CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

BLA 125103/0

Medical Review(s)

Medical Officer's Consultation Review of BLA 125103/0
Ophthalmology Consult

Submission date: 6/15/04
Consult request date: 11/24/04
Review date: 11/30/04

Name: Palifermin (recombinant human keratinocyte growth factor) (KGF)

Sponsor: Amgen, Incorporated

Drug class: Growth factor

Submitted: Electronic submission of Study 20000162.

Request from Division of Therapeutic Biological Oncology Products: Please review slit lamp data for pivotal study for original BLA for Palifermin, a keratinocyte growth factor (KGF). There are KGF receptors on the lens, therefore slit lamp exams were done as part of the safety evaluation.

Response: The study results were reviewed. The study is of very limited value from an ophthalmologic prospective because of problems in study design, study execution and the applicant's analysis. The data generated is therefore not sufficient to support any labeling statements or to address any potential toxicity concerns.

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability

Approvability decision is deferred to the primary review team.

B. Recommendation on Phase 4 Studies and Risk Management Steps

Additional studies are recommended to investigate the long-term ocular consequences of treatment with Palifermin.

II. Summary of Clinical Findings

The submitted study report is flawed in study design, study execution and applicant's analysis. The data generated is therefore not sufficient to support any proposed labeling statements or concerns of potential ocular toxicity.

STUDY 20000162

Comments in this review are limited to areas of ophthalmologic concern.

STUDY DESIGN

A Phase 3, Randomized, Double-blind, Placebo-controlled Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) for Reduction of Mucositis in Patients with Hematologic Malignancies Undergoing Total Body Irradiation (TBI) and High-dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell (PBPC) Transplantation. Subjects received investigational product for 3 days before radiotherapy and chemotherapy and again for 3 days after PBPC transplantation (study day 0). Subjects were observed until day 28; they then entered long-term follow-up study KGF 960226. Ophthalmologic Testing consisted only of a LOCS III evaluation of the lens at baseline, after the end of treatment, sometime between days 28 and 127.

Reviewer's Comments:

1. *The majority of patients obtained follow-up examinations within 60 days of treatment. It is unlikely that cataract development, even if induced by the rHuKGF would be detectable within 60 days.*
2. *LOCS III only permits evaluation of visible changes to the lens. The earliest changes to the lens are detected by changes in the refractive power of the lens. Baseline and final refractions, together with best corrected visual acuity should have been evaluated in this study.*

STUDY EXECUTION

Reviewer's Comments:

1. *Twenty-one (20%) of the placebo subjects and 19 (18%) of the rHuKGF subjects did not have a follow-up eye examination. Without these examinations, a high potential rate of cataracts cannot be ruled out.*

2. *The investigator at site 38 never recorded a lens score above the minimal value of 0.1. Of the 25 patients examined at site 38, it is highly unlikely and not physiologic for the patients' ages that all patients would have only the minimal value at both baseline and follow-up visits.*

3. *Patient 3702 had a score of 0 for each part of the lens at baseline. The LOCS III score does not go below 0.1.*

4. *Several patients (3104, 4501, 4504, 4509, 4511 and 4512) had scores recorded in hundredths of a unit when the score is only defined to tenths of a unit.*

STUDY ANALYSIS

Reviewer's Comments:

1. *The analysis presented only evaluates nuclear opalescence. It suggests that only one placebo patient had a grade shift of ≥2. The analysis plan does not evaluate nuclear color, cortical cataracts, or posterior subcapsular cataracts.*

   a. *Patient 3408, who received rHuKGF, had a change in posterior subcapsular cataracts in the right of 4 units and in the left eye of 2.8 units.*

   b. *Patient 3605, who received rHuKGF, had a change in cortical cataract score of 1.8 in the right eye.*

   c. *Patients 3116 and 3106, who received rHuKGF, had changes nuclear color of their lens.*

2. *The analysis presents shift tables categorized in one unit increments instead of utilizing the actual score with its value in tens of a unit.*

SUMMARY OF CLINICAL FINDINGS

The study design, execution, analysis are insufficient to draw conclusions.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

