

**Product: Palifermin**  
**Abbreviated Clinical Study Report: 20030185**  
**Date: 23 September 2008**

**Name of Sponsor:** Amgen Inc

**Name of Finished Product:** palifermin

**Name of Active Ingredient:** Recombinant human keratinocyte growth factor (rHuKGF)

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**Title of Study:** A Phase 2 Study to Evaluate the Efficacy and Safety of Palifermin (Recombinant Human Keratinocyte Growth Factor) in the Reduction of Dysphagia in Patients Receiving Concurrent Chemoradiotherapy followed by Consolidation Chemotherapy for Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

**Investigators and Study Centers:** This study was conducted at 42 sites globally, with 25 sites enrolling subjects in this study: 18 in the United States (51 subjects), 2 in Germany (24 subjects), 2 in Poland (11 subjects), 2 in Spain (12 subjects), and 1 in France (2 subjects).

**Publications:** No publications based on this study have been written to date.

**Study Period:** 06 January 2005 (first subject enrolled) to 20 December 2007 (last visit of last subject)

**Development Phase:** 2

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**Introduction and Objectives:** Palifermin has demonstrated a clinical effect in reducing the incidence and duration of severe oral mucositis in two different clinical studies in patients with hematologic malignancies undergoing total body irradiation with high-dose chemotherapy and autologous peripheral blood stem cell support (Amgen studies 980231 and 20000162; Spielberger et al, 2001; Spielberger et al, 2003).

This study was designed to evaluate the efficacy of palifermin in reducing dysphagia induced by concurrent chemoradiotherapy in subjects with unresectable stage III NSCLC. The primary objective was to evaluate the efficacy of palifermin administered at single weekly doses of 180 µg/kg in reducing the incidence of dysphagia (grade ≥ 2) induced by concurrent chemoradiotherapy (CT/RT) followed by consolidation chemotherapy in patients with unresectable stage III non-small cell lung cancer (NSCLC).

The following were the secondary objectives:

- To evaluate the safety of palifermin administered at single weekly doses of 180 µg/kg (a total of 7 doses)
  - To assess the effect of palifermin on treatment-related clinical sequelae
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**Methodology:** Study subjects were screened within a period of up to six weeks before study randomization, dependent on the required assessment or procedure. Randomization to placebo or active treatment occurred by calling the interactive voice response system (IVRS) within 48 hours before the first planned dose of investigational product. The following information was recorded on the applicable case report forms and collected during the second IVRS call, to allow for stratification before a subject's randomization: disease stage (stage IIIa vs IIIb), ECOG performance status (0 or 1 vs 2), and the subject's estimated weight loss (< 5% vs 5 to 10%) within the 3 months prior to study randomization.

The only palifermin dose level that was tested in this study was 180 µg/kg. A single dose of blinded investigational product was administered 3 days before the initiation of concurrent CT/RT, then once weekly during weeks 1 through 6, typically on the Friday following the last radiotherapy (RT) fraction of the week, for a total of 7 doses.

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Concurrent CT/RT (administered for 6 to 7 weeks) was given as follows:

- standard radiotherapy 2 Gy once daily x 30 to 33 fractions (6 to 7 weeks) for a total target dose of 60 to 66 Gy
- paclitaxel 50 mg/m<sup>2</sup> IV (1-hour infusion) on days 1, 8, 15, 22, 29, 36 (and day 43 for those receiving 66 Gy)
- carboplatin dosed at AUC 2.0 IV on days 1, 8, 15, 22, 29, 36 (and day 43 for those receiving 66 Gy).

Consolidation chemotherapy (21-day cycle x 2 cycles) was given as follows:

- paclitaxel 225 mg/m<sup>2</sup> IV (3-hour infusion) during weeks 7 and 10 (or weeks 8 and 11 for those who received 66 Gy)
- carboplatin dosed at AUC 6.0 IV during weeks 7 and 10 (or weeks 8 and 11 for those who received 66 Gy)

Note: consolidation therapy of paclitaxel and carboplatin could have been administered any day of the week during weeks 7 and 10 or weeks 8 and 11 for those who received 66 Gy, at the discretion of the investigator.

