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(palifermin)

Oncologic Drugs Advisory Committee Pediatric Subcommittee Meeting

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
ANC	absolute neutrophil count
AUC	area under the curve
B-NHL	B-cell non-Hodgkin's lymphoma
BLA	biologics license application
CI	confidence interval
CMH	Cochran-Mantel-Haenszel test
COG	Children's Oncology Group
Da	dalton
FDA	Food and Drug Administration
FGF	fibroblast growth factor
G-CSF	granulocyte colony-stimulating factor (filgrastim)
GM-CSF	granulocyte-macrophage colony-stimulating factor
Gy	Gray (measure of radiation)
IV	intravenous
KGF	keratinocyte growth factor
LMB-2	an experimental immonotoxin
MASCC	Multinational Association of Supportive Care in Cancer
mITT	modified intent to treat
NHL	non-Hodgkin's lymphoma
r-metHuG-CSF	recombinant methionyl human granulocyte colony-stimulating factor (filgrastim)
rHuKGF	recombinant human keratinocyte growth factor
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results (program)
TD	transdermal
VDS	verbal descriptive scale
WHO	World Health Organisation

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1. Executive Summary

Amgen believes that innovative new therapies for children who have cancer can best be developed in collaboration with cooperative groups, investigators, patients, and regulatory authorities. Amgen is grateful for the opportunity at the Oncologic Drugs Advisory Committee Pediatric Subcommittee Meeting (20 October 2005) to highlight the challenges and issues inherent in the development of pediatric oncology drugs and to contribute ideas to enhance this development. Amgen believes that the study of oncology drugs in children merits special consideration and strongly supports the use of adequate safety and efficacy evaluation in the framework of controlled clinical trials in the pediatric population. Most children receive cancer therapy as participants in clinical research protocols that have become the standard of care in pediatric oncology. The Children's Oncology Group (COG), which has a mission to cure and prevent childhood and adolescent cancer through scientific discovery and compassionate care, is a key partner in the design, conduct, and evaluation of these trials in pediatric hematology and oncology.

Unfortunately, differences in tumor biology and drug pharmacokinetics and pharmacodynamics in children and adults make it difficult to extrapolate clinical drug effects from adults to children. Consequently, there may be potential risks in relying on the pharmacokinetic and safety data gathered from studies of a cancer drug in adults to define the appropriate use of that drug in children. Therefore, it is imperative to evaluate the effectiveness and safety of new cancer drugs in pediatric populations.

Amgen incorporates development plans for pediatric use within the initial clinical development of all new products that could be used in children. Through collaboration with cooperative groups and regulatory agencies, Amgen develops specific protocols to examine the safety and efficacy of these oncology therapies in children of various age groups. Initiating and completing such protocols in a timely manner, however, remains difficult. The issues presented in this document are common in pediatric oncologic drug development and include a limited patient population, competition for eligible patients among studies, issues with study design, and rapid changes in medical practice. Unlike the adult patient population in the United States, most children with cancer are enrolled in clinical studies that are typically run by cooperative groups. Because of the association of specific tumor types with age groups in the pediatric population, a trial with a single tumor type and regimen may not cover all possible age ranges within the

pediatric population. In addition, because differences exist in the metabolism and biologic responses between adults and children, the pharmacokinetic and pharmacodynamic data generated from studies in adults can only be used as a guide for dosing in children. Therefore, dose-finding studies usually are required before initiating efficacy studies in children. Finally, most malignancies in children are considered to be curable, a fact that typically favors participation in a therapeutic clinical trial of a novel chemotherapy treatment rather than a supportive-care trial.

Although the cooperative groups, regulatory agencies, and Amgen work together, improvement is needed in the process of pediatric drug registration. One approach to facilitate the generation of appropriate data for registration would be to have all parties work together concurrently, before initiation of any study, so that the results from the studies will address the various needs of the different groups and ultimately lead to effective treatments for the pediatric population.

2. Background Information

2.1 Mucositis

2.1.1 Description of Disease Setting

Chemotherapy and radiotherapy, given individually or in combination, kill rapidly proliferating tumor cells, but in the process they frequently kill or damage rapidly dividing normal cells of the gastrointestinal tract. The resulting clinical condition is mucositis. Mucositis can occur anywhere along the gastrointestinal tract and can become the dose-limiting factor for chemotherapy, radiotherapy, or both. The loss of integrity of the protective mucosal barrier can cause different symptoms depending on the anatomic site effected, such as pain and swallowing impairment (oral mucositis and esophagitis), nausea and vomiting (gastritis and enteritis), and diarrhea (colitis), with accompanying clinical sequelae, such as hypoalimentation, dehydration, and electrolyte imbalance that require parenteral nutrition. Pain from oral mucositis and esophagitis can be so severe as to require narcotic analgesia. Additionally, mucositis can provide an entry portal for bacteria and fungi that can cause serious and potentially life-threatening infections, particularly when concomitant neutropenia is present. Finally, mucositis can limit the amount of chemotherapy or radiation therapy, with curative intent, that can be administered to a patient.