CLINICAL REVIEW

Application Type	BLA
Submission Number	125103/0
Submission Code	
Letter Date	6/15/04
Stamp Date	6/15/04
PDUFA Goal Date	12/15/04
Reviewer Name	Patricia Anne Dinndorf
Through	Joseph E. Gootenberg Team Leader, DTBOP
Through	Patricia Keegan Division Director, DTBOP
Review Completion Date	12/15/04
Established Name	Palifermin
(Proposed) Trade Name	Kepivance™
Therapeutic Class	Growth Factor
Applicant	Amgen
Priority Designation	P
Formulation	Vials of 6.25 mg lyophilized powder for solution
Dosing Regimen	60μg/kg/day as an intravenous bolus injection 3 consecutive days before and 3 consecutive days after administration of cytotoxic chemotherapy
Indication	Decrease incidence and duration of severe oral mucositis
Intended Population	Patients with Hematologic Malignancies Undergoing Hematopoietic Stem Cell Transplantation

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The United States Food and Drug Administration (FDA) Division of Therapeutic Biological Oncology Products (DTBOP) clinical review team recommends approval of palifermin to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support. Confirmation of clinical benefit is based on an analysis of the results of a randomized phase 3 double blind placebo trial and the results of a cohort of subjects on a phase 2 double blind placebo controlled trial treated at the same dose and schedule as that administered in the phase 3 trial.

The assessment of benefit in this application is based on the decrease in duration of World Health Organization (WHO) scale grade 3 and 4 oral mucositis in the phase 3 trial from a median duration of 9 days in the placebo treated subjects and to a median duration of 3 days for the palifermin treated subjects (p-value <0.001). In addition, the incidence of WHO grade 4 mucositis was decreased from 62% in the placebo treated subjects to 20% in the palifermin treated subjects. An additional clinical benefit demonstrated in the phase 3 study was a decreased requirement for parenteral opioid analgesics from a median of 527 mg parenteral morphine equivalents in the placebo treated subjects to 212 mg parenteral morphine equivalents in the palifermin treated subjects.

The phase 2 trial provides supportive evidence for the improvement in duration of WHO grade 3 and 4 oral mucositis. Because of the exploratory nature of the phase 2 trial, it was not useful in supporting the results regarding opioid analgesic use.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The major potential risk identified at this time is tumor promotion. Amgen proposes to address the potential risk through routine labeling and pharmacovigilance. The pharmacovigilance plan includes the following:

- Post-marketing surveillance with special attention to malignancies
- Long-term follow-up of patients enrolled in clinical studies conducted in the hematologic malignancy setting
- A prospective cohort study using available US International Bone Marrow Transplant Registry and the Autologous Blood and Marrow Transplant Registry databases to establish an adequate control group for the long-term follow-up studies

1.2.2 Required and/or Agreed Upon Phase 4 Commitments

Product Post Marketing Commitments

1. 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 multi-agent 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.

2. To complete and submit data from study protocol 960226, a long-term observational follow-up study of subjects previously enrolled in any palifermin study conducted in the myelotoxic therapy setting. Interim results will be provided to the FDA annually with amendments to the label if applicable, beginning 15 December 2005, for 10 years. The final study report will be submitted to the FDA by 30 June 2015.

3. To complete and submit data from study protocol 990123, a long-term observational follow-up study of subjects with head and neck cancer previously enrolled in palifermin studies in the fractionated chemoradiotherapy setting. Interim results will be provided to the FDA annually with amendments to the label if applicable, beginning 15 December 2005, for 10 years. The final study report will be submitted to the FDA by 30 June 2015.

4. To submit the final study report for protocol 20030142, a phase 1 study to evaluate the pharmacokinetics of palifermin in subjects with renal impairment. The study was completed by May 2004 and a final study report will be submitted to the FDA by January 2005.

5. To conduct an *in vivo* study inhealthy volunteers to evaluate the drug-drug interaction of palifermin with heparin. The study protocol will be submitted to the FDA by 1 September 2005, will be initiated by 1 November 2005 and will be completed by 30 September 2006 and final study report submitted to the FDA by 30 March 2007.

6. To conduct an *in vitro* study to evaluate the drug-drug interaction of palifermin with low molecular weigh heparins. The study protocol will be submitted to the FDA by 1 July 2005, will be initiated by 1 October 2005; the study will be completed by 30 April 2006 and final study report submitted to the FDA by 30 October 2006.

7. To conduct an *in vivo* study in healthy volunteers, contingent on the results of the *in vitro* study, to evaluate the drug-drug interaction of palifermin with low molecular weight heparin. If required, the study protocol will be submitted to the FDA by 30 September 2006, will be initiated by 30 November 2006; the study will be completed by 30 September 2007 and final study report submitted to the FDA by 30 March 2008.

