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Phase I Study of the Tolerability and Pharmacokinetics of Palifermin in Children Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

The maximum tolerated dose of palifermin, a keratinocyte growth factor, in children is not known, and its pharmacokinetics in this population has not been well studied. This is a phase I study of palifermin was designed to evaluate its tolerability at doses of 40, 60, and 90 μg/kg/day in children age 2–18 years of age, receiving a myeloablative preparative regimen for allogeneic hematopoietic stem cell transplantation (HSCT). In each cohort, palifermin was given for 3 consecutive days before the preparative regimen and for 3 days after the stem cell infusion. Twelve patients were enrolled. Palifermin 90 μg/kg/day was tolerated in 6 patients without dose-limiting toxicity. All patients had at least 1 adverse event, mostly National Cancer Institute grade 1 or 2 severity. Skin rash, grade 2 or lower, was the most common adverse event, seen in 67% of patients. Only 3 patients (25%) had mucositis. The area under the concentration–time curve increased proportionally to the dose, and approximately 97% of palifermin exposure occurred in the first 24 hours after administration. Palifermin clearance increased linearly with body weight, supporting dosing by body weight. The mean clearance was 1893 mL/hour/kg, and it did not change significantly between administration of the first and last doses (P =.80). The mean elimination half-life was 4.6 hours. Our data show that palifermin was tolerated at a dose of 90 μg/kg/day, and exhibits linear pharmacokinetics in children undergoing allogeneic HSCT.

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Keywords

Keratinocyte growth factor; Toxicity; Clearance

INTRODUCTION

Mucositis is a major factor contributing to morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HSCT), commonly developing after radiation-based conditioning regimens [1,2]. As a consequence of damage to the oral, esophageal, gastric, and colonic mucosa, HSCT recipients may require i.v. analgesia and total parenteral nutrition. Mucositis secondary to radiation and chemotherapy predisposes to systemic infections and graft-versus-host disease (GVHD) [3].

Palifermin (recombinant human keratinocyte growth factor [KGF]; Kepivance; Biovitrium, Stockholm, Sweden) was approved in December 2004 by the U.S. Food and Drug Administration for the prevention of mucositis in adults with hematologic malignancies receiving myeloablative radiation and chemotherapy with stem cell support. KGF receptor is 1 of 4 fibroblast growth factors expressed on epithelial cells of the gastrointestinal system, liver, lung, pancreas, bladder, and skin, but not on hematopoietic cells [4]. Palifermin affects epithelial cell differentiation, proliferation, and growth, resulting in increased thickness of the epithelial mucosa in the oral mucosa and gastrointestinal tract [5]. Preclinical murine models indicate that recombinant KGF is highly protective for gastrointestinal [6] and pulmonary toxicity [7] in mice receiving radiation and chemotherapy, and may have beneficial effects in ameliorating GVHD [8]. Peritransplantation administration of palifermin has been shown to improve thymopoiesis and speed immune reconstitution in rodents [9,10] and nonhuman primates [11].

Clinically, palifermin at a dose of 60 μg/kg/day has been shown to reduce the incidence and duration of severe oral mucositis in adult patients with hematologic malignancies undergoing autologous HSCT [12]. However, published clinical and pharmacokinetic data on palifermin treatment in children and adolescents are limited, and palifermin dosing has not been established in the pediatric setting.

The objectives of this prospective Phase I study were to (1) determine the maximum tolerated dose (MTD) of palifermin, evaluating its use at 3 dose levels (below, at, and above the recommended adult dose), (2) describe the nonhematologic toxicities related to palifermin administration in children with hematologic malignancies undergoing a first HSCT, and (3) study the pharmacokinetics of palifermin at each dose level.

METHODS

Study Population

The study was conducted at St. Jude Children's Research Hospital in Memphis, Tennessee, and was approved by the hospital's Institutional Review Board. Consent was obtained from all parents/guardians, and assent was obtained from all children age >7 years.

Eligibility criteria included age ≥2 to <18 years, a diagnosed hematologic malignancy, and scheduled to receive a bone marrow stem cell graft from a 5/6 or 6/6 HLA allele-matched related or unrelated donor after a total body irradiation (TBI)- and cyclophosphamide (Cy)-based preparative regimen. Patients had to have adequate renal, hepatic, cardiac, and pulmonary function as determined by institutional guidelines. Exclusion criteria included oral ulcerations and gastrointestinal bleeding active or within 30 days of enrollment; known

hypersensitivity to *Eschericia coli*–derived proteins; any active bacterial, fungal, or viral infection within 2 weeks before enrollment; and previous autologous or allogeneic HSCT. All patients had a performance score of 100.