To assess efficacy, subjects underwent acute dysphagia assessments which were graded using the Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAE v3.0) dysphagia scale twice weekly during weeks 1 through 7, and twice weekly thereafter (weeks 8 through 12) and once weekly after week 12 until dysphagia resolved to grade  $\leq 1$  but not beyond week 16. For comparative purposes, esophageal toxicity was also graded utilizing the RTOG toxicity criteria. Tumor response was evaluated by computed tomography scan (CT) or magnetic resonance imaging (MRI) of the chest and abdomen at the end of week 12, as determined by the investigator. If abdominal CT or MRI was not the institutional standard of care, chest imaging only could have been performed but must have included the upper abdomen (ie, liver and adrenal glands). Alternatively, a positron emission tomography (PET) scan of the abdomen could have been performed. A protocol-specific limiting toxicity (PSLT) was defined as any grade  $\geq 3$  CTCAE v3.0 adverse event that was considered to be related to investigational product and prompted discontinuation of investigational product, with the exception of non-symptomatic elevated serum amylase and/or lipase levels. Amgen was notified within 1 work day of such events. Unless a subject withdrew informed consent, the study assessments continued per protocol. An independent Data Monitoring Committee reviewed, on a regular basis, all serious adverse events. A planned DMC safety review was conducted when at least 15 subjects per treatment group completed 6 weeks on study. The DMC had the right to request additional meetings, if needed. The DMC made recommendations to the sponsor regarding the conduct of this study, ie, continue enrollment, hold enrollment until further review, amend the protocol, or stop the study early.

To assess quality-of-life issues, subjects were asked to complete patient-reported outcome (PRO) questionnaires according to the same schedule as the dysphagia assessments (described above). The PRO questionnaires were completed before any other procedures were performed or treatment was administered. During weeks 8 through 12, PRO assessments were discontinued if dysphagia resolved (or previously resolved) to CTCAE v3.0 grade  $\leq 1$ . Subjects were to have 2 consecutive assessments of grade  $\leq 1$  before discontinuing the biweekly PRO assessments. Although the data was collected, no analyses based on a PRO efficacy evaluable subset were done in accordance with the changes in Amendment 3.

Safety assessments included incidence and severity of adverse events; clinical laboratory results including serum amylase and lipase testing; and anti-palifermin antibody samples. Optional pharmacogenetic samples are being stored at ICON for future analysis if warranted. The following are being assessed during long-term follow-up: PRO and dysphagia assessments at month 6 and pneumonitis assessments at months 6, 9, and 12. Subjects with unresolved dysphagia (grade  $\geq 2$ ) at month 6 will be classified as having chronic dysphagia. Disease

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progression, second primary tumors, other malignancies, and survival will be documented at months 6, 9, 12, 15, 18, 21, and 24 and once yearly thereafter until death or loss to follow-up.

**Number of Subjects Planned:** Approximately 100 subjects were to be enrolled.

**Number of Subjects Enrolled (Full Analytical Set):** 100 subjects (49 placebo, 51 palifermin)

**Sex, n (%):** 71 (71%) male, 29 (29%) female

**Age, mean (SD):** 63.0 (8.8) years

**Ethnicity (Race), n (%):** White or Caucasian – 88 (88%)

Black or African American – 7 (7%)

Hispanic or Latino – 2 (2%)

Asian – 1 (1%)

Japanese – 1 (1)

Other – 1 (1)

**Diagnosis and Criteria for Eligibility:**

**Inclusion Criteria:**

- subjects with a histologically or cytologically proven diagnosis of NSCLC
- unresectable (locally advanced) stage IIIa or IIIb disease
- life expectancy  $\geq$  6 months
- estimated weight loss  $\leq$  10% in the previous 3 months before study randomization
- measurable disease
- initial RT field of treatment to encompass  $\geq$  30% of the esophagus
- 18 years of age or older
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- screening laboratory assessments meeting the following criteria:
  - hemoglobin (hgb)  $\geq$  10 g/dL without transfusional support or growth factor use in the 4 weeks before study randomization
  - absolute neutrophil count (ANC)  $\geq$   $1.5 \times 10^9$ /L without growth factor use in the 2 weeks before study randomization
  - platelet count  $\geq$   $100 \times 10^9$ /L
  - serum creatinine  $\leq$  2.0 mg/dL  
Subjects with a serum creatinine  $\geq$  1.4 mg/dL and  $\leq$  2.0 mg/dL must have had a 24-hour urinary creatinine clearance  $\geq$  50 mL/min
  - negative serum or urine pregnancy test for female subjects of childbearing potential
- for subjects with reproductive capability: agreement to practice adequate contraception methods
- signed protocol-specific informed consent form.