The underlying pathophysiology of oral mucositis is essentially the same regardless of the type of insult that causes it. Understanding of the biology of the condition has increased during the past decade (Sonis, 2004). Sonis has described the development of mucositis in 5 stages: initiation, primary damage response, signal amplification, ulceration, and healing. The cascade of events that begins in the submucosa ultimately destroys the mucosa, but in the initial phases of mucositis, the clinical manifestations are minimal. Although some mucosal erythema may be present, the tissue remains intact, and patients have few symptoms before ulceration develops. The ulcerative phase of oral mucositis is the most significant phase of the 5 phases for both the patient and the caregiver. Finally, resolution of oral mucositis occurs as epithelial cells migrate to the damaged area, proliferate, and differentiate into new tissue. The healing process may require days to weeks and depends on the severity of the insult and ulceration and the dynamics of mucosal recovery.

Most pediatric cancers are highly sensitive to chemotherapy and radiotherapy, and many of them can be successfully treated with curative intent with the use of intensive

cytotoxic treatments. The continuous improvement in the overall survival rate in childhood cancer, particularly leukemia, can be attributed to the development of highly effective, multiagent and combined modality cytotoxic regimens. The success of these regimens, however, in terms of both response rate and long-term outcome, is based on the ability to deliver the cytotoxic therapy on time and without dose reduction. This goal can be severely challenged by the development of severe chemotherapy- or radiotherapy-induced mucositis.

2.1.2 Description of Currently Available Therapies

Currently, no approved treatments are available to pediatric patients to prevent oral mucositis induced by chemotherapy, radiotherapy, or both. Palifermin, a recombinant human keratinocyte growth factor (rHuKGF), recently received marketing approval from the FDA for the reduction of the incidence and duration of severe oral mucositis in patients aged 18 years and older who have hematologic malignancies and are receiving high-dose cytotoxic therapy that requires hematopoietic stem cell support. The safety and efficacy of palifermin have not been established in the setting of nonhematologic malignancies. Other interventions primarily are supportive and are aimed at palliating symptoms such as pain (eg, topical anesthetics, coating agents, and opioid analgesics), addressing the inability to eat and drink (eg, parenteral feeding and hydration), reducing local trauma (eg, dental care), and decreasing the risk of secondary infections (eg, prophylactic antibiotics) (Pico et al, 1998; Ruescher et al, 1998). Although benzydamine hydrochloride, a topical agent with anti-inflammatory, anesthetic, and antimicrobial properties has been recommended by the Multinational Association of Supportive Care in Cancer (MASCC) for the prevention of radiation-induced oral mucositis in patients with head-and-neck cancer who are receiving moderate dose radiotherapy(< 50 Gray [Gy]), it is not approved for the prevention of radiation-induced oral mucositis and has not shown efficacy in other settings (Rubenstein et al, 2004).

A number of other experimental approaches to preventing oral mucositis have been studied, including topical and systemic granulocyte-colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), laser and cryotherapies, and radioprotectants such as amifostine (Dazzi et al, 2003). To date, these approaches have failed to demonstrate conclusively any benefit in reducing oral mucositis.

Treatment breaks and dose reduction often are used to manage severe oral mucositis with unknown effects on disease outcome. Although efficacy is the primary consideration in choosing a therapeutic regimen for an individual patient, toxicities (including the risk of developing serious oral mucositis) also may influence the choice of treatment regimens that could influence disease outcome.

2.2 Clinical Development of Palifermin for the Treatment of Adult Patients With Mucositis

Drug development is a highly ordered and regulated process in which multidisciplinary sciences are used to examine the safety and efficacy of potentially therapeutic drugs. The development of palifermin followed such a process.

Keratinocyte growth factor (KGF) was first described in 1989 as a member of the fibroblast growth factor (FGF) family (Finch et al, 1989; Rubin et al, 1989). Endogenous KGF is synthesized and released by fibroblasts and other mesenchymal cells and is a ligand for the KGF receptor. KGF exhibits strict specificity of action for epithelial cells expressing the KGF receptors. Expression of KGF receptors has been demonstrated in epithelial cells from a variety of tissues, including upper and lower gastrointestinal tract, lung, urogenital tissue, skin, mammary gland, kidney, and cornea (Farrell et al, 1999; Farrell et al, 1998; Finch et al, 1989; Rubin et al, 1989). KGF stimulates proliferation, differentiation, and survival of epithelial cells and is physiologically produced in response to injury of epithelial tissue.

Palifermin is a recombinant human KGF that is produced using an *Escherichia coli* expression system. Palifermin is a 140-amino acid protein with a molecular mass of 16.277 daltons (Da). The amino acid sequence of palifermin is identical to endogenous KGF except for deletion of the first 23 N-terminal amino acids, giving the molecule greater thermal stability than the endogenous form, but with similar biologic activity.

