2. SYNOPSIS

Name of Sponsor: Amgen Ltd., United Kingdom

Name of Finished Product: Palifermin

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

Title of Study: A Phase 1/2 Study to Evaluate Safety, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of Weekly Doses of Palifermin (rHuKGF) for the Reduction of Oral Mucositis in Subjects with Locally Advanced Head and Neck Cancer (HNC) Receiving Postoperative Radiotherapy with Concurrent Chemotherapy

Investigator and Study Center: This study was conducted at 1 center in Germany

Publications: No publications.

Study Period: 19 July 2005 to 28 July 2015

Development Phase: 1/2

Previous Reports for This Study: Original report, dated 07 November 2007

Objectives:

The primary objectives of the study were the following:

- To evaluate the palifermin pharmacokinetic profile and biological activity on buccal mucosae of palifermin administered at the dose of 120 µg/kg intravenously in a cohort of at least 16 (3 palifermin:1 placebo) locally advanced HNC subjects receiving radiotherapy (RT) with concurrent chemotherapy (CT) as adjuvant treatment for their disease (post-operative setting).
- To evaluate the safety and tolerability of palifermin when administered at the dose of 120 µg/kg weekly for up to 8 consecutive weeks to patients with locally advanced HNC receiving RT with concurrent CT as adjuvant treatment for their disease (post-operative setting).

The secondary objectives of the study were the following:

- To assess the preliminary efficacy of 120 µg/kg palifermin in reducing the incidence and duration of severe oral mucositis (adapted Radiation Therapy Oncology Group [RTOG]/European Organization for Research and Treatment of Cancer [EORTC] grade $\geq$ 3).
- To assess the preliminary efficacy of palifermin on the clinical sequelae of oral mucositis, including:
  - Patient-reported mouth and throat soreness
  - Use of opioid analgesics and supplemental nutrition
  - Unplanned treatment breaks
- To evaluate the long-term effects of palifermin on disease outcome and survival in this patient population.

Methodology: This was a randomized phase 1/2 single-center, 2-cohort, double-blind, placebo-controlled study of palifermin administered at the dose of 120 µg/kg 3 days before RT start, then weekly until the onset of oral mucositis grade $\geq$ 3 (per RTOG/EORTC criteria). Enrollment was planned for 40 subjects stratified by

postsurgical residual tumor stage (no residual tumor [R0] vs microscopic residual tumor [R1] only).

Subjects began receiving investigational product 3 days before the start of RT, which consisted of 200 cGy per day for 5 days per week to a total target dose of 6600cGy. After each week's final RT fraction, subjects received weekly doses of investigational product until the onset of oral mucositis (grade ≥ 3) or until 8 doses had been administered.

Subjects also received cisplatin 100 mg/m2 intravenously on days 1, 22, and 43.

Number of Subjects Planned: 40

Diagnosis and Main Criteria for Eligibility: Subjects ≥18 years of age with newly diagnosed histologically confirmed squamous cell carcinoma (American Joint Committee on Cancer stage II, III, IVA, or IVB) involving either the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx, postsurgical resection (R0, R1) and who were candidates for adjuvant RT/CT were eligible for enrollment into this study.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Palifermin doses of 120 µg/kg were administered by intravenous injection. The manufacturing batch numbers of palifermin used in this study were 024D049513 and D051927. Matching placebo doses were administered by intravenous injection. The manufacturing batch number of placebo used in this study was 024A054178.

Duration of Treatment: Dosing began 3 days before the start of RT and continued weekly after each week's final RT fraction for a maximum of 8 doses or until the onset of oral mucositis (grade ≥ 3) occurred.

Study Endpoints:

Pharmacokinetic endpoints: These included, but were not limited to, systemic clearance, volume of distribution at steady state, area under the concentration-time curve from time 0 to the last quantifiable concentration and extrapolated to infinity, estimated initial concentration, terminal half-life, and mean residence time.

Pharmacodynamic endpoints: The primary pharmacodynamic endpoint was buccal mucosal cell proliferation assayed by staining for cell cycle proliferation marker Ki67.