8. To conduct a study to determine the incidence of cataracts, and decreased visual acuity in patients who have received palifermin. This study will be a component of the clinical study 20040253 in patients with metastatic breast cancer receiving multicycle chemotherapy. The final protocol will be submitted to the FDA by 30 September 2005, will be initiated by 30 January 2006; the study will be completed by 30 July 2008 and the final study report submitted to the FDA by 31 December 2008.

9. To evaluate the incidence and characteristics (severity, duration, reversibility and clinical sequelae) of proteinuria in patients receiving palifermin. Appropriate testing will be conducted in a clinical study of adequate size. The study protocol will be submitted to the FDA by 30 September 2005, will be initiated by 30 February 2006, will be completed by 30 June 2008 and the final study report will be submitted to the FDA by 31 December 2008.

10. To complete study 103599 to evaluate the potential of palifermin to enhance the incidence of spontaneous tumors in the Tg.rasH2 transgenic mouse model. This study was initiated in July 2004. An audited draft report will be available by June 2005. The final report will be submitted to the FDA by December 2005.

11. To conduct a prospective cohort study using the available International Bone Marrow Transplant Registry (IBMTR) and Autologous Blood and Bone Marrow Registry (ABMTR) databases, to evaluate the incidence of secondary malignancies, cancer relapse rates and survival in patients who received palifermin compared to a matched patient control group who have not received palifermin. The study protocol will be submitted to the FDA by 30 July 2005, will be initiated by 31 January 2006. Interim data will be provided to the FDA at 2-year intervals for a period of 10 years, beginning 31 July 2008. The final study report will be submitted to the FDA by 31 July 2016.

12. To re-evaluate the following:

    a) Action and acceptance limits for Palifermin Drug Substance yields after manufacture of ~ lots;
    b) In-process controls, release, and stability specifications on all Drug Product lots manufactured through the end of 2007; and
    c) In-process controls, release, and stability specifications on all Drug Substance lots manufactured through the end of 2008.
    Results of these re-evaluations will be submitted to the agency by March 31, 2008 for d rug product and March 31, 2009 for drug substance.

13. To evaluate the photo stability of Palifermin Drug Product under conditions that are representative of the conditions for use of the lyophilized and reconstituted Palifermin Drug Product, and to submit the results of the study with revised labeling, if necessary, by September 30, 2005.

14. To evaluate the specificity of the ELISA[ ] Method as an identity test for the Palifermin Drug Product, by a quantitative comparison of cross-reactivity to a series of FGF-related growth factors that are highly homologous in amino acid sequence to Palifermin, and report the results of this study by December 31, 2005.

15. To establish an in-process control test [ ] in the manufacture of Palifermin Drug Substance by September 30, 2005.

16. To submit ED50 control limits for the reference standard used in the bioassay [ ] by September 30, 2005.

17. To evaluate [ ] in Palifermin Drug Product vials exposed to accelerated storage conditions including heat and light, and to report results of the study by September 30, 2005.

1.2.3 Other Phase 4 Requests

There are none.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Palifermin is recombinant human keratinocyte growth factor (rHuKGF), a growth factor for epithelial cells. Palifermin is administered intravenously. Palifermin can reduce radiation and chemotherapy-induced injury to the oral and gastrointestinal tract mucosa and salivary glands. Palifermin exerts this effect by increasing mucosal thickness resulting in enhanced structural integrity of the gastrointestinal epithelium, maintenance of gut barrier and absorptive functions, and improved glandular function in the setting of radiochemotherapy.

Fast track designation was granted December 31, 2003 for the development plan for palifermin for the indication [ ]

Amgen has submitted two trials supporting the efficacy of palifermin, 20000162 and 980231.

- 20000162 is a multi-center, phase 3, Randomized, Double-blind, Placebo-controlled Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) for Reduction of Mucositis in Patients with Hematologic Malignancies Undergoing Total Body Irradiation (TBI) and High-dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell (PBPC) Transplantation. The study enrolled 214 patients and was conducted in 13 sites in the United States.

- 980231 is a multi-center, phase 2 Randomized, Double-blind, Placebo-controlled, Dose-escalation Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Patients with Hematologic Malignancies Undergoing Total Body Irradiation (TBI) and High-dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell (PBPC) Transplantation. The study enrolled 169 patients and was conducted in 12 North American sites.

1.3.2 Efficacy

The DTBOP clinical review team is recommending approval of palifermin to decrease the incidence and duration of severe oral mucositis in adult patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.