In animal models of chemotherapy- and radiotherapy-induced gastrointestinal injury, short-term systemic administration of palifermin before cytotoxic treatment increases oral and intestinal mucosal thickness and activation of cellular mechanisms to protect gastrointestinal mucosa (Farrell et al, 1998). As a result, in these animal models, use of palifermin improved survival by ≥ 55%, reduced weight loss after cytotoxic injury, accelerated weight gain during recovery, reduced the incidence of ulceration after radiotherapy, and reduced overall mucositis rates.

As of March 2005, palifermin has been administered to approximately 700 subjects in clinical trials. The postmarketing commercial experience with a few hundred patients has not revealed any new safety findings to date. Clinical trials with palifermin have shown that palifermin is safe and well tolerated at the doses and schedules tested.

2.2.1 Summary of Efficacy in Adults

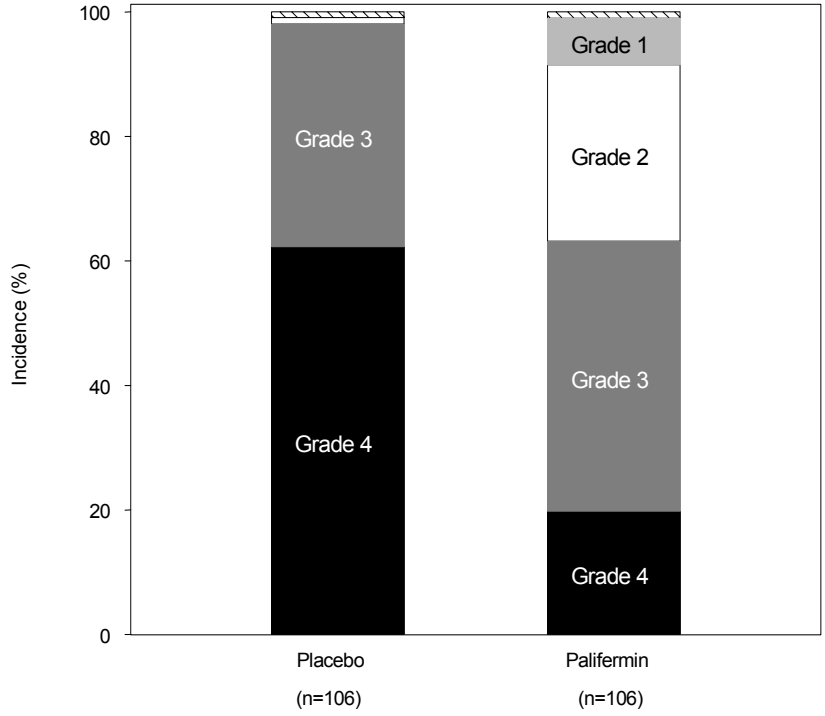
Palifermin has demonstrated efficacy in reducing the incidence and duration of severe oral mucositis in a phase 3 clinical study in subjects with hematologic malignancies who were receiving total body irradiation in conjunction with high-dose chemotherapy and peripheral blood stem cell support (Spielberger et al, 2004). This pivotal study was a double-blind, placebo-controlled, multicenter study that enrolled subjects with non-Hodgkin's lymphoma (NHL), Hodgkin's disease, multiple myeloma, or leukemia. Most subjects had been diagnosed with either NHL or Hodgkin's disease. The subjects ranged in age from 18 to 69 years. Eligible subjects were randomly assigned to receive placebo (n = 106) or palifermin (n = 106) at 60 μg/kg/day for 3 consecutive days before the conditioning regimen and for 3 consecutive days after hematopoietic stem cell transplantation. Conditioning therapy consisted of total body irradiation (12 Gy in 6, 8, or 10 fractions over 3 to 4 days) followed by high-dose chemotherapy (etoposide and cyclophosphamide). Study drug was administered on days -11, -10, -9, 0, 1, and 2 at 60 μg/kg (day 0 was the day of hematopoietic stem cell transplantation). All subjects received filgrastim (r-metHuG-CSF) from day 0 until neutrophil recovery (defined as an absolute neutrophil count [ANC] > 1.0 x 10^9/L for 3 consecutive days or > 10 x 10^9/L for 1 day or until day 21, whichever occurred first).

Efficacy results from the phase 3 study unequivocally demonstrated that palifermin reduced the incidence, duration, and severity of oral mucositis and related clinical sequelae in subjects with hematologic malignancies who are undergoing high-dose myelotoxic therapy that requires hematopoietic stem cell support. Treatment with palifermin consistently produced statistically significant and clinically relevant improvements in the efficacy endpoints analyzed. The median of the primary endpoint, the duration of severe mucositis for the modified intent-to-treat population, was reduced by 67% in subjects who received palifermin compared with subjects who received placebo (median duration: 3 days versus 9 days; $p < 0.001$, respectively). This result was reproducible across study centers, underlying disease, and number of radiotherapy fractions used in the conditioning regimen.