The secondary pharmacodynamic endpoints were buccal mucosal cell proliferation assayed by staining for other markers; apoptosis assayed through terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling and other assays applicable to fixed tissue; cell differentiation assayed through expression of integrins, keratins, transglutaminase, and other epithelial differentiation markers; expression of detoxifying enzymes involved in oxidative stress assayed through the expression of glutathione-S-transferase, glutathione peroxidase, and other antioxidant enzymes; and expression of keratinocyte growth factor receptor.

Efficacy endpoints: Incidence and duration of oral mucositis and severe oral mucositis; time to onset of oral mucositis and severe oral mucositis; opioid analgesic use (incidence and total dose of morphine equivalents); incidence of unplanned radiotherapy and chemotherapy breaks; incidence of use of percutaneous gastrostomy/nasogastric tube(s), total parenteral nutrition, and intravenous hydration; and average subject-reported mouth and throat soreness score.

Safety endpoints:

Short-term: Proportion of subjects with protocol-specific limiting toxicity; incidence of adverse events and laboratory abnormalities; changes in performance status and body

weight; incidence of xerostomia; disease progression at week 12; and incidence of serum anti-palifermin antibody formation.

Long-term: Incidence of second primary tumors; incidence of other malignancies; progression-free survival; overall survival; and incidence of leukoplakia.

Statistical Methods: The prospectively planned analyses were not conducted because of the small sample size. Disposition, demographics, baseline disease characteristics, tumor response, and adverse events were presented in the original clinical study report (CSR). Administration of investigational product, concomitant chemotherapy and radiotherapy; recurrence of primary tumor and development of secondary malignancy at month 4 of the long-term follow-up period, formation of anti-palifermin antibodies, and incidence of proteinuria were also presented the original CSR.

This report presents the results of the safety follow-up analysis.

Summary of Results:

Subject Disposition: Five subjects were enrolled in this study after which the study was closed to further enrollment because of administrative changes at the study center and slow enrollment. Two subjects were randomized to the placebo group, and 3 subjects were randomized to the palifermin group. All subjects were white men who had stage IVA squamous cell carcinoma of the oropharynx.

Safety Results: One subject in the palifermin group died during the acute oral mucositis evaluation period. Subject 124500003, a 52-year-old white man, received 5 doses of palifermin and discontinued at week 5 because of grade 3 oral mucositis. The subject received 33 fractions of RT (total dose of 6600 cGy) and 2 of the 3 scheduled doses of cisplatin. The subject had serious adverse events of increased blood creatinine, increased red blood cell count, and increased white blood cell count. The subject also developed septic shock with positive cultures for *Staphylococcus aureus*. The subject died because of multi-organ failure.

Three additional subjects (1 palifermin and 2 placebo) died during long-term follow-up after completion of treatment.

- Subject 124500002, a 44-year-old white man, completed treatment with palifermin and received 32 fractions of RT (total dose of 6400 cGy) and all 3 scheduled doses of cisplatin. The subject had sepsis with multi-organ failure and died 69 days after the last dose of palifermin.
- Subject 124500005, a 38-year-old white man, completed treatment with placebo and received 33 fractions of RT (total dose of 6600 cGy) and all 3 scheduled doses of cisplatin. The subject died because of pneumonia and progressive metastatic disease 57 days after the final dose of placebo.
- Subject 124500004, a 68-year-old white man, completed treatment with placebo and received 32 fractions of RT (total dose of 6400 cGy) and 2 of the 3 scheduled doses of cisplatin. The subject died of non-cancer-related causes 1146 days after the final dose of placebo.

The remaining subject, Subject 124500001, a 65-year-old white man who completed treatment with palifermin and received 33 fractions of RT (total dose of 6600 cGy) and all 3 scheduled doses of cisplatin, developed leukoplakia during year 10 of follow-up (Listing 14-2).

Conclusions: No formal conclusions could be made based on the long-term follow-up data because of the small number of subjects involved.