This approval is based on the results of the Amgen pivotal trial Study 20000162. This study was a double blind, placebo controlled evaluation of palifermin given at a dose of 60μg/kg per day intravenously for 3 consecutive days prior to administration of a preparative regimen consisting of 1200 cGy fractionated total body irradiation, etoposide 60 mg/kg, and cyclophosphamide 100 mg/kg and for 3 consecutive days after infusion of a minimum of 1.5×10^6 cryopreserved autologous CD 34 positive peripheral blood stem cells.
The efficacy endpoints of this study outlined in the Statistical Analysis Plan dated 10/30/02 (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 904) were:
Primary:

- duration (days) of grade 3 or 4 oral mucositis determined using the WHO toxicity scale 'Oral Toxicity'

Secondary:

- subjects' daily assessment of mouth and throat soreness (patient-reported outcome [PRO])
- use of parenteral or transdermal opioid analgesics (in mg morphine equivalents)
- incidence of grade 4 oral mucositis determined using the WHO scale
- duration (days) of grade 2, 3, and 4 oral mucositis determined using the WHO scale
- duration of oral mucositis determined by Western Consortium for Cancer Nursing Research (WCCNR) scale, descriptor lesions grades 2 and 3, and Radiation Therapy Oncology Group (RTOG) grades 3 and 4

A summary of the scales used to evaluate mucositis in palifermin trials is presented in the table below:

Table 1-1 Comparison of Mucositis Scales Used in Trial 20000162 to Assess Severity of Mucositis

Table 1.1 Comparison of Mucositis Scales Used in Trial 20000162 to Assess Severity of Mucositis					
Grade	**0**	**1**	**2**	**3**	**4**
WHO[1]	None	Soreness and erythema	Erythema, ulcers Patient can swallow solid diet	Ulcers, extensive erythema Cannot swallow solid diet	Mucositis to the extent that alimentation is not possible
RTOG[2]	None	Erythema of the mucosa	Patchy pseudo-membraneous reaction <1.5 cm in diameter, noncontiguous	Confluent pseudo-membraneous reaction >1.5 cm in diameter, contiguous	Necrosis or deep ulceration; may include bleeding not induced by trauma or abrasion
WCCNR[3]	Lesions: none Color: pink Bleeding: none	Lesions: 1-4 Color: slight red Bleeding: N/A	Lesions: > 4 Color: moderate red Bleeding: with eating and oral hygiene	Lesions: Coalescing Color: very red Bleeding: spontaneous	N/A

[1] World Health Organization- WHO handbook for reporting results of cancer treatment. Geneva: World Health Organization, 1979
[2] Radiation Therapy Oncology Group. Acute radiation morbidity scoring criteria. Available from UKL: http://www.rtog.org/members/toxicity.
[3] Western Consortium for Cancer Nursing Research. Development of a staging system for chemotherapy-induced stomatitis. Cancer Nurse. 1991;14:6-12.

The FDA evaluation of the endpoints of Study 20000162 trial are summarized in the table below:

Table 1-2 FDA Evaluation of Efficacy Endpoints Study 20000162

Table 1.2 FDA Evaluation of Efficacy Endpoints Study 20000162				
Endpoint	**Measure**	**Placebo N = 106**	**Palifermin N = 106**	**Statistical Significance**
Duration days WHO 3 or 4 Mucositis[2]	**Mean (SD)** **Median (Q1,Q3)**	10.3 (6.1) 9.0 (6,13)	3.7 (4.1) 3.0 (0,7)	$p < 0.001$[1]
Duration days WHO 2, 3, or 4 Mucositis	**Mean (SD)** **Median (Q1,Q3)**	15.7 (7.8) 14.3 (11,19)	8.4 (5.8) 8.0 (4, 12)	$p < 0.001$[3]
Duration days WCCNR 2 or 3 Mucositis	**Mean (SD)** **Median (Q1,Q3)**	9.9 (9.3) 7.0 (4, 13.2)	3.2 (5.2) 1.0 (0, 5)	$p < 0.001$[3]
Duration RTOG 3 or 4 Mucositis	**Mean (SD)** **Median (Q1,Q3)**	8.1 (8.5) 6.0 (3, 11)	2.2 (3.5) 0.0 (0, 4)	$p < 0.001$[3]
Mean mg Morphine equivalents	**Mean (SD)** **Median (Q1,Q3)**	1049.3 (1487.3) 527.2 (268.7, 1362.5)	520.4 (1251.9) 211.6 (3, 516.0)	$p < 0.001$[1]

[1] Both Generalized Cochran-Mantel-Haenszel test based on the standardized mid-ranks (modified Ridit scores) within each stratum and Wilcoxon rank sum test were performed. Both p-values were less than 0.001.
[2] Duration of mucositis was computed based on the time span between the first date when the mucositis became grade 3 or 4 to the last date when the mucositis grade was still 3 or 4
[3] Generalized Cochran-Mantel-Haenszel test based on the standardized mid-ranks (modified Ridit scores) within each stratum.

