
Clinical Pharmacology Review

NDA	125103
Submission Date:	12/21/2011, 12/21/2012
Brand Name:	Kepivance
Generic Name:	Palifermin
Formulation:	6.25 mg lyophilized powder in single use vials
OCP Reviewers:	Rachelle M. Lubin, Pharm.D
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OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Hematology Products
Applicant:	Swedish Orphan Biovitrum AB
Submission Type:	BLA Labeling Supplement / S-146 / SDN 216
Dosing regimen:	60 mcg/kg/day for 3 consecutive days before and 3 consecutive days after myelotoxic therapy, for a total of 6 doses
Indications	Oral mucositis

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1 EXECUTIVE SUMMARY

Kepivance (palifermin) is a recombinant form of human keratinocyte growth factor (rHuKGF), which was approved in December 2004 for the treatment of oral mucositis. The current submission provides results from a pediatric dose-escalation study conducted with palifermin to address a post-marketing requirement (PMR) # 38-1 issued in the December 15, 2004 approval letter (below) and update the label with the pediatric findings.

38 PMR#1: To conduct a deferred pediatric study under PREA to determine whether well-tolerated and pharmacologically active doses of palifermin in three patient cohorts defined by age (1-2, 3-11, and 12-16 years) with hematologic malignancies treated with myelotoxic therapy and undergoing hematologic stem cell transplant. In study 20010133, "A Phase 1 Dose-escalation Study to Evaluate the Safety and Pharmacokinetics (PK) of Palifermin in Pediatric Subjects with Acute Leukemias Undergoing Myeloablative Therapy and Allogeneic Hematopoietic Stem Cell Transplant (HSCT)," that will be conducted at approximately seven sites registered with the Pediatric Blood and Marrow Transplant Consortium (PBMTTC), 18 to 54 subjects will be treated in the specified age groups. The study will evaluate the safety and pharmacokinetics of palifermin in patients with acute leukemias receiving myelotoxic therapy followed by hematologic stem cell transplant. Three doses (40/mg/kg/day, 60/mg/kg/day, 80/mg/kg/day) [correction (40/mcg/kg/day, 60/mcg/kg/day, 80/mcg/kg/day)] will be evaluated in each age cohort in a dose escalation manner. Age cohorts will be treated simultaneously with the objective to identify a safe, well-tolerated, efficacious dose in each age cohort. The amended protocol for study 2001013 was submitted July 14, 2006, accrual was initiated August 30, 2006, accrual will be completed August 30, 2008, the treatment portion of the study will be completed by October 30, 2008, and the final study report will be submitted by August 30, 2009. As each age cohort completes the study, patients in the same age range will begin enrollment in study 20050164.

On December 21, 2011, the sponsor submitted the final clinical study report (#20010133) entitled, "A Phase 1 Dose-Escalation Study to Evaluate the Safety and PK of Palifermin in Pediatric Subjects with Acute Leukemias Undergoing Myeloblative Therapy and Allogeneic Hematopoietic Stem Cell Transplant". The objective of the study was to determine the well tolerated and pharmacologically active doses (40, 60 and 80 µg/kg/day) of palifermin in 3 patient cohorts (n=9/cohort) defined by age (1-2, 3-11, and 12-16 years old). The primary endpoint was the development of dose limiting toxicities.

The results of this study suggest that age did not influence the pharmacokinetics of palifermin following IV administration of Kepivance 40, 60, and 80 µg/kg per day. Exposure did not appear to increase with increasing doses. No accumulation was observed following 3 consecutive daily doses of Kepivance.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology V has reviewed the information contained in sBLA 125103 (SDN 216) and considers this sBLA submission acceptable from a clinical pharmacology perspective.

The sponsor has fulfilled the post-marketing commitment #38-1 from the December 2004 approval letter

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1.2 Summary of Important Clinical Pharmacology Findings

Palifermin, a recombinant human keratinocyte growth factor (rhKGF) with a molecular weight of approximately 16.3 kDa, stimulates growth of epithelial cells from a wide variety of tissues. Palifermin is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support and as supportive care for preparative regimens predicted to result in WHO \geq Grade 3 mucositis in the majority of patients. The approved dosing regimen is 60 $\mu\text{g}/\text{kg}/\text{day}$ for 3 consecutive days before and 3 consecutive days after myelotoxic therapy for a total of 6 doses administered as an intravenous (IV) bolus injection

In the approval letter dated December 15, 2004, the Agency issued a PMC to the Sponsor to conduct a deferred pediatric study required under section 2 of PREA. (b) (4)
. The current submission includes a final study report for study 20010133 conducted to fulfill PMR #38-1.