In addition, 35% fewer subjects experienced World Health Organisation (WHO) grade 3 to 4 oral mucositis in the palifermin group relative to the placebo group (63% versus 98%, respectively, $p < 0.001$). The incidence of grade 4 oral mucositis was reduced to 20% in the palifermin group compared with 62% in the placebo group ($p < 0.001$).

The distribution of subjects by incidence of oral mucositis at each WHO grade level indicates a shift from higher to lower WHO grades in subjects who were treated with palifermin compared with subjects who received placebo (Figure 1).

Figure 1. Incidence of Oral Mucositis by WHO Grade



hatched area = grade 0 (no mucositis)

Patient-reported mouth and throat soreness and its limitations on related daily activities (ie, swallowing, drinking, eating, and sleeping) was significantly reduced in subjects who received palifermin compared with subjects who received placebo. Consequent statistically significant decreases in the use of opioid analgesics and percentages of subjects who required total parenteral nutrition were reported for subjects who received palifermin compared with subjects who received placebo. The incidence of febrile neutropenia (an endpoint that was not prespecified in the phase 3 trial) was reduced

significantly in the group of subjects who received palifermin compared with the group who received placebo (Table 1).

Table 1. Key Efficacy Results

	Placebo (N = 106)	Palifermin 60 μg/kg/day (N = 106)	p-value [b]
WHO Grade 3 or 4 - Duration (days)			
Median (25th, 75th percentile)	9 (6, 13)	3 (0, 6)	<0.001
WHO Grade 3 or 4 - Incidence -			
n (%)	104 (98)	67 (63)	< 0.001
WHO Grade 3 and 4 - Duration (days)			
Median (25th, 75th percentile) - Affected subjects	9 (6, 13)	6 (3, 8)	
WHO Grade 4 - Incidence - n (%)	66 (62)	21 (20)	< 0.001
Patient-reported Mouth and Throat Soreness VDS Scale (AUC) [a]			
Median (25th, 75th percentile)	46.8 (37.5, 65.5)	29.0 (17.5, 40.9)	< 0.001
IV or TD opioid analgesic use[c]- Incidence - n (%)	103 (97)	83 (78)	< 0.001
Cumulative Dose of Opioid Analgesics			
Median (25th, 75th percentile)	535 (269, 1429)	212 (3, 558)	< 0.001
Supplemental Feeding - Incidence - n (%)	58 (55)	33 (31)	< 0.001
Febrile Neutropenia - Incidence - n (%)	97 (92)	79 (75)	< 0.001

AUC = area under the curve; CI = confidence interval; IV = intravenous; mITT = modified intent to treat; SD = standard deviation; TD = transdermal; VDS = verbal descriptive scale; WHO = World Health Organisation. Unless specified, all analyses used the mITT population, defined as those subjects who received at least 1 dose of investigational product (1% of subjects who were randomly assigned to treatment did not receive investigational product.

[a] Likert-type scale (0 = no soreness; 4 = extreme soreness)

[b] All p-values were calculated using a generalized Cochran-Mantel-Haenszel test (CMH) test stratified for study center.

[c] morphine mg equivalent

2.2.2 Summary of Safety in Adults

To date, > 1000 subjects have participated in clinical studies of palifermin, and approximately 700 of these subjects have received at least 1 dose of palifermin. Additionally, several hundred patients have received palifermin in the postmarketing setting since its approval in December 2004. In general, palifermin appears to be safe

and well tolerated at the doses and schedules evaluated in the clinical development program.

The overall adverse event profile was similar between patients who received palifermin and patients who received placebo; this profile reflected adverse events that would be expected in a patient population with hematologic malignancies who were receiving high-dose myelotoxic chemotherapy with hematopoietic stem cell support. Few treatment-related adverse events were serious (palifermin, n = 8; placebo, n = 2) and 10 patients in either group discontinued study drug because of adverse effects. Of these 10 patients (palifermin, n = 7; placebo, n = 3), erythema, rash, flushing, or pruritus were factors in the discontinuation for 5 of 7 subjects in the palifermin group and 1 of 3 subjects in the placebo group.

Because of the distribution of KGF receptors on epithelial tissues, some palifermin-related adverse events reflect its pharmacologic mechanism of action. These effects (ie, erythema, flushing, tongue discoloration and thickness, and change in taste sensation) were reversible, usually mild in severity, and infrequently led to discontinuation of study drug. These events were observed largely in the palifermin group compared with the placebo group and in the first dosing period (ie, from the first dose of study drug to the day of peripheral blood stem cell transplantation) compared with other dosing periods. It is more difficult to draw conclusions about the second dosing period (ie, after transplantation) because of the confounding effects of chemotherapy-induced toxicities. In the first dosing period, the corresponding median time to onset for skin- and oral-related events was 4 and 5 days, respectively, after the first dose of palifermin, with a median duration of 4 and 5 days, respectively.

