1 \) equals \( C_{\text{infusion}} \) at infusion stop. Fitted parameters were \( C_0 \), \( C_1 \), \( C_2 \), \( \lambda_1 \), \( \lambda_2 \) and \( \lambda_3 \).

At screening, patient medical history and underlying conditions were noted, and physical examination, vital signs, electrocardiogram, chest X-ray and risk factors for pneumonia were recorded. Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) and CPIS scores were calculated at study entry. Except APACHE II, they were assessed daily until day 30 or discharge from the intensive care unit (ICU).

Blood samples were obtained at study entry, at panobacumab administration and during the course of the study, for blood culture and characterization of the inflammatory response: procalcitonin (PCT) and C-reactive protein (CRP); for measurements of complement level and potential immunogenicity; for PK parameters; and for haematology and clinical chemistry follow-up. Respiratory samples were evaluated for quantitative BAL lung bacterial burden using the reference method and, in some patients, for the presence of panobacumab. Panobacumab, 1.2 mg/kg body weight, was administered as a 2 h infusion on days 1, 4 and 7, at the same time on each of those days. This dose was selected based on its safety and PK profile from the Phase 1 study and to maintain panobacumab serum concentrations in the target population at ≥ 1.0 L.11

-20% of all *P. aeruginosa* isolates. Panobacumab demonstrated a dose–response relationship for protection against lethal challenges with *P. aeruginosa* in a murine burn wound sepsis model and protection from local infection in an acute lung infection model in mice. In a Phase 1 study in healthy volunteers, single ascending doses of between 0.1 and 4 mg/kg panobacumab were infused over 2 h. The study drug was safe and well tolerated and no immunogenicity to panobacumab was detected. Panobacumab has shown linear pharmacokinetics, with a half-life (mean ± SD) of between 70 ± 24 and 95 ± 20 h, and a volume of distribution (mean ± SD) of between 4.8 ± 1.1 and 5.5 ± 1.0 L.11

A multicentre, open pilot Phase 2a trial was carried out to evaluate the safety, pharmacokinetics and potential efficacy of repeated doses of panobacumab in patients with nosocomial pneumonia caused by *P. aeruginosa* serotype O11.
study drug. BAL and ETA samples were taken according to clinical need and were used to test for the presence of panobacumab. Samples contaminated with blood were excluded. The occurrence of adverse events was monitored throughout the study.

The clinical outcome of HAP or VAP was determined by assessment of clinical signs and symptoms as well as analysis of chest X-rays. Outcome was reported as resolution, recurrence (relapse if caused by the same pathogen), continuation or death during the study period.

Study profile and analysis

Figure 2 summarizes the profile of the study and subsequent analysis. The safety population was defined as all patients enrolled in the study who received at least one dose of study medication and who reported at least one subsequent treatment assessment. The intent to treat (ITT) population was defined as patients in the safety population who had pneumonia caused by *P. aeruginosa* O11 and who received at least one dose of panobacumab. The PK population was defined as all patients with data on panobacumab serum levels in whom PK assessment could be determined. The per protocol (PP) population was defined as patients who completed the three study drug administrations. Efficacy analysis was performed in the ITT and PP populations. Adverse events were coded using the definitions of the medical dictionary for regulatory activities (MedDRA). When an adverse event occurred more than once for any patient the maximal severity and worst case causality were counted. Assessment of immunogenicity was performed by analysing the presence of circulating anti-idiotype antibodies to panobacumab as previously described.11

Statistical analysis

Data management and statistical analysis were performed using SAS version 9.2. A sample size of at least 12 patients evaluable for safety with at least two consecutive infusions of panobacumab was considered sufficient for this pilot Phase 2a trial. All data are presented as median (interquartile range; IQR) unless otherwise stated.

Results

**Patient demographic data and characteristics**

Eighteen critically ill patients (15 VAP and 3 HAP) with confirmed nosocomial pneumonia caused by *P. aeruginosa* O11 were enrolled. A second assessment did not confirm
Table 1. Patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Population</th>
<th>Safety (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) (years)</td>
<td>71.5 (15.3)</td>
</tr>
<tr>
<td>Female:Male</td>
<td>3:15</td>
</tr>
<tr>
<td>BMI, median (IQR) (kg/m²)</td>
<td>26.1 (4.6)</td>
</tr>
<tr>
<td>VAP-HAP</td>
<td>15.3</td>
</tr>
<tr>
<td>Pneumonia (polybacterial:monobacterial)</td>
<td>12:6</td>
</tr>
<tr>
<td>Empirical antibiotic therapy (appropriate:inappropriate:NA)</td>
<td>14:3:1</td>
</tr>
<tr>
<td>CPIS</td>
<td>9.0 (1.8)</td>
</tr>
<tr>
<td>APACHE II</td>
<td>17.0 (4.0)</td>
</tr>
<tr>
<td>COPD</td>
<td>6</td>
</tr>
<tr>
<td>SOFA</td>
<td>6.0 (3.5)</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>11</td>
</tr>
<tr>
<td>Time from hospital admission to suspicion of pneumonia/median (IQR) (days)</td>
<td>16.0 (14.3)</td>
</tr>
<tr>
<td>Time from ICU admission to suspicion of pneumonia/median (IQR) (days)</td>
<td>9.5 (9.5)</td>
</tr>
</tbody>
</table>