**Exclusion Criteria:**

- metastatic disease (M1)/stage IV NSCLC
- pleural or pericardial effusion greater than 100 mL in volume as documented by appropriate imaging (positron emission tomography, computed tomography scan, or

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ultrasound)

If an effusion greater than 100 mL was documented by cytology to be free from malignancy and the investigator felt the subject was capable of receiving RT/CT for their primary disease/NSCLC, the investigator discussed the subject with the study physician at Amgen. Effusions smaller than 100 mL were acceptable, unless the investigator suspected that the effusion was malignant, in which case the effusion was evaluated by cytology. Sponsor approval was obtained before subject was randomized.

- plan to remove the tumor surgically before completing the protocol CT/RT course
- prior chemotherapy, radiotherapy (RT) or surgery for NSCLC
- shielding of the esophagus during RT (including posterior spinal cord shielding)
- prior invasive malignancy during the past 3 years other than non-melanomatous skin cancer

Note: Subjects with prior surgically-cured malignancies (eg, stage I breast cancer or prostate cancer, and in-situ carcinoma of the cervix) were not excluded; however, sponsor approval had to be obtained before subject was randomized.

- presence or history of dysphagia or conditions predisposing to dysphagia, eg, uncontrolled gastroesophageal reflux disease (GERD) or dyspepsia
- history of pancreatitis
- 4 weeks or less since completion of treatment using an investigational product/device in another clinical study or presence of any unresolved toxicity from previous treatment
- known to be sero-positive for human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV)
- previous treatment on this study or with a fibroblast growth factor
- known sensitivity to E coli derived products
- pregnant or breastfeeding women
- compromised ability of the subject to give written informed consent and/or to comply with study procedures
- refusal to sign an informed consent form to participate in this study, and sign the hospital information release form, if applicable
- unwilling or unable to complete the PRO questionnaires
- psychological, social, familial, or geographical reasons that would prevent regular follow-up

**Investigational Product and, Dose and Mode of Administration:** 6.25 mg single-dose vials of lyophilized palifermin for reconstitution with 1.2 mL sterile Water for Injection (United States Pharmacopeia [USP]/European Pharmacopoeia [PhEur]), to be administered as an IV bolus injection at a dose of 180 µg/kg.

**Duration of Treatment:** For most subjects, the acute dysphagia evaluation phase of the study lasted approximately 12 weeks, including 6 to 7 weeks of treatment with CT/RT and the concomitant administration of 7 weekly doses of blinded investigational product, followed by two 3-week cycles of consolidation chemotherapy.

**Reference Therapy and Dose and Mode of Administration:** 6.25 mg single-dose vials of lyophilized placebo for reconstitution with 1.2 mL sterile Water for Injection ([USP/ PhEur]), to be administered as an IV bolus injection.

## **Study Endpoints**

### **Primary Endpoints:**

Incidence of dysphagia (grade  $\geq 2$ ) measured using the CTCAE v 3.0 dysphagia scale

### **Secondary Endpoints:**

#### Efficacy

- duration (days) of grade  $\geq 2$  dysphagia
- maximum severity of dysphagia
- incidence of severe (grade  $\geq 3$ ) dysphagia
- change in performance status and body weight (kg)
- incidence of unplanned breaks in RT (to include discontinuations of RT)
- incidence of hospitalization

### **Safety Endpoints**

#### Short-term:

- incidence of adverse events (AEs) and laboratory abnormalities using the CTCAE v 3.0 toxicity criteria
- incidence of serum anti-palifermin antibody formation
- tumor response at week 12

#### Long-term

- incidence of chronic dysphagia defined as unresolved dysphagia (grade  $\geq 2$ ) at month 6
- incidence of pneumonitis measured using the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Schema
- incidence of second primary tumors
- incidence of other malignancies
- progression-free survival (PFS)
- overall survival (OS)