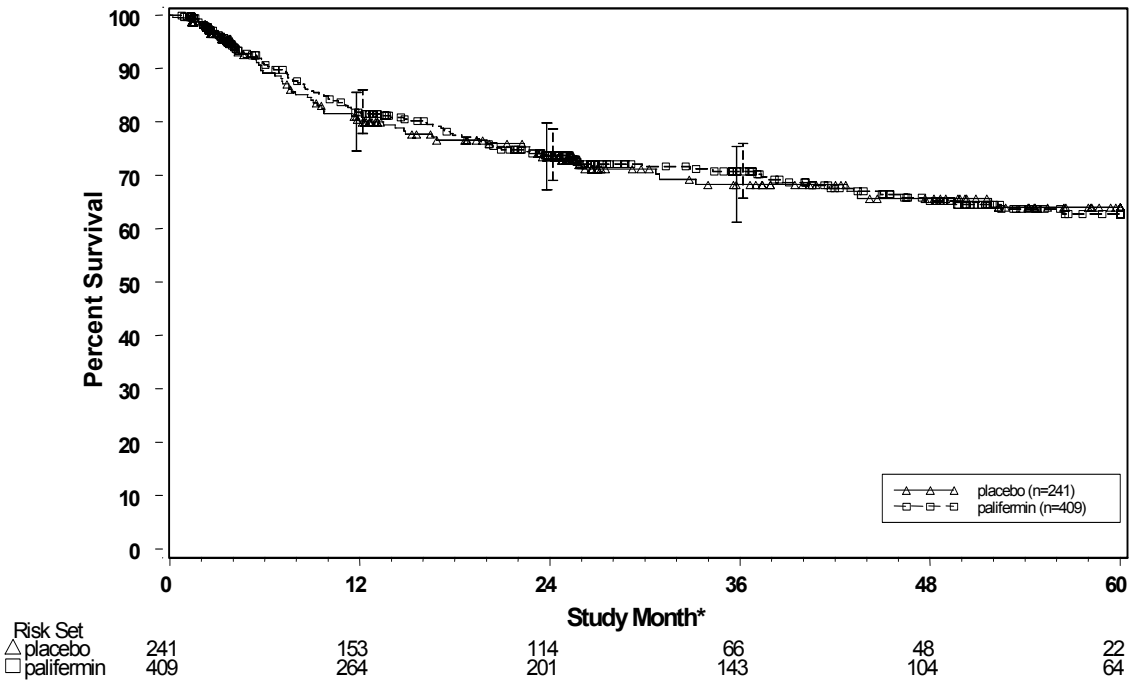
Palifermin's potential effects on pancreatic function are of interest because of the presence of KGF receptors on the exocrine ductal and glandular components of the pancreas and observations from nonclinical toxicology studies of increases in serum amylase and lipase after administration of palifermin. Approximately 65% of subjects had increases in laboratory values for amylase, lipase, or both without clinical sequelae. Such increases in laboratory values were reversible and returned to baseline values by the time of peripheral blood stem cell transplantation. Isoamylase fractionation showed that the increased amylase was primarily of salivary origin, although an increase in the pancreatic component was detected. Of note, in the setting of high-dose myelotoxic therapy, increases in amylase and lipase were observed in both the palifermin and

placebo groups, although the incidence and magnitude of the increase was higher in the palifermin group. The increases in amylase or lipase were not associated with clinical sequelae (eg, pancreatitis).

Palifermin is a supportive-care agent, so it is important to ensure that it does not interfere with myelotoxic therapy and to evaluate its potential to interact directly with the tumor. Palifermin has been shown to enhance the growth of some epithelial tumor cell lines that are known to express KGF receptors in in vitro and in vivo xenograft experiments. In nonclinical studies, palifermin did not interfere with the cytotoxic activity of 5-fluorouracil or radiotherapy (Farrell et al, 1998; Ning et al, 1998). Because hematologic malignancies do not express the KGF receptor, palifermin would not be expected to have a direct stimulation or protective effect on these malignancies.

To address long-term safety concerns, subjects in the 4 myelotoxic therapy studies in the setting of hematologic malignancies (Amgen Studies 960189, 980231, 20000162, and 20010182 Part A) are being followed in a long-term observational study (Amgen Study 960226). Overall long-term survival has been evaluated for these 650 subjects (palifermin, n = 409; placebo, n = 241) who received at least 1 dose of investigational product. Data from a median follow-up period of approximately 24 months are available. The survival rates are consistent with those reported in the published literature for this patient population (Meehan et al, 1995). The Kaplan-Meier estimate of the 2-year overall survival rate for all subjects who received study drug in the parent studies was similar between treatment groups, with nearly identical survival curves (Figure 2).