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

P. aeruginosa O11 as the causative pathogen in one patient. Baseline patient demographics and characteristics are outlined in Table 1. All patients were under intensive care management and reasons for ICU admission were respiratory failure (n=7), multiple trauma (n=3), CNS disorders (n=3) and miscellaneous (n=5).

Six patients presented a monobacterial and 12 a polybacterial pneumonia. Associated pathogens were: Serratia marcescens (n=2), Klebsiella pneumoniae (n=2), Streptococcus spp. (n=2) and enterobacteria, Providencia rettgeri, Klebsiella oxytoca, Staphylococcus spp., Proteus mirabilis and Escherichia coli (n=1). Candida spp. were cultured from the respiratory samples of five patients.

From antibiograms collected from 16 patients, 7 P. aeruginosa were resistant to carbapenems, 6 to ciprofloxacin, 2 to aminoglycosides, 3 to ceftazidime and 1 to piperacillin/tazobactam, and in 5 out of 11 cases P. aeruginosa was resistant to ticarcillin and clavulanic acid.

Of 18 patients, 15 were initially treated with at least one of the following antibiotics: piperacillin/tazobactam, ceftazidime, imipenem/cilastatin, meropenem or aztreonam. Four out of 18 patients were initially given single antibiotic therapy and the remaining patients a combination of two or more antibiotics. Overall, aminoglycosides were administered to nine patients, ciprofloxacin and ceftazidime to eight, nebulized colistin to one and piperacillin plus tazobactam to four patients. Antibiotic treatment lasted from 6 to 27 days, and its mean duration was 12.06 ± 5.47 days. Empirical antibiotic treatment was considered inappropriate in two patients.

Pharmacokinetics of panobacumab

Panobacumab pharmacokinetics was assessed in 17 patients (PK population), including 13 who received three doses (PP population). Table 2 shows detailed PK parameters in all patients.

The serum concentration–time curves of the PP population followed either a one- (n=3) or a two- (n=10) compartment model by visual inspection. While the terminal kinetic phase was well defined in all concentration–time curves (t₁/₂ in Table 3), the fast phases of the individual concentration–time curves were not well defined. We therefore averaged the serum concentrations of all patients in the PP population and applied a two-compartment model fit (Figure 3). The two-compartment model demonstrated a t₁/₂ in the fast phase of 10.3 h (41% of extrapolated concentration at t₀). The t₁/₂ of the slow phase (59% of extrapolated concentration at t₀) was 90.1 h, similar to the average shown in Table 2. For comparison, the fit with the one-compartment model resulted in a shorter t₁/₂ of 58.2 h compared with the value in Table 3 and significant deviations between the fit and the serum concentrations (Figure 3), indicating that the two-compartment model is more appropriate. As shown in Table 2 and Figure 3, Cₘₐₓ and Cₘᵟᵢₙ (C at 72 h after infusion start) increased from the third to the first infusion.

Panobacumab was detected in BAL and ETA samples in 4 out of 12 patients in several samples throughout the study period (days 3–21).

Safety

No local or systemic adverse events to the infusion of panobacumab were directly reported. Electrocardiographic measurements, including of QTc, did not show any trend relating to the study drug (data not shown).

A total of 96 adverse events were reported in the safety population, most of which were laboratory abnormalities associated with the underlying disease. Four patients experienced a total of eight adverse events evaluated to be potentially related to panobacumab. Erythema was reported by two patients, one of whom experienced concomitant eosinophilia. Both cases resolved without treatment within 5 days and both patients continued the study. One patient had evolving cholestasis prior to study drug administration. This patient received one dose of study drug but worsening cholestasis followed by neutropenia and gastrointestinal bleeding precluded further administration of panobacumab. He died on day 17 from multi-organ failure linked to this event, which was probably caused by the deterioration of his general condition. This patient was excluded from the PP population for analysis. Increased prothrombin time after cardiac arrest was deemed possibly related to panobacumab and was reported by the fourth patient. This patient also received one dose of study drug and died on day 17 after a second cardiac arrest, which was judged unrelated. This patient was also excluded from the PP population.