The objective of study 20010133 was to determine the well tolerated and pharmacologically active doses of Palifermin in 3 patient cohorts (n=9/cohort) defined by age. This was a Phase 1, single-arm, open-label, dose-escalation study in pediatric patients, which consisted of 3 different age groups (ages 1–2, 3–11 and 12–16 years). The study design followed a traditional dose-escalation design (3+3) with 3 subjects per age group enrolled sequentially into 3 dosing cohorts (40, 60 and 80 $\mu\text{g}/\text{kg}/\text{day}$). Palifermin was given IV once daily for 3 consecutive days before the start of the conditioning regimen and after HSCT (Day -10, -9, -8 and Day 0, +1, +2, respectively). The primary endpoint was incidence of dose limiting toxicities (DLTs).

Age did not appear to affect the PK of palifermin with increasing doses (range: 40-80 $\mu\text{g}/\text{kg}$). Palifermin concentrations declined in the first 30 minutes after dosing. An increase in palifermin concentrations occurred at around 2-4 hours post-dose for some subjects, which was followed by a second, slow decline phase. The maximum tolerated dose (MTD) was not reached in any of the age groups studied. The mean half-life range was 2.6 to 5.6 hours in pediatric patients following the first 60 $\mu\text{g}/\text{kg}$ dose of palifermin. No accumulation was observed following 3 consecutive doses of palifermin. Palifermin exposure did not increase linearly with increasing doses. The first dose AUC_{0-inf} (mean) of palifermin 60 mcg/kg/day in pediatric patients (1 to 16 years) was 46.1 ng*hr/mL (range of means: 22.8 to 81.6). The mean clearance was 2481 mL/hr/kg (range of means: 1700 to 3460) in pediatric patients.

The efficacy endpoint (lower incidence of grade 3 or 4 oral mucositis (OM)) evaluated in this study was considered exploratory. Lower incidence of severe (grade 3 or 4) OM was observed in subjects receiving palifermin 80 $\mu\text{g}/\text{kg}/\text{day}$. The incidence of grade 3 or 4 OM overall was 37%, at the 80 $\mu\text{g}/\text{kg}/\text{dose}$ the incidence was 11%, at the 60 $\mu\text{g}/\text{kg}/\text{dose}$ the incidence was 62%, and in the 40 $\mu\text{g}/\text{kg}/\text{dose}$ the incidence was 44%.

No DLTs or treatment related serious adverse events (AEs) were reported during the treatment period. There was an increase incidence of treatment related AEs with increasing dose. The most common AEs were rash and pruritus. All subjects tested negative for the presence or development of anti-palifermin antibodies.

2 QUESTION BASED REVIEW

2.1 General Attributes

See the original BLA submission dated December 15, 2004

2.2 General Clinical Pharmacology

See the original BLA submission dated December 15, 2004

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Study 20010133 was a Phase 1, single arm, open-label, dose-escalation study to determine a safe and tolerable dose of palifermin in three different age groups and to evaluate the pharmacokinetics in pediatrics. This study followed a traditional 3+3 dose escalation design with 3 subjects per age group (1-2, 3-11 and 12-16 years) enrolled sequentially into 3 dosing cohorts (40, 60 and 80 µg/kg/day). A total of 27 subjects (3 groups) were enrolled. The primary endpoint was the incidence of dose limiting toxicities (DLTs). Palifermin was given by IV bolus injection once daily for 3 consecutive days before the start of the conditioning regimen and after hematopoietic stem cell transplant (HSCT; day -10, -9, -8, and day 0, +1, +2, respectively).

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Oral mucositis was recorded using the WHO Oral Toxicity criteria. Subjects were evaluated for evidence of and clinical stage of acute graft versus host disease (GVHD; skin, liver and gut).