Patients with a matched sibling donor (MSD) received conditioning with Cy 60 mg/kg/day on days −6 and −5 and 12 Gy TBI in 8 fractions of 150 cGy each given twice daily on days −4 to −1. GVHD prophylaxis was given with cyclosporine starting on day −2 and mycophenolate mofetil starting on day 0. Patients with a matched unrelated donor (MUD) received conditioning with 12 Gy TBI on days −8 to −5, thiotepa 5 mg/kg/dose twice daily on day −4, Cy 60 mg/ kg/day on days −3 and −2, and rabbit antithymocytic globulin 3 mg/ kg/day on days −3 to −1. GVHD prophylaxis included a calcineurin inhibitor starting on day −2 and pentostatin 1 mg/m^2 given on days +1, +3, and +6 in 8 patients, and tacrolimus, sirolimus, and methotrexate in 1 patient. Methotrexate was given at doses of 15 mg/m^2 on day + 1 and 10 mg/m^2 on days +3, +6, and +11. Patients at risk for cytomegalovirus or herpes simplex virus reactivation received prophylaxis with acyclovir, and all patients received prophylaxis with metronidazole, co-trimoxazole, and micafungin in accordance with institutional guidelines.

Palifermin Dose Schedule

Palifermin was administered as an i.v. bolus once daily for 3 consecutive days before the start of the conditioning regimen (days −9 to −7 for MSD HSCT and days −11 to −9 for MUD HSCT) and for 3 additional daily doses on days +1, +2, and +3. The drug was given at 3 dose levels of 40 μg, 60 μg, and 90 μg/ kg/day to 3 patients each, with progression to the next dose level if no patient experienced a dose-limiting toxicity (DLT) at the previous dose level. Patients were dosed by actual body weight.

Pharmacokinetic Testing

Blood samples for pharmacokinetic testing were obtained at approximately 1, 3, and 6 hours after administration of the first dose of palifermin; 24 hours after administration of the third dose; and 1, 3, 6, 8, 12, and 24 hours after administration of the last dose on day +3. Samples were also obtained before administration of each dose. The samples were spun, and sera were cryopreserved, batched, and run at a later date.

Serum palifermin concentrations were measured with the Quantikine Kit (R&D Systems, Minneapolis, MN), which uses the quantitative sandwich enzyme immunoassay technique. All of the reagents used in the assay, including the standard KGF and microplate, were provided with the kit. The sandwich enzyme immunoassay plates were coated with a monoclonal antibody specific for palifermin. After 100 μL of sample or standard was pipetted into the wells, the plates were incubated for 3 hours at room temperature. Palifermin present in the samples was bound by the immobilized antibody during incubation. After any unbound substances were washed away, an enzyme-linked polyclonal antibody specific to palifermin was added to the wells. After a wash to remove any unbound antibody-enzyme reagent, a stabilized tetramethylbenzidine solution was added to the wells. Color developed in proportion to the amount of palifermin in the samples. The intensity of the color was measured at 450 nm with a BioTek plate reader (BioTek, Winooski, VT). The wavelength correction was set at 540 nm. All samples, standards, and controls were run in duplicate. A calibration curve was included in each plate. The calibrators had the following concentrations of KGF: 0 (blank), 62.5, 125, 250, 500, 1000, 2000, and 3000 pg/mL. For those samples with concentrations exceeding the upper range, dilution with calibrator diluent was required. The validated assay linear range was 62.5–3000 pg/mL. The clinically reportable concentration range was 62.5–40,000 pg/ mL. Intraday precisions were 8.9% at

100 pg/mL and 9.6% at 650 pg/mL. Interday precision was 9.3% at 62.5 pg/mL and 5.3% at 2000 pg/mL. Recovery was 75% at 1000 pg/mL and 77.6% at 100 pg/mL.