Figure 2. Kaplan-Meier Survival Curves by Treatment in Subjects With Hematologic Malignancies (as of 04 August 2004)



*Relative to the date of randomization. Vertical lines represent 95% confidence intervals.

Note: The median follow-up time is 23.1 months for the placebo group and 23.8 months for the palifermin group.

The Kaplan-Meier estimates of the 2-year disease progression rate and the 2-year progression-free survival rate for all subjects who received investigational product in the parent studies also were similar between treatment groups.

For the 650 subjects who were enrolled in Study 960226, the number of subjects who had at least 1 secondary malignancy was in the range expected for this patient population, and the proportions were similar between treatment groups (6%). The most common secondary malignancies reported were acute lymphoblastic leukemia, acute myeloid leukemia, and nonmelanoma (squamous and basal cell carcinomas) skin cancer. The proportions of subjects with either acute lymphoblastic leukemia or acute myeloid leukemia were similar between treatment groups and were comparable with those reported in the literature for this patient population (Sevilla et al, 2002). The percentage of patients with nonmelanoma skin cancer was similar for subjects who received palifermin (1.2%, n = 4) and placebo (1.0%, n = 2).

Overall, the duration of follow-up for the palifermin hematologic malignancy population is not yet long enough to provide a definitive conclusion as to whether secondary malignancies are increased in subjects who received palifermin before conditioning therapy and at the time of hematopoietic stem cell transplantation. At this time, because overall survival, disease progression, progression-free survival, and incidence of secondary malignancies have been similar between placebo and palifermin groups and because these measures have been in the range expected for this patient population, this information provides no evidence to cause concern regarding the long-term effects of palifermin on patient outcomes in the hematologic transplant setting.

2.2.3 Experience with Palifermin in the Pediatric Population

Currently, no clinical trials have been conducted in the pediatric setting.

2.2.4 Conclusions

The development program for palifermin in adult subjects with hematologic malignancies who were receiving high-dose chemotherapy with peripheral blood stem cell support demonstrated that palifermin is well tolerated and is an effective antimucositis agent in this patient population.

3. Description of Amgen-sponsored Palifermin Development Program in Pediatric Setting

3.1 Regulatory History

Amgen initiated discussion with the Food and Drug Administration (FDA) on the palifermin pediatric program in September 2000, during the end-of-phase-2 meeting. It was felt that although the pathogenesis of chemotherapy- and radiotherapy-induced oral mucositis is expected to be the same between adults and pediatric patients, a clinical evaluation of palifermin in the pediatric patient population would be necessary. In the pediatric setting, oral mucositis represents an unmet medical need, and both the profile of the injury of oral mucositis (eg, timing, degree, healing) and the pharmacokinetics and pharmacodynamics of cytotoxic drugs or palifermin or both could be different in pediatric subjects compared with adult subjects. However, at that time, Amgen requested a deferral of pediatric studies since the pivotal phase 3 in adult subjects to establish conclusive safety and efficacy data was outstanding.

In June 2001, Amgen submitted to the FDA the synopsis of a phase 1-2 study while confirming the request for deferral. The submitted phase 1-2 study (A Randomized,

Double-blind, Placebo-controlled Safety and Pharmacokinetic Trial of Recombinant Human Keratinocyte Growth Factor in Pediatric Patients Undergoing Allogeneic Bone Marrow Transplantation) was deemed sufficient by the FDA to provide safety and pharmacokinetic information. However, the FDA indicated that an additional study would be required to assess efficacy in this patient population.

In August 2001, the FDA accepted Amgen's request for deferral of pediatric studies and indicated that Amgen should initiate such a program by the time of the biologics license application (BLA) submission.

In September 2003, during the pre-BLA meeting, Amgen presented to and discussed with the agency a modified phase 1-2, dose-escalation study that evaluated the safety, pharmacokinetics, and efficacy of palifermin in children and adolescents with stage 1 unresected and stage 2 B-cell NHL who were receiving multiagent chemotherapy. The study was to be conducted by Amgen in collaboration with the COG. The phase 1 portion was a dose-escalation study to evaluate safety and pharmacokinetics of palifermin at different dose levels and the phase 2 portion was designed to evaluate efficacy using the optimal dose established in the phase 1 part of the study. The FDA agreed that the proposed chemotherapy regimen was associated with a high incidence of severe oral mucositis and that the study was designed appropriately to assess safety, pharmacokinetics, and efficacy. It was noted, however, that the development program for pediatric patients with hematologic malignancies who are undergoing myeloablative therapy was not in place, and the FDA stated that such a program would be required to support a future potential label extension for the hematologic transplant setting.