2.2.3 Are the active moieties in the plasma (or the biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Palifermin was measured in human serum for the measurement of both anti-palifermin antibody levels and palifermin concentrations. Details on the analytical methods are discussed in section 2.6.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.1.1 Pediatrics

A pediatric study was performed in 27 subjects who were given doses of palifermin at 40, 60 or 80 µg/kg/day. Nine subjects (n=3 per dose) in each of three age groups (n=3: 1-2 years, 3-11 years, 12-16 years) received palifermin. The starting dose (40 µg/kg/day) for this trial was based

on data from previous adult population trials. The maximum dose of 80 $\mu\text{g}/\text{kg}/\text{day}$ (a 33% increase relative to the MTD seen in adult patients) was chosen based on the data from study 200110192 (healthy volunteer study with 60-250 $\mu\text{g}/\text{kg}/\text{day}$ dose levels) and study 960189 (hematologic malignant patients, MTD: 60 $\mu\text{g}/\text{kg}/\text{day}$).

Blood samples were collected at pre-dose and at 2, 15 and 30 minutes and 1, 2, 4, 6, 10, and 24 hours after the first dose (day -10) and the third dose (day -8) for the measurement of palifermin serum concentrations. Blood samples were collected (day -10, +30, +100) for the measurement of anti-palifermin antibody levels.

Results show that palifermin concentrations declined rapidly in the first 30 minutes post-dose. An increase in palifermin concentrations occurred at around 2-4 hours post-dose for some subjects ($n=3$), which was followed by a second, slow decline phase. Those 3 subjects [dose: 60 $\mu\text{g}/\text{kg}$ (3-11 years) and 80 $\mu\text{g}/\text{kg}$ (3-11 and 12-16 years)] had higher AUC values. The $\text{AUC}_{0-\text{inf}}$ values for 42% of subjects on Day -10 could not be reliably estimated due to $\text{AUC}_{\text{extrap}}$ value greater than 20% or R^2 for λ_z estimation less than 0.9. Palifermin exposure did not increase linearly with increasing doses. The first dose $\text{AUC}_{0-\text{inf}}$ (mean) of palifermin 60 mcg/kg/day in pediatric patients (1 to 16 years) was 46.1 $\text{ng}\cdot\text{hr}/\text{mL}$ (range of means: 22.8 to 81.6). No accumulation was observed following 3 consecutive daily doses of palifermin. Palifermin concentrations were not quantifiable 24 hours post-dose in most subjects. The mean clearance was 2481 $\text{mL}/\text{hr}/\text{kg}$ (range of means: 1700 to 3460) in pediatric patients. The mean half-life range was 2.6 to 5.6 hours in pediatric patients following the first 60 $\mu\text{g}/\text{kg}$ dose of palifermin. **Figures 1 and 2** provide the $\text{AUC}_{0-\text{tau}}$ and $t_{1/2,z}$ (respectively) for palifermin versus dose by study day (-10 and day -8) and age group. **Figure 3** provides the individual plots of $\text{AUC}_{0-\text{inf}}$ and CL values of palifermin vs. dose by age group on day -10.

Figure 1 (Sponsor Generated): Individual Values of $\text{AUC}_{0-\text{tau}}$ for Palifermin versus Dose by Study Day and Age Group

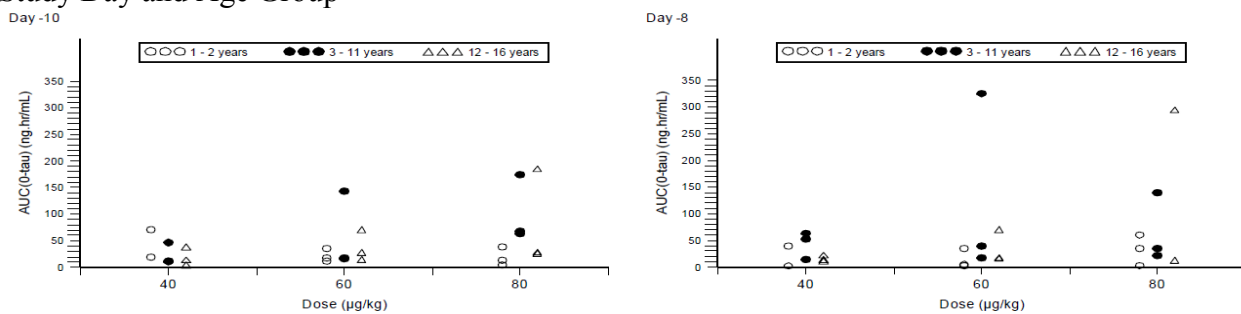


Figure 2 (Sponsor Generated): Individual Values of $t_{1/2,z}$ for Palifermin versus Dose by Study Day and Age Group