Table 1-3 FDA Evaluation Incidence of Worst Grade of WHO Mucositis in Study 20000162

Table 1.3 FDA Evaluation Incidence of Worst Grade of WHO Mucositis in Study 20000162		
Endpoint	***Placebo*** **N = 106**	***Palifermin*** **N = 106**
Worst Score for WHO Grade Oral Mucositis		
Grade 4	66(62)	21(20)
Grade 3	38(36)	46(43)
Grade 2	1(1)	30(28)
Grade 1	0(0)	8(8)
Grade 0	1(1)	1(1)
Worst Score for WHO Grade Oral Mucositis		
n	106	106
Mean (SD)	3.6 (0.6)	2.7 (0.9)
Median (Min, Max)	4.0 (0.0, 4.0)	3.0 (0.0, 4.0)
Q1,Q3	3.0, 4.0	2.0, 3.0

The Generalized Cochran-Mantel-Haenszel test based on the standardized mid-ranks (modified Ridit scores) within each stratum was used to evaluate the statistical significance of the worst grade of WHO mucositis and the result was $p < 0.001$.

For the evaluation of the Secondary Endpoint, Patient Reported Outcome (PRO), the subjects' daily assessment of mouth and throat soreness was measured by subject response to a question contained in the Oral Mucositis Daily Questionnaire (OMDQ). Although there were problems identified in Dr. Lisa Kammerman's review of the validation of the questionaire, specifically that there was no documentation of a rigorous approach in the development of the composite scales used in the instrument, the evaluation of the analysis of mouth and throat soreness supports a statement in the label: "Compared with placebo-treated subjects, palifermin-treated subjects reported less mouth and throat soreness."
This trial demonstrates palifermin, given at this dose and in this schedule decreases the incidence and duration of severe oral mucositis in adult patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support. These results also demonstrate palifermin decreases the requirement for parenteral opioid analgesics in these patients. These results provide evidence of benefit to patients.

The second clinical trial used to support the efficacy claims for palifermin is Amgen Study 980231. This trial was the phase 2 double blind placebo controlled evaluation of palifermin in a transplant setting. The preparative regimen consisted of 1200 cGy fractionated total body irradiation, etoposide 60 mg/kg, and cyclophosphamide 75-100 mg/kg followed after 3 consecutive days by infusion of a minimum of 1.5×10^6 cryopreserved autologous CD 34 positive peripheral blood stem cells. In the initial phase of the trial patients were randomized in a 1:1:1 ratio to palifermin 7 doses; palifermin 4 doses and placebo 3 doses; or placebo 7 doses. The dose of palifermin in this trial was 60µg/kg per day given intravenously. The timing of 6 doses of the investigational agent was identical to the timing in Study 20000162 trial; the fourth dose of investigational agent was given on the last day of total body irradiation prior to chemotherapy.

Early in the course of this trial, the fourth dose of palifermin given at the end of total body irradiation was determined to be deleterious and the study was amended to the schedule used in Study 20000162. There were 40 patients in the placebo group, and 46 patients in the palifermin group treated identically to those in the 20000162 trial. The results in this subset of patients support the results seen in the pivotal trial.

The FDA evaluation of the endpoints in Study 980231 trial that supported the efficacy results of Study 20000162 trial are summarized in the table below:

Table 1-4 FDA Evaluation of Primary Efficacy Endpoint Study 980231

Table 1.4 FDA Evaluation of Primary Efficacy Endpoint Study 980231				
Endpoint	**Measure**	**Placebo N = 40**	**Palifermin N = 46**	**Statistical Significance[1]**
Duration days WHO 3 or 4 Mucositis[2]	**Mean (SD)** **Median (Q1,Q3)**	7.8 (7.3) 6.0 (3.5,11)	4.1 (4.1) 4.0 (0, 6)	p = 0.0041 p < 0.0089

[1] The first p-value was based on Generalized Cochran-Mantel-Haenszel test with the standardized mid-ranks (modified Ridit scores) within each stratum while the second p-value was based on Wilcoxon rank sum test.
[2] Duration of mucositis was computed based on the time span between the first date when the mucositis became grade 3 or 4 to the last date when the mucositis grade was still 3 or 4.