Two other patients were excluded from the PP population after the occurrence of a serious adverse event evaluated to be unrelated to panobacumab administration. One patient died on day 3 of the study due to gastrointestinal haemorrhage. One patient was excluded from the study after suffering haemolysis due to a mismatch in blood group antigens during a transfusion. These two patients had received one dose of the study drug. Eventual immunogenicity was not detected in any patient (data not shown).
Overall 30 day survival was 82% and 100% in the ITT and PP populations, respectively (Table 3). Both populations had comparable APACHE II scores, but three patients in the ITT population died, one on day 3 and two on day 17. In all cases, they had received only one dose of panobacumab. As mentioned above, reasons for death were irreversible multi-organ failure, cardiac arrest and massive gastrointestinal haemorrhage. Of the four patients in the ITT population who received one dose of study drug, none achieved clinical resolution at any time during the study period. In contrast, all patients who received three doses of panobacumab (PP population) did achieve clinical resolution (time to clinical resolution $9.0 \pm 2.7$ days), including two patients who received inappropriate empirical antimicrobial therapy. Of these patients, two experienced a recurrence 17 and 20 days after initial resolution that was again caused by $P. \text{aeruginosa}$ O11. The average time from suspicion of pneumonia to panobacumab administration was $1.5 \pm 0.8$ days for patients who achieved clinical resolution and did not experience a recurrence. It was $3.5 \pm 0.7$ days for the two patients with recurrence. Both were tracheotomized without resolution of the underlying primary reason for ICU admission at time of relapse. Five other patients achieved clinical resolution as well as having a tracheostomy. Among them, two had received inappropriate empirical antimicrobial therapy.

The evolution of biological parameters was similar in all groups. Patients with clinical resolution showed rapid decrease in serum panobacumab levels. The elimination phase half-life was $102.3 \pm 47.8$ hours ($35.0 – 179.0$ hours) for the three-dose group. Five other patients achieved clinical resolution as well as having a tracheostomy. Among them, two had received inappropriate empirical antimicrobial therapy.

### Table 2. PK parameters of panobacumab at a dose of 1.2 mg/kg in the PP and PK populations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PP ($n = 13$)</th>
<th>PK ($n = 17$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>$78.0 \pm 28.4$ (53 – 135)</td>
<td>$77.2 \pm 26.3$ (53 – 135)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (1st dose, C at 2 h), µg/mL</td>
<td>$21.2 \pm 5.0$ (12.5 – 28.5)</td>
<td>$21.2 \pm 5.1$ (12.5 – 28.5)</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (1st dose, C at 72 h), µg/mL</td>
<td>$6.2 \pm 3.4$ (0.14 – 11.5)</td>
<td>$6.2 \pm 3.4$ (0.14 – 11.5)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (2nd dose, C at 74 h), µg/mL</td>
<td>$28.9 \pm 6.0$ (19.9 – 37.6)</td>
<td>$28.9 \pm 6.0$ (19.9 – 37.6)</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (2nd dose, C at 144 h), µg/mL</td>
<td>$10.7 \pm 4.5$ (3.4 – 16.3)</td>
<td>$10.7 \pm 4.5$ (3.4 – 16.3)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (3rd infusion, C at 146 h), µg/mL</td>
<td>$33.9 \pm 8.0$ (24.3 – 47.1)</td>
<td>$33.9 \pm 8.0$ (24.3 – 47.1)</td>
</tr>
<tr>
<td>C at 216 h, µg/mL</td>
<td>$13.7 \pm 4.9$ (7.6 – 20.4)</td>
<td>$13.7 \pm 4.9$ (7.6 – 20.4)</td>
</tr>
<tr>
<td>AUC$_{\text{total}}$, µg h/mL</td>
<td>$5397 \pm 1993$ (2477 – 8600)</td>
<td>$5397 \pm 1993$ (2477 – 8600)</td>
</tr>
<tr>
<td>$t_{1/2}$, h (linear terminal phase of 3rd dose)</td>
<td>$102.3 \pm 47.8$ (35.0 – 179.0)</td>
<td>$102.3 \pm 47.8$ (35.0 – 179.0)</td>
</tr>
<tr>
<td>Volume of distribution, L</td>
<td>$7.5 \pm 2.8$ (4.1 – 12.7)</td>
<td>$7.5 \pm 2.8$ (4.1 – 12.7)</td>
</tr>
<tr>
<td>Serum clearance, mL/h</td>
<td>$57.9 \pm 21.7$ (25.7 – 94.7)</td>
<td>$57.9 \pm 21.7$ (25.7 – 94.7)</td>
</tr>
</tbody>
</table>

*Results shown are mean ± SD (range).

*Patients received three infusions (0–2 h, 72–74 h, 144–146 h).