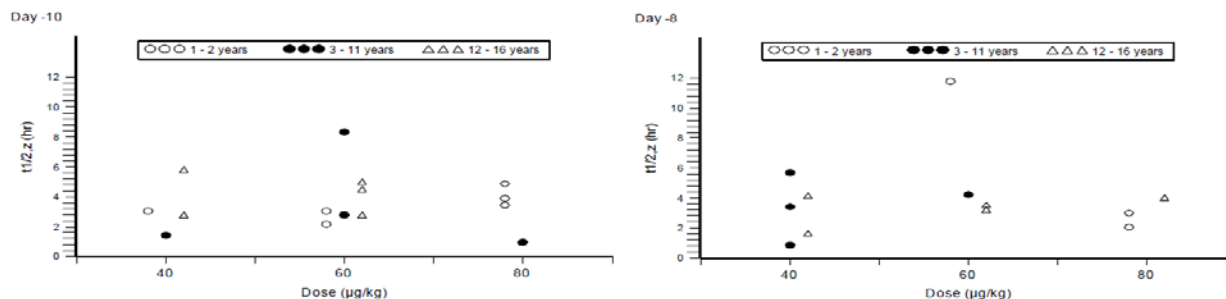
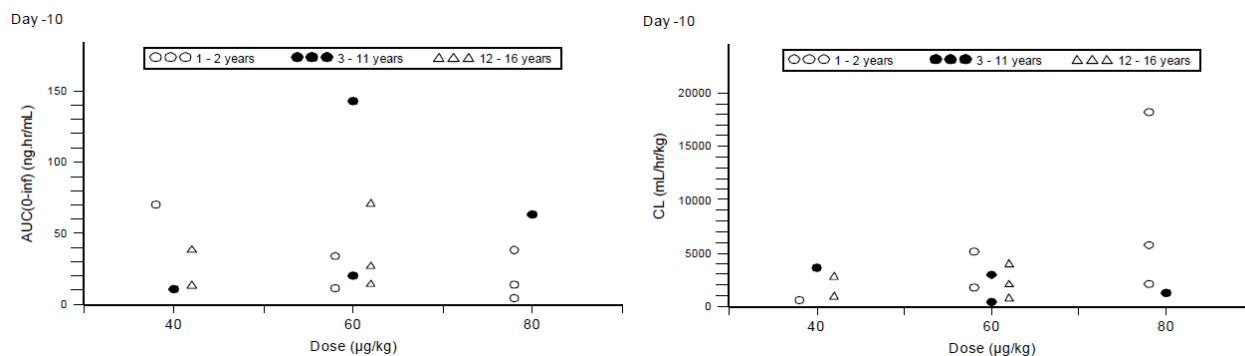


Figure 3 (Sponsor Generated): Individual Values of AUC_{0-inf} and CL for Palifermin versus Dose by Age Group on Day -10



Reviewer Note: The AUC_{0-inf} values for 11 of 26 (42%) subjects on Day -10 could not be reliably estimated due to an AUC_{extrap} value greater than 20% or R^2 for λ_z estimation < 0.9 . The same is true for other variables that are calculated using λ_z ($t_{1/2,z}$, CL, and V_{ss}).

In regards to efficacy, the incidence of \geq grade 3 mucositis in study 20010133 was 37%. In the 80 $\mu\text{g}/\text{kg}$ cohort only one subject (11%) developed \geq grade 3 mucositis compared to 50% of subjects in the combined 40 and 60 $\mu\text{g}/\text{kg}$ cohorts. There was no grade 4 mucositis observed in the 80 $\mu\text{g}/\text{kg}$ cohort compared to 33% (6 of 18) in the combined 40 and 60 $\mu\text{g}/\text{kg}$ cohorts.

2.3.2 Immunogenicity

2.3.2.1 What is the incidence (rate) of the formation of anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after treatment, time profiles and adequacy of the sampling schedule?

Twenty-seven subjects were tested for anti-palifermin antibodies. Serum samples were collected from day -10 (baseline), day +30 and day +100. Samples were analyzed by an electrochemiluminescence (ECL) based bridging immunoassay method.