The endpoints of duration of WHO grade 2, 3, 4 oral mucositis, duration of WCCNR grade 2 and 3 oral mucositis, and use of parenteral opioid analgesics were exploratory in this trial. Amgen's analysis of these endpoints is presented in the table below.

Table 1-5 Amgen's Evaluation of Exploratory Efficacy Endpoints Study 980231

Table 1.5 Amgen's Evaluation of Exploratory Efficacy Endpoints Study 980231				
Endpoint	**Measure**	**Placebo N = 40**	**Palifermin N = 46**	**Statistical Significance[1]**
Duration days WHO 2, 3, or 4 Mucositis	**Mean (SD)** **Median (Q1,Q3)**	17.7 (11.3) 12.5 (10, 27.5)	11.1 (9.7) 9.0 (4, 15)	p = 0.001
Duration days WCCNR 2 or 3 Mucositis	**Mean (SD)** **Median (Q1,Q3)**	8.8 (9.1) 6.0 (3, 10)	2.9 (3.5) 0 (0, 6)	p < 0.001
Mean mg Morphine equivalents	**Mean (SD)** **Median (Q1,Q3)**	1163 (1776) 523.9 (236.6, 1380)	514.4 (922.2) 204.9 (16, 574.5)	p < 0.001

[1]Generalized Cochran-Mantel-Haenszel test based on the standardized mid-ranks (modified Ridit scores) within each stratum.

COMMENT: *The results of this analysis on a smaller group of patients of the activity of palifermin to reduce incidence and duration of severe mucositis in the transplant setting supports the results demonstrated in the Study 20000162. There was no mention of a decision rule with regard to the analysis of the secondary endpoints in the 980231 trial. Therefore for this study, these must be considered exploratory.*

Study 20000162 was an adequately designed and adequately conducted trial. This study demonstrated a clinically meaningful improvement in incidence and duration of severe mucositis in the transplant population studied. Study 980231 results supported the results of Study 20000162 regarding the duration of mucositis in a similar group of patients treated with the same regimen of palifermin.

1.3.3 Safety

Extent of safety testing - Safety data were available for a total of 1164 subjects: 783 palifermin, and 381 placebo. The safety database included the following: Healthy volunteers in 6 trials (950170, 960136, 970276, 9702136, 970290, 20010192), 210 total, 160 palifermin and 50 placebo; Hematologic Malignancy Transplantation subjects in 4 trials (20010182, 960189, 980231, 20000162), 650 total, 409 palifermin and 241 placebo; Solid tumor subjects in 2 trials for head and neck cancer (970149, 990119), 159 total, 113 palifermin and 46 placebo; subjects in a primary trial for colorectal cancer (950225), 145 total, 82 palifermin, and 63 placebo; subjects in an extension trial (950275), 48 total, all palifermin; 19 subjects who received placebo in 950225 and received palifermin in the continuation study; and 29 subjects who received palifermin in 950225. In addition, there are 3 Long-term follow up cohorts of subjects consisting of 828 subjects, 545 palifermin and 283 placebo, previously enrolled in the treatment studies (950226, 960226, and 990123).

See table below for a summary of number of subjects with exposure to investigational agent:

Table 1-6 Summary of Subjects in the Safety Pool for Palifermin

Table 1.6 Summary of Subjects in the Safety Pool for Palifermin			
Category	**Placebo**	**Palifermin**	**Total**
Healthy Volunteer	50	160	210
Transplant	241	409	650
Head and Neck	46	113	159
Colorectal	44	101	145
Total	381	783	1164

Exposure - In the primary Safety Pool B, which comprises the combined hematologic transplant subjects who received a total of 3, 6, or 7 per protocol doses, the median number of doses was 6. The median average daily dose by age was 60μg/kg/day.

Clinical findings - Palifermin is intended for use in patients at risk to develop severe mucositis. The efficacy can only be determined in patients who have received a sufficient dose of chemo-radiotherapy to predictably cause severe mucositis. At the required doses of chemo-radiotherapy, multiple severe side effects are inevitable.