### Table 3. Efficacy of panobacumab in the safety, ITT, PK and PP populations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Safety ($n = 18$)</th>
<th>ITT ($n = 17$)</th>
<th>PK ($n = 17$)</th>
<th>PP ($n = 13$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patient survival at 30 days/ end of study</td>
<td>15 (83.3%)</td>
<td>14 (82.4%)</td>
<td>15 (88.2%)</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>Clinical outcome resolution</td>
<td>11 (61.1%)</td>
<td>11 (64.7%)</td>
<td>11 (64.7%)</td>
<td>11 (84.6%)</td>
</tr>
<tr>
<td>recurrence</td>
<td>2 (11.1%)</td>
<td>2 (11.7%)</td>
<td>2 (11.7%)</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>continuation*</td>
<td>5 (27.8%)</td>
<td>4 (23.5%)</td>
<td>4 (23.5%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Three patients with continuation died, one on day 3 and two on day 17.

### Figure 3. Averaged serum concentration–time curves of panobacumab.

Comparison of a one-compartment model fit (a) and a two-compartment model fit (b). Symbols show average serum concentrations with standard deviations; the red lines show the fitted functions.
in PCT and CRP values, with increase in those with clinical continuation or recurrence.

Discussion

Panobacumab displays linear, disease-independent pharmacokinetics with an elimination $t_{1/2}$ and a volume of distribution comparable to other IgM antibodies. Despite the severity of the underlying inflammatory lung disease, the PK profile of panobacumab, including $C_{\text{max}}$ after first infusion, serum half-life and inter-individual variability, was close to that reported in healthy volunteers receiving a single administration. The $t_{1/2}$ values of the elimination phase did not differ significantly between the data from this study and those from the Phase 1 study. The fast concentration decrease starting at infusion stop observed in most patients probably reflects the distribution of panobacumab from serum to interstitial fluid of well-perfused tissue. Serum panobacumab accumulation was observed over successive administrations, raising the question of increasing the interval between each administration in further studies. It is not known whether panobacumab accumulation is beneficial or not. It has to be pointed out, however, that panobacumab, like most IgM antibodies, was well tolerated and induced neither immunogenicity nor serious adverse effects.

The high clinical cure, and mostly the survival rate, are in contrast to the severity of the enrolled population and its expected mortality following the assessment with validated scoring systems such as APACHE II, SOFA and CIRS. This suggests a potential therapeutic impact of panobacumab as an adjunctive therapy; nevertheless, this open-label, Phase 2a study on the safety and pharmacokinetics of panobacumab presents some major limitations that may bias the interpretation of potential efficacy. First, the population size was small. Second, in the absence of a control group, the survival benefit provided by panobacumab cannot be definitively demonstrated. Eventually, the effect of antimicrobial therapy on outcome and clinical cure rate cannot be separated from the study drug effect. At the time of panobacumab administration, some patients had been receiving antibiotics for >1 day. This was due to the duration of the screening process since the $P. \text{aeruginosa}$ serotype O11 had to be confirmed prior to study drug administration and the consent process. The survival rate of 100% in the group of patients who completed the full treatment cycle may have been biased by the exclusion of patients who died rapidly. Finally, the current findings are restricted to serotype O11 and not for other $P. \text{aeruginosa}$ strains.

The incidence of pneumonia recurrence after initial infection by $P. \text{aeruginosa}$ ranges from 25% to 40%. Interestingly, in the present study, the recurrence rate of pneumonia was also low compared with previous studies. It may be due to a prolonged biological effect of the antigen in tissues. Detection of an IgM monoclonal antibody in BAL and ETA samples of patients with pneumonia was shown here for the first time. The passage of panobacumab from the blood into the alveolar space might partially explain its efficacy.

We conclude that these data demonstrate the safety and favourable PK profile of panobacumab, a fully human anti-LPS monoclonal IgM, in critically ill patients with $P. \text{aeruginosa}$ O11 nosocomial pneumonia. Moreover, high clinical cure and survival rates suggest potential clinical efficacy of this adjunctive immunotherapy, warranting further clinical trials.

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Transparency declarations

V. G.-K., M. R., V. G., H. L., H. K. and A. P. are employees of Kenta Biotech (Bern, Switzerland). All other authors: none to declare.

The sponsor (Kenta Biotech, Bern, Switzerland) had no role in data collection and storage, which was undertaken by independent investigators. The sponsor had full access to all the data, was involved in the writing of the report and had final responsibility for the decision to submit the paper for publication.

Author contributions

M. T., P. E., J. C., H. L., M. D. R., A. P. and V. G. were involved in the study design. M. T., P. E., J. G., J. J. R., Q. L., A. D., E. M., P. F. L., E. J. G., H. K., H. L., M. D. R., A. P. and V. G. were involved in patient enrolment, data collection, analysis or interpretation. S. D. K. performed the PK analysis and interpretation. All authors contributed to the manuscript.

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