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**Statistical Methods:** Assuming a reduction of 20% in the incidence of grade  $\geq 2$  dysphagia (80% vs 60%), with 100 subjects (50 per group), the half-width of the 95% confidence interval of the observed difference in proportions is 0.175. The primary analysis for the efficacy endpoints included all subjects who were randomized (intent-to-treat population). Summary statistics were provided by treatment group. For continuous variables, the mean, standard deviation, median, and range were calculated. For categorical variables, the frequency and percentage in each category were displayed. The safety subset included subjects who received at least 1 dose of investigational product and were analyzed based on the treatment actually received. All adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Subject incidence was tabulated by system organ class and preferred term. The long-term safety data of overall survival (OS) and progression-free survival (PFS) were analyzed using the Kaplan-Meier method; the Kaplan-Meier estimates with the corresponding 95% confidence intervals were provided. The stratified Cox model was utilized (using the stratification factors for randomization) to estimate the hazard ratio of the placebo group to the palifermin group.

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### **Summary of Results:**

**Subject Disposition:** Of the 100 subjects who were randomized to a treatment group, 2 subjects (1 subject from each group) did not receive investigational product. Of those who received investigational product, a lesser percentage of subjects who received placebo completed treatment (63%) and the acute dysphagia evaluation phase (59%) compared with those who received palifermin (84% and 80%, respectively). Seven subjects were withdrawn from the study due to adverse events: 5 (10%) in the placebo group and 2 (4%) in the palifermin group.

In the subjects who received investigational product, 19 of the 48 subjects (39%) in the placebo group discontinued the acute dysphagia phase compared with 9 of the 50 subjects (18%) in the palifermin-treated group. Withdrawal of consent was the most common reason for discontinuation from both treatments: 6 subjects (12%) in the placebo group and 3 subjects (6%) in the palifermin group. The following were other reasons for discontinuation: adverse events (placebo: 5 subjects, 10%; palifermin: 2 subjects, 4%), death (placebo: 4 subjects, 8%; palifermin 2 subjects, 4%), and other (placebo: 3 subjects, 6%; palifermin: 0 subjects).

**Efficacy Results:** The primary efficacy endpoint was the incidence of dysphagia (grade  $\geq 2$ ) measured using the CTCAE v 3.0 dysphagia scale. Because this was an exploratory study, the sample size was not powered to achieve statistical significance. The incidence of grade  $\geq 2$  dysphagia was lower in the palifermin group (32 subjects, 63%) compared with the placebo group (34 subjects, 69%,  $p = 0.3137$ ). Efficacy results for important secondary endpoints followed a pattern consistent with the primary efficacy endpoint results. The mean number of days of grade  $\geq 2$  dysphagia was lower for the palifermin subjects with 25.3 days compared with 32.6 days for the placebo group ( $p = 0.2315$ ). Similarly, the incidence of grade  $\geq 3$  dysphagia was lower in the palifermin group (12 subjects, 24%) compared with the placebo group (15 subjects, 31%).

**Safety Results:** Of the 98 subjects in the safety subset (48 in the placebo group and 50 in the palifermin group), adverse events were reported for 47 subjects (98%) in the placebo group and all 50 in the palifermin group. Nausea was the most frequently reported adverse event (25 subjects in each group). The following adverse events were also reported by more than 20% of subjects in each treatment group: anemia, cough, fatigue, leucopenia, neutropenia, vomiting, and constipation. Two subjects, both in the placebo group, experienced protocol specified limiting toxicities that required discontinuation of investigational product and were considered by the investigator to be related to investigational product: subject 185059003 experienced grade 3 dizziness and subject 185066002 experienced grade 4 pancytopenia.

Fatal adverse events were reported for 7 subjects (7%), 5 of the 48 subjects (10%) in the placebo group and 2 of the 50 subjects in the palifermin group (4%); none of the adverse events was considered by the investigator to be related to treatment. Serious adverse events were reported for 52 subjects (53%) in the safety subset: 31 subjects (65%) in the placebo group and 21 subjects (42%) in the palifermin group. Febrile neutropenia was the most frequently reported serious adverse event in both groups: 5 subjects (10%) in the placebo group and 7 subjects (14%) in the palifermin group. Treatment-related serious adverse events were reported for 4 subjects (8%) in the placebo group and 2 subjects (4%) in the palifermin group. All of these events occurred in 1 subject each.

No subject had a positive result for anti-palifermin neutralizing antibodies during this study. Overall tumor response was numerically better for subjects in the palifermin group compared with those in the placebo group: 34 of 50 subjects (68%) in the palifermin group had complete or partial response compared with 22 of 48 subjects (46%) in the placebo group.