Treatment with palifermin is associated with skin (e.g., rash, pruritus, erythema, and edema) and oral (eg, mouth/tongue discoloration or thickness, and taste disorders) adverse events. These reactions are reversible, and usually mild to moderate in severity. Rashes and skin toxicity categorized as serious were reported in less than 1% of transplant subjects. Most subjects were able to tolerate these side effects without discontinuing palifermin.

In the transplant setting, the median time to onset for skin and oral related events was 6 days after the first of 3 consecutive daily doses, with a median duration of 5 days.
Skin related adverse events were reported in 88% of subjects treated with palifermin and 79% of subjects treated with placebo. Oral related adverse events occurred in 38% of subjects treated with palifermin and 27% of subjects treated with placebo.

Skin-related adverse events were also observed in the healthy volunteer studies, and their incidence in dose-escalation studies was dose related.

Palifermin is a drug that has no expected abuse potential. There is no data on overdose. There are no pregnancy or lactation studies of palifermin. There is minimal pediatric experience.

Limitations of available data – The safety data that supports this application has been collected in the autologous transplant setting. The data supporting safety of palifermin in the allogeneic setting is limited. Amgen has included data from an investigator sponsored IND on 100 subjects, 69 treated with palifermin and 31 treated with placebo, in the allogeneic setting. Within the limitation of the study, the adverse event profile was similar to the adverse event profile in the autologous setting.

The efficacy of palifermin is dependent on dose and schedule relative to chemotherapy and radiotherapy. Many transplant protocols use different chemotherapy and treatment schedules for the preparative regimen. Timing of palifermin in relationship to the preparative regimen may affect the efficacy. If timed incorrectly, mucositis may be more severe as Amgen observed in the 7-dose schedule of Study 980231 (eCTD 5.3.5.1.3, Clinical Study Report 980231 page 131).

COMMENT: *The data in this application supports the safety profile of palifermin in the setting of hematologic transplant relative to benefits of decreased incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.*

Role in treatment armamentarium – There are no available drugs that prevent or decrease the severity of mucositis in the transplant or any other setting.

1.3.4 Dosing Regimen and Administration

The recommended dose of palifermin in the hematologic transplant setting is 60µg/kg IV for a total 6 doses. The schedule is 3 doses prior to starting total body irradiation, and 3 doses after stem cell infusion.

1.3.5 Drug-Drug Interactions

There were no formal *in vivo* nonclinical and clinical pharmacokinetic drug interaction studies conducted with palifermin. The possibility of drug interactions was addressed as a component of animal model evaluations. Granulocyte colony-stimulating factor (G-CSF), which is likely to be used in the indicated patient population, was used in combination with palifermin in murine and nonhuman primate chemotherapy/ radiotherapy models, and there was no evidence of a drug interaction.

It is known that endogenous keratinocyte growth factor (KGF) is a heparin binding protein. Palifermin is a recombinant human KGF and it has been shown that palifermin binds to heparin *in vitro*.

1.3.6 Special Populations

The data included in this study adequately supports the use of palifermin in the transplant setting, with the exception of the pediatric population. Although the experience is limited in geriatric subjects, subjects older than 65 are rarely treated with transplantation. Amgen has agreed to study the pharmacokinetics of palifermin in pediatric patients undergoing chemotherapy for non-Hodgkin's lymphoma.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Generic Name:	palifermin, rHuKGF
Proposed Trade Names:	Kepivance™
Pharmacological Category:	Epithelial growth factor
New Molecular Entity:	Yes
Drug Class:	Recombinant human growth factor
Route of Administration:	Intravenous
Dose and regimen:	60ug/kg/day daily starting 3 days before preparative regimen, then 3 days starting day 0. (Total 6 doses)
Population Studied:	Adult patients with hematologic malignancies undergoing peripheral blood progenitor cell transplantation
Proposed Indication:	To decrease the incidence and duration of severe oral mucositis

2.2 Currently Available Treatment for Indications

There are no drugs currently available that reduce the incidence and duration of severe chemotherapy or radiotherapy induced mucositis. The only treatment for chemotherapy and radiotherapy induced mucositis is the use of opioid analgesics to reduce the pain associated with mucositis.

2.3 Availability of Proposed Active Ingredient in the United States

Palifermin is a new molecular entity and currently is not marketed in this country.

2.4 Important Issues With Pharmacologically Related Products

There are no licensed pharmacologically related products.