In April 2004, during a phone conference to discuss with the FDA the reviewable units for the upcoming BLA submission, the FDA advised Amgen to request a pediatric protocol deferral in the BLA that would include milestones for completion of the study.

On 15 December 2004 palifermin received marketing approval with the following postmarketing commitment: "To conduct study protocol 20010133, a 174 pediatric patient, multicenter, dose-escalation study to evaluate the safety, pharmacokinetics, and efficacy of palifermin in children and adolescents with stage 1 (unresected) and stage 2 B-cell non-Hodgkin's lymphoma (B-NHL) undergoing multiagent chemotherapy. The final study protocol will be submitted April 2005, the study will be initiated by May 2005, patient accrual will be completed by November 2007, the study will be completed by

January 2008, and the final study report with revised labeling if applicable, will be submitted by April 2008."

Amgen, in collaboration with COG, completed the writing of the proposed phase 1-2 study to support the postmarketing commitment. In March 2005, Amgen was notified by COG that the proposed study in favorable stage NHL receiving an experimental immunotoxin (LMB-2)-based chemotherapy was no longer feasible since the proposed chemotherapy regimen was no longer the standard of care for this patient population based on recently available data. The superceding chemotherapy regimen for this population is not as mucotoxic and will not support a study for the treatment of oral mucositis. Amgen notified FDA of COG's concern regarding the study design and also indicated that the first milestone of the pediatric palifermin postmarketing commitment would be missed. COG expressed its commitment to work with Amgen on an alternative study where safety, pharmacokinetics, and efficacy could be assessed in pediatric subjects who are undergoing myeloablative chemotherapy and stem cell transplant. COG facilitated a partnership that would allow Amgen to conduct the initial phase 1 study with the Bone Marrow Consortium and a subsequent phase 2 study with COG. In June 2005, the FDA provided comments on the newly designed phase 1 and 2 studies and required further amendments to the study design. These comments have been incorporated in the phase 1 study, and the phase 2 study development is ongoing with COG and FDA.

In summary, Amgen has been active in developing a pediatric clinical program since 2000 and has modified this program to reflect changes in medical practice while trying to maintain a study design appropriate to support regulatory requirements. Since approval of palifermin in December 2004, Amgen has made significant progress in overcoming many of the issues initially encountered in developing the pediatric program.

Section 3.2 summarizes the newly planned phase 1 study and the subsequent phase 2 study.

3.2 Summary of Study Sites for Phase 1 Study

This study will be a multicenter study. Seven sites, all members of the Pediatric Bone Marrow Transplant Consortium, in the United States have been identified as potential participants.

3.3 Patient Population for Phase 1 Study

The patient population for the phase 1 study includes children aged 1 to 16 years. Approximately 36 to 72 subjects are planned to be entered into the study, with 12 to 24 subjects targeted for each age group (1 to 2 years, 3 to 11 years, and 12 to 16 years).

Subjects eligible for inclusion in the study will have a diagnosis of acute lymphoblastic or acute myeloid leukemia that requires hematopoietic stem cell transplantation.

3.4 Study Endpoints for Phase 1 Study

The primary endpoint of the phase 1 study is the incidence of dose-limiting toxicities for each age group at each dose level. The secondary endpoints are the incidence and severity of adverse events, change in vital signs, and the incidence of laboratory abnormalities; determination of pharmacokinetic parameters of palifermin after intravenous bolus injections for multiple dose levels; and the incidence of serum palifermin antibody formation.

An exploratory endpoint is the incidence of grade 3-4 oral mucositis (as determined by the WHO Oral Toxicity grading scale). The WHO scale provides a clinically meaningful, practical, and feasible tool for objectively measuring oral mucositis, and it has been used consistently over the clinical development program of palifermin.

Long-term follow-up will assess disease status (eg, progression-free survival and overall survival) and the incidence of secondary malignancies.

3.5 Treatment Schema for Phase 1 Study

After informed written consent is obtained, study subjects will have screening assessments. These assessments will include a complete medical history, documentation of disease status, demographic data collection, and confirmation of eligibility for allogeneic transplantation. Before enrollment, subjects will have a physical examination and determination of baseline oral mucositis score; blood will be drawn for hematology and chemistry panels and for determination of the presence, if any, of palifermin antibodies.

Palifermin will be administered by intravenous bolus injection on 3 consecutive days before conditioning therapy and after peripheral blood stem cell transplantation. Blood

samples for pharmacokinetic analysis will be collected at regular, prespecified times. Oral mucositis will be assessed.

Blood will be drawn for hematology assessment on the first day of palifermin administration and daily until the subject's ANC is $\geq 2.0 \times 10^9$/L for 3 days. After ANC recovery, blood will be drawn for hematology assessments weekly at a minimum.

At the end of treatment (day 30) or at early withdrawal, study subjects will have a physical examination and assessment of disease status and oral mucositis; adverse event reports will be taken; and blood will be drawn both for hematology and chemistry panels and for assessment of presence of palifermin antibodies.