Pharmacokinetic Data Analysis

The population pharmacokinetic and individual post hoc estimates were derived using nonlinear mixed-effects modeling analysis performed with Monolix version 3.1 (www.monolix.org). A one-compartment pharmacokinetic model with first-order elimination was fit to the data. Parameters estimated included systemic clearance (mL/hour or mL/hour/ kg) and volume of distribution (mL or mL/kg). The distribution of the parameters was assumed to be log-normal, and both interindividual and interoccasion variability were modeled. A proportional residual error model was used with assumed normal distribution of the residuals. Estimates of area under the concentration curve from 0–24 hours ($AUC_{0\text{-}24}$; ng/hour/mL) were determined using the individual post hoc estimated concentration–time curves.

The effects of weight and day of treatment (day −11/−9 versus day +3) on the pharmacokinetic parameters were analyzed. These covariates were considered significant in a univariate analysis if their addition to the model reduced the objective function value by at least 3.84 units ($P < .05$, based on the χ^2 test for the difference in the −2 log-likelihood between 2 hierarchical models that differ by 1 degree of freedom), and the covariate term was significantly different than 0 ($P < .05$, *t* test).

Toxicity

Maximum DLT was defined as a grade IV life-threatening, nonhematologic toxicity definitely attributable to study drug administration from the first dose of palifermin up to day +6 after HSCT. Adverse events and toxicities due to palifermin were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, from the day the first dose was administered to day +6 after HSCT. Grade 1 mucositis was characterized by erythema of the oral mucosa; grade 2, by patchy mucosal ulceration; grade 3, by confluent ulceration; grade 4, by tissue necrosis or significant spontaneous bleeding; and grade 5, by death. Oral mucositis was assessed daily during hospitalization. Assessment of mucositis in all patients was confirmed by the study's principal investigator (A.S.).

GVHD was assessed weekly during the first 100 days after HSCT, in accordance with published criteria [13]. Daily physical examination and blood testing, including complete blood count and serum chemistries, were obtained from the day of the first dose of palifermin to day +6 post-HSCT, 3 days after the last dose. As an indirect measure of the severity of mucositis, information on the median number of days of receipt of total parenteral nutrition (TPN) and the median narcotic usage of morphine equivalents within the first 100 days post-HSCT was collected from electronic pharmacy records.

Statistical Design

The MTD was determined using a Phase I study design with cohorts of 3 patients each. The first cohort was treated as the dose level of 40 μg/kg/day. If no toxicity related to the drug was seen within 14 days posttransplantation, then the next cohort of 3 patients received 60 μg/kg/day. If 1 patient exhibited unacceptable toxicity, then an additional cohort of 3 patients were treated at the same dose level. The dose was escalated to 90 μg/kg/day if no more than 1 episode of toxicity was observed in 6 patients treated at that dose level.

The MTD was defined as the dose level immediately below the level at which 2 patients out of a cohort of 3–6 patients experienced a DLT. If no patient experienced a DLT at any of the dose levels, then another cohort of 3 patients were treated at the highest dose level of 90 μg/

kg/day. Patients were enrolled in the study between October 2007 and December 2010. All patients received the doses of palifermin as scheduled. No patient was lost to follow-up. SAS version 9.2 (SAS Institute, Cary, NC) and StatXact (Cytel, Cambridge, MA) Windows version 8 were used for statistical analysis.

RESULTS

A total of 12 patients (7 females and 5 males; mean age, 9.2 years; range, 2–16 years; median, 9 years) were enrolled in the study. The underlying disease was acute myelogenous leukemia in 7 patients and acute lymphoblastic leukemia in 5 patients. Seven patients were in complete remission (CR) status CR1, 4 were in CR2, and 1 was in CR3. The mean pretransplantation weight was 34.2 kg (range, 13–68 kg; median, 31.3 kg). Three patients underwent MSD HSCT, and 9 underwent MUD HSCT, 4 with a donor matched at 5 of 6 HLA loci. The mean times to neutrophil and platelet engraftment were 22 days (range, 12–34 days) and 27 days (range, 16–40 days), respectively. The mean $CD34^+$ cell dose was 7×10^6 cells/kg (range, $3.75–14.5 \times 10^6$ cells/kg). Two patients had delayed neutrophil engraftment, at 33 days and 34 days, both of whom underwent MUDHSCT with a donor matched at 5 of 6 HLA loci. These 2 patients received rabbit antithymocytic globulin, had a $CD34^+$ cell dose of 5.3 and 4.6×10^6 cells/kg, respectively, and received palifermin at 40 and 90 μg/kg/day, respectively. Grade II–IV GVHD was seen in 1 patient; no patients had chronic GVHD. With a mean follow-up of 2.7 years (range, 1.1–4.1 years), 10 of the 12 patients (83%) were surviving at the time of this report, 9 (75%) without progression of disease. One patient relapsed 9 months after HSCT, underwent a second allogeneic HSCT, and is alive and well. One patient died of progressive disease, and another died from adenoviral sepsis.