All 27 subjects tested negative for the presence or development of anti-palifermin antibodies.

2.4 Extrinsic Factors

See the original BLA submission dated December 15, 2004.

2.5 General Biopharmaceutics

See the original BLA submission dated December 15, 2004.

2.6 Analytical Section

2.6.1 What are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Palifermin concentrations and anti-rHuKGF (palifermin) was evaluated in human serum using a enzyme-linked immunosorbent assay (ELISA) and a electrochemiluminescenc (ECL)-based immunoassay method, respectively.

2.6.2 What bioanalytical methods are used to assess concentrations?

Listed in **Table 1** is a summary of the analytical methods used for measuring palifermin concentrations in human serum (Project DVO/RNV Analytical Report).

Table 1: Established Stability and Method Validation

Report	Matrix/ Analytes	Method	Assay Performance description
ELISA Analysis of rHuKGF (Kepivance) in Human Serum	Human serum/ palifermin	ELISA	Lower limit of quantification: 0.072 Assay Range: 0.072 to 1.8 ng/mL Calibrator Range: 0.060 to 2.4 ng/mL %CV of calculated concentration between duplicates in QCs: ≤ 15 (≤ 20 LLOQ) % Diff of QC: ± 15 (± 20 LLOQ) Freeze thaw stability: 4 cycles Long term stability (-70°C to -90°C): 496 days Long term stability (-15°C to -30°C): 30 days Bench top stability (thawed at nominal 37C & stored on wet ice: 4 hours Bench top stability (thawed at nominal 37C & stored at room temperature: 1 hour

2.6.3 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Method ICDIM 64: Partial Validation of an Immunoassay to Detect Antibodies to rHuKGF in Human Serum using the MSD Analyzer: This electrochemiluminescence (ECL)-based immunoassay method (non-GLP) utilizes the Meso Scale Discovery (MSD) PR100 platform and follows a two-tiered assay approach consisting of a screening assay and an immunodepletion test. The positive controls, 100 ng/mL (screening assay) and 90 ng/mL (confirmatory assay) anti- rHuKGF (palifermin) antibody were prepared in pooled normal

human serum (pNHS). The screening assay is performed on samples to detect the presence of binding antibodies to rHuKGF. Samples with a signal-to-noise (S/N) value greater than the assay threshold are then tested to confirm specificity of the response by immunodepletion. Drug treated samples that deplete in the presence of excess soluble drug are reported as positive for the presence of anti-rHuKGF antibodies. Samples are diluted to 20% human serum prior to analysis.

The relative sensitivity of the assay was determined using the rabbit anti-human rHuKGF polyclonal antibody. Antibody concentrations of 0, 10, 25, 50, 100, 150, 200, and 300 ng/mL anti-rHuKGF antibody in pNHS were analyzed by two analysts. The sensitivity based on the final AT (assay threshold: 1.10) was determined to be less than 10 ng/mL anti-rHuKGF antibody.

The lower limit of reliable detection (LLRD) was defined as the lowest concentration where specific anti-rHuKGF antibodies can be detected 100% of the time. Based on the sensitivity curve, the 3 lowest concentrations with less than 20% CV were evaluated as the potential LLRD. Eight donors were tested at 3 concentrations (10, 25 and 50 ng/mL anti-rHuKGF antibody) and analyzed by 2 analysts in the screening assay. The LLRD was confirmed at 50 ng/mL anti-rHuKGF antibody. The antibody response criterion (ARC) is the lowest post-dose/pre-dose (or S/N) ratio of a sample that can be ascribed to a true increase in antibody level. The ARC is determined by the mean S/N of all 50 donors spiked at the LLRD (50 ng/mL), which was calculated to be 2.11.

The immunodepletion threshold is the percent reduction of the net ECL signal needed to confirm a positive response detected in the screening assay. To determine the immunodepletion threshold, eight individual human serum samples were analyzed in the immunodepletion assay by 2 analysts spiked at the LLRD concentration.

2.6.3.1 What is the performance of the binding assay(s)?

Seventy five samples had an S/N ratio < the assay threshold value in the screening assay and were reported negative for antibodies against Kepivance. Two samples were subjected to the immunodepletion test and were reported negative for antibodies against Kepivance. No samples were subjected to the confirmatory cell based assay for detection of neutralizing antibodies.

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/s/

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05/30/2013

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