All subjects will receive the same myeloablative conditioning regimen that includes total body irradiation followed by chemotherapy (etoposide and cyclophosphamide). After a 1-day rest period, the subjects will receive an allogeneic peripheral blood stem cell transplant (day 0), with graft-versus-host disease prophylaxis, and filgrastim.

The study will follow a conventional dose-escalation design, with 3 subjects per age group (1 to 2, 3 to 11, and 12 to 16 years) enrolled sequentially into 4 planned dosing cohorts for palifermin (20, 40, 60, and 80 μg/kg). Enrollment and dose escalation will occur independently for each age group. If a dose-limiting toxicity occurs in a given cohort, the cohort will be expanded to enroll 6 subjects.

3.6 Efficacy and Safety Monitoring for Phase 1 Study

A data review team composed of Amgen clinical scientists and clinical investigators will review the safety data from each cohort. The data review team will decide when dose escalation to the next cohort can occur and will amend the study as needed or stop enrollment into the study.

All subjects will be followed to obtain long-term overall survival, disease-free progression, and secondary malignancies data.

3.7 Statistical Analyses for Phase 1 Study

Data will be summarized by each dose level and age group using descriptive statistics for the primary and secondary endpoints. Because of the small sample size, no hypothesis testing will be done. Descriptive statistics on continuous measurements will include means, standard deviations, medians, and range. Categorical data will be summarized using frequency counts and percentages.

The safety analysis will include summaries of dose-limiting toxicities, adverse events and serious adverse events, deaths (incidence and cause), changes in clinical laboratory measurements, performance status, and vital sign measurements in all subjects who receive at least 1 dose of palifermin. Summaries of dose-limiting toxicities and adverse events will include the number and percentage of subjects reporting any dose-limiting toxicity and any treatment-emergent adverse events, which will be tabulated by system organ class and preferred term.

Pharmacokinetic parameters will be estimated using standard noncompartmental methods and will be summarized by dose level using means, standard deviations, medians, and min/max. Individual subject pharmacokinetic parameters will be reported.

The incidence of oral mucositis will be summarized for all subjects as an exploratory endpoint. Kaplan-Meier plots will be provided for the overall survival and progression-free survival for subjects who receive at least 1 dose of palifermin.

4. Issues in Conducting Pediatric Trials

Studies in children with cancer are formidable for a variety of reasons, including:

- Limited patient population (ie, the pediatric oncology population represents 1% of the total oncology population)[1] and, consequently, a greater proportion of the patient population need to be enrolled in registrational studies in the pediatric setting compared with the adult setting.
- Most children with cancer in the United States are treated on clinical study protocols (Sateren et al, 2002). Cooperative groups that specialize in clinical studies for children have successfully evaluated and developed innovative treatments in the pediatric oncology population, and they enroll most of the children in such clinical studies. Access to children eligible to participate in clinical trials is limited, particularly for a supportive care product such as palifermin, because patients usually are enrolled in cancer treatment studies that may have life-saving effects with the new treatment.
- Limited hospital centers are available to support studies in children, and children with cancer are treated most frequently at specialized pediatric oncology centers.
- Study design issues required for scientific rigor, such as intensive monitoring and blood sampling, make study feasibility challenging.

[1] US estimated prevalence counts were estimated by applying US population to SEER 9 limited duration prevalence proportions. Populations from January 2000 were based on the average of the July 1999 and July 2000 populations estimates from the US Census Bureau.

- The data needed to be useful to multiple interested parties vary, making a single study difficult to implement. Multiple studies further reduce the pool of available patients.

In addition, specific to the development of palifermin:

- Concerns have been raised about the safety profile, particularly of long-term toxicity (ie, the potential for interference with tumor outcomes).
- While both the FDA and COG are concerned with safety, the FDA has expressed particular concerns about long-term safety, whereas COG has indicated an interest in determining maximal efficacy. As a consequence, the study designs must be different to accommodate these divergent needs.

Since palifermin is a supportive care therapy, it will be important to evaluate its potential to interfere with myelotoxic therapy or to interact directly with the tumor. Palifermin has been shown to enhance the growth of some epithelial tumor cell lines that are known to express KGF receptors in in vivo xenograft studies (Ning et al, 1998). Although palifermin could theoretically interact with human tumors and could potentially increase proliferation and growth of these tumors, hematologic malignancies do not express KGF receptors, and palifermin would not be expected to have either direct stimulation or protective effect on these malignancies themselves. This action of palifermin may be a factor in enrollment.

5. Summary and Conclusions

Although the cooperative groups, regulatory agencies, and Amgen are working together, improvement is needed in the process of pediatric drug registration. One approach to facilitate the generation of appropriate data for registration would be to have all parties work together concurrently, before initiation of any study, so that the results from the studies will address the various needs of the different groups.

6. References

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