Toxicity

Palifermin at a dose of 90 μg/kg/day was tolerated, with none of the 6 patients experiencing a DLT. All of the 12 patients enrolled (100%) experienced at least one adverse event, most of which were of NCI grade 1 or 2 severity. Six patients had maximal NCI grade 1 adverse events, 4 patients had maximal grade 2 adverse events, and 2 patients had maximal grade 3 adverse events. The most common adverse effect was macular rash, which was seen in 8 patients (67%). Four of these 8 patients were at dose level 3, 2 patients were at level 2, and 2 patients were at level 1. Rash occurred within 48–72 after the first dose in all but 3 patients, who developed rash at 8, 10, and 14 days after the first dose. The rash lasted for 48–72 hours in all patients but 1, in whom it persisted for 7 days. It was localized to the face, upper neck, shoulders, and groin and was classified as grade 1 in 3 patients, generalized grade 1 in 3 patients, and generalized grade 2 in 2 patients. The rash was macular and pruritic and in 1 patient was accompanied by grade 1 facial edema that persisted for 3 days. Another patient had edema of the lip and eyelid of grade 1 severity on day −5. Mucositis of NCI grade 1–2 severity developed in 3 of the 12 patients (25%), on days +2, +3, and +5. The median duration of total parenteral nutrition administration was 41 days (range, 0–104 days), and the median cumulative dose of morphine equivalents was 21 mg (range, 0–6257 mg) within the first 100 days posttransplantation.

Grade 2–3 abdominal pain was noted in 2 patients, beginning at 5 and 8 days after the first dose of palifermin and lasting for 3 days. One patient had grade 1 diarrhea and another had grade 2 vomiting on day +2. Other adverse effects included grade 1 headache in 1 patient on day +6; grade 1–2 foot numbness on days +3 and +4 in 2 patients, lasting for 3 days; and grade 1 dry mouth and skin in 2 patients occurring 3 days after the first dose and lasting for 7 days and 11 days.

Grade 1 elevation of aspartate aminotransferase was seen in 3 patients, and grade 2 elevation in 1 patient, with onset between day −7 and day −2 and persistence for 1–2 days. Transient grade 1 elevation of gamma glutamyl transpeptidase was seen in 4 patients between days +2 and +6. One patient had grade 2 elevated alanine amino transferase and grade 3 hypokalemia at dose level 3 on day −7, which resolved in 4 days. A transient grade 1 elevation of alanine amino transferase was also seen in 2 patients with an onset on day −6, lasting for 2 days. No patients had a significant elevation in serum amylase or lipase. The patient who received methotrexate for GVHD prophylaxis had a grade 1 elevation of aspartate aminotransferase, but did not develop mucositis.

Pharmacokinetic Profile

The pharmacokinetics of palifermin after administration of the first dose (pretransplantation) and last dose (posttransplantation), subdivided by dose level, are summarized in Table 1. The observed concentration versus time along with the model-estimated curves after administration of the first dose are shown in Figure 1. Palifermin clearance was seen to increase linearly with body weight ($P < 10^{-4}$) (Figure 2). Specifically, the intersubject variability of clearance decreased from a 41% coefficient of variation (CV) for non–weight-normalized clearance to a 29% CV for weight-normalized clearance. The mean clearance was 1893 mL/hour/kg, and this value did not change significantly between the administration of the first dose and the last dose ($P = .80$). In addition, the mean elimination half-life was 4.6 hours, and this value also did not change between the first and last doses ($P = .30$). The clearance did not change significantly ($P = .40$) over the studied dose range (40–90 μg/kg/ day), supporting linear pharmacokinetics over this dose range. Approximately 97% of the exposure to palifermin occurred within the first 24 hours after dosing.

DISCUSSION

Palifermin at a dose of 60 μg/kg/day administered starting 3 days before conditioning and continuing for 3 days after stem cell infusion has been shown to reduce the incidence and duration of severe oral mucositis in adult patients with hematologic malignancies undergoing autologous [12] or allogeneic HSCT [14]. Decreased use of parenteral nutrition and opiates has been reported in some studies [15] but not in others [16], albeit with a lower incidence of mucositis. No beneficial effects on engraftment, GVHD prevention, or survival have been demonstrated [10,14]. There are no published studies on the efficacy of palifermin in children with cancer or on the pharmacokinetics of palifermin in children.

In this study, a dose of 90 μg/kg/day starting 3 days before conditioning and continuing for 3 days after stem cell rescue did not reach the MTD. Only 3 of 12 patients (25%) had mucositis. This compares favorably with the 37%, 57%, and 7% rates of mild, moderate, and severe mucositis, respectively, reported in patients receiving TBI with tacrolimus and sirolimus for GVHD prophylaxis [2]. Palifermin may confer mucosal protection by inducing hypertrophy of the mucosal lining, as demonstrated by increased epithelial hyperplasia and expression of the proliferative marker Ki-67 [17]. A 3-fold increase in Ki-67 staining 48 hours after a single i.v. injection, defined as the histological criterion for response, occurred in one-half of healthy adult volunteers at a dose of 120 μg/kg and in the majority of subjects at a dose of ≥160 μg/kg [18].

Methotrexate given for GVHD prophylaxis impairs mucosal regeneration after conditioning, worsening and prolonging mucositis. Thus, epithelial cell proliferation after palifermin may be impaired in patients receiving methotrexate. However, Blazar et al. [14] reported no effect of a palifermin–methotrexate interaction on the severity of mucositis in adults. The sole patient who received methotrexate in the present study did not develop mucositis.

Macular rash was the most common adverse event, seen in 67% of our patients, similar to other studies, but no case was of sufficient severity to constitute a DLT or cause withdrawal from the study. The rash was most likely related to the effects of KGF on squamous epithelium of the skin and was reversible, short-lasting, and not associated with any residual changes in skin texture or pigmentation. Other adverse effects included abdominal pain, vomiting, diarrhea, headache, sensory neuropathy, and altered liver enzymes, all of which were reversible and none of which constituted a DLT. Studies on adults undergoing autologous HSCT have reported rash (55%), edema (27%), alteration in taste (22%), and paresthesias (10%) as the most common side effects [12]. Skin rash (94%), edema (78%), and local pain (88%) were also the most common adverse events in adults undergoing allogeneic HSCT who received palifermin [14].

Palifermin exhibited linear pharmacokinetics in children, and most of the drug was eliminated within 24–48 hours of administration. In our children, clearance was faster (mean ± SD, 1893 ± 505 mL/hour/ kg) and AUC_{0-24} was lower (mean ± SD, 40.6 ± 17.6 ng/hour/ mL) compared with healthy adult volunteers, who had a reported clearance of 528 ± 185 mL/hour/ kg with an AUC_{0-24} of 247 ± 86 ng/hour/mL after a single i.v. injection of 120 μg/ kg and clearance of 661 ± 162 mL/hour/kg with an AUC_{0-24} of 251 ± 68 ng/hour/mL after a single i.v. injection of 160 μg/kg [19]. The mean drug half-life was 5.22 hours and 4.89 hours at these 2 dose levels in those adults, comparable to the mean half-life of 4.6 hours in our children. A single collapsed dose of 180 μg/kg demonstrated dose-linear pharmacokinetics compared with the standard dose in adults [19], although no randomized studies comparing the safety and efficacy of the 2 regimens have been reported to date. Clearance in children was not affected by repeat drug administration. The relationship between clearance of palifermin and body weight shown in this study is a novel observation that supports dosing by body weight.

In conclusion, palifermin at a dose of 90 μg/kg/day was well tolerated in children with hematologic malignancies after allogeneic HSCT. This is the first study to detail the pharmacokinetics of palifermin in this population. Randomized controlled trials in children undergoing allogeneic HSCT with this dose are needed to study the efficacy of palifermin in reducing mucositis and its effect on thymic regeneration and lymphocyte recovery. Palifermin has been found to reduce the incidence and duration of severe oral mucositis in adult patients undergoing autologous HSCT [12]. Randomized trials to study the efficacy of palifermin in reducing mucositis in children undergoing autologous HSCT using melphalan-based chemotherapy may be beneficial.

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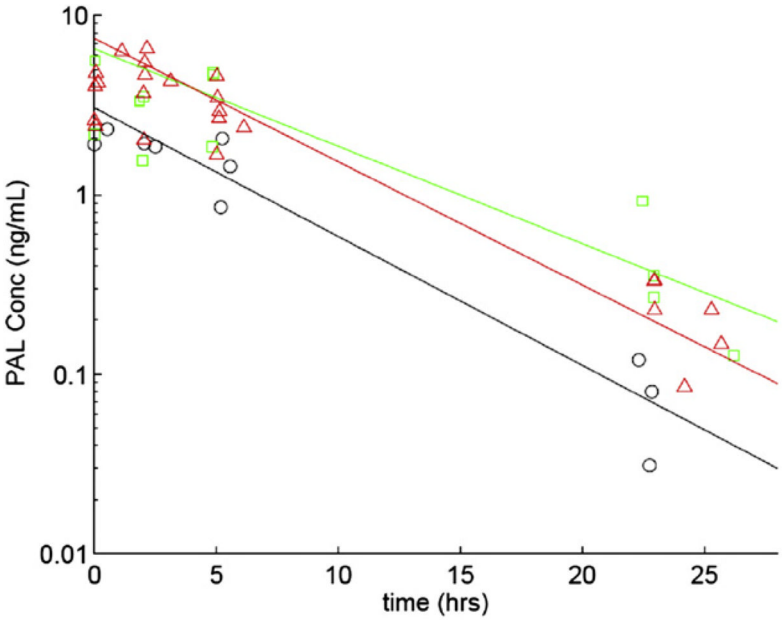

Figure 1.
Concentration-versus-time plots for palifermin (ng/mL) after the first dose (μg/kg), along with the posthoc fit to data (black, 40 μg/kg; green, 60 μg/kg; red, 90 μg/kg).

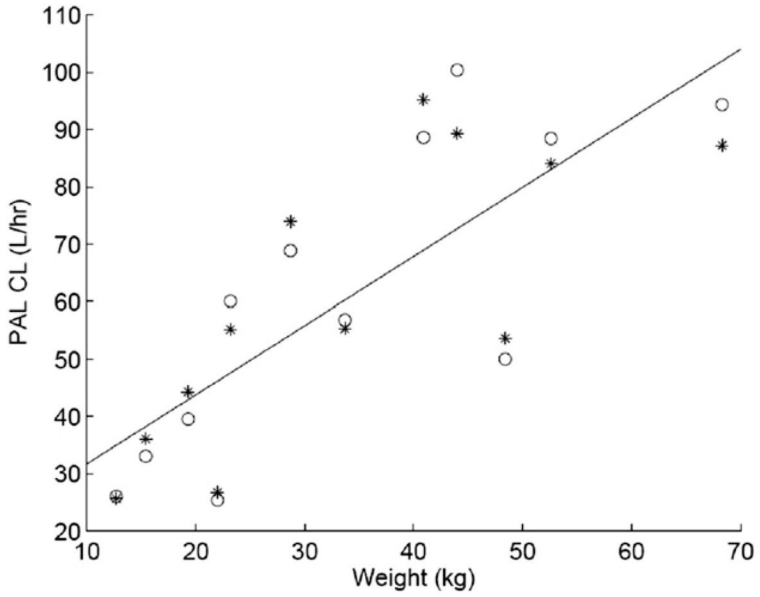

Figure 2.
Clearance of palifermin (L/hour) with respect to body weight in kilograms (open circles, day −11/−9 dose; stars, day +3 dose).

Table 1

Pharmacokinetics of Palifermin after Administration of the First (Day −11/−9) and Last (Day +3) Doses

Day	Number	Dosage, μg/kg/day	Clearance, mL/hour/kg, Mean ± SD	AUC, ng/hour/mL, Mean ± SD	Half-Life, Hours, Mean ± SD
−11/−9	12	40–90	1885 ± 497	40.5 ± 17.0	4.7 ± 0.7
	3	40	2268 ± 285	17.9 ± 2.3	4.1 ± 0.6
	3	60	1412 ± 554	46.7 ± 15.6	5.4 ± 0.8
	6	90	1930 ± 403	48.8 ± 11.2	4.7 ± 0.5
+3	12	40–90	1901 ± 513	40.7 ± 18.1	4.5 ± 0.5
	3	40	2243 ± 194	18.0 ± 1.7	4.1 ± 0.2
	3	60	1541 ± 656	43.5 ± 15.1	4.6 ± 0.5
	6	90	1911 ± 493	50.7 ± 14.0	4.7 ± 0.5