2.5 Presubmission Regulatory Activity

2.5.1 Chronology of BLA 125103

Table 2-1 Chronology of BLA 125103 Milestones

Table 2.1 Chronology of BLA 125103 Milestones	
Date	**Milestone**
November 1995	IND[ ]original submission
February 1997	Clinical Trial 960189 (Ph1/2) Initiated
May 1997	Clinical Trial 960226 (LTFU) Initiated
February 1999	Clinical Trial 980231 (Ph2) Initiated
July 1999	Clinical Trial 960189 (Ph1/2) Concluded
September 1999	End of Phase 2 Meeting
July 2000	Clinical Trial 980231 (Ph2) Concluded
September 2000	Pre-Phase 3 Meeting
March 2001	Clinical Trial 20000162 (Ph3) Initiated
October 2002	Clinical Trial 20000162 (Ph3) Concluded
October 2002	Clinical Trial 20010182 (PK) Initiated
October 2003	Clinical Trial 20010182 (PK) Concluded
December 2003	Fast Track Designation Granted
September 2003 December 2003 April 2004	Pre-BLA Discussions
May 2004	BLA 125103/0 Initial Reviewable Units Submitted
June 2004	BLA 125103/0 Final Reviewable Units Submitted

2.5.2 Major Clinical Regulatory Agreements During Development Of Palifermin

The following major clinical regulatory agreements were reached during the development of Palifermin:

End-of-Phase 2

- Acceptability of WHO oral mucositis scale as an endpoint tool for measuring prevention and/or treatment of oral mucositis induced by chemotherapy.
- Clinical benefit will be demonstrated by improvement in WHO grades 3 and 4 mucositis
- Median duration of WHO grades 3 and 4 mucositis is an important endpoint
- The RTOG and WCCNR scales will be used as secondary endpoints to confirm the primary endpoint
- Opiate requirement will be secondary endpoint

- Amgen will collect data on amylase and lipase levels on all patients and will make attempts to determine the source of the amylase. Amylase and lipase testing will be performed at a reference laboratory to minimize risk of unblinding of investigators. Amylase and lipase results will be evaluated by a physician not involved in the patient's care, who will alert the investigator in case of a serious (e.g., grade 3-4) elevation.

- Amgen will conduct additional studies to investigate the possibility of tumor promoting effects

<u>During Phase 3</u>

- Amgen will conduct Tg.rasH2 Mouse Model study to investigate the potential risk of secondary tumor development with the use of KGF

- HRQOL
  1. HRQOL endpoint will be tested only if the primary clinical endpoint is significant.
  2. FDA notified Amgen that collecting redundant data in the HRQOL questionnaire that does not provide additional information should be avoided.
  3. Excessive missing data points will call the entire analysis into question and conclusions regarding HRQOL may not be able to be drawn. Amgen agreed to insist on high compliance.
  4. The method proposed for administration of the HRQOL questionnaire is acceptable.
  5. The method for handling missing data is acceptable.
  6. The method for analyzing multiple comparisons is acceptable.
  7. FDA notified Amgen that the basis for eliminating questions from the questionnaire was not scientifically valid. Questions were eliminated if they did not appear to correlate with the primary endpoint or if too few subjects answered the question. Only those questions unlikely to be affected by the intervention should be eliminated from a questionnaire.

- The BLA filing would be accepted with deferral of the pediatric data, if the pediatric trial were actively enrolling patients at the time of BLA submission for the adult indication

<u>Pre-BLA Discussions</u>

- The proposed organization of the eCTD BLA is acceptable

- BLA is acceptable for CMA Pilot 1

- The preclinical reviewable unit will be submitted May 2004

- The filing will be complete in June 2004

- The final clinical study report (CSR) for study 20030142 in renally-impaired subjects can be submitted as a post-approval commitment.

- The draft labeling, the pediatric deferral request, financial disclosure, debarment certification, and the most recent Investigator Brochure should be included in the BLA. The pediatric deferral request should include defined milestones leading to completion of the study.

- The Tg.rasH2 carcinogenicity study is necessary, but completion can be a post-marketing commitment. The BLA should include defined milestones leading to completion of the study.

- Submission of long-term safety data and information from the sponsor-investigator IND study 990750 at the Day 120 safety update is acceptable.

- PRO results and validation for studies 960189, 980231, and 20000162 will be submitted. Case report forms for 20000162 will be submitted.

2.6 Other Relevant Background Information

Amgen has [redacted]

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

3.1.1 CMC Assessments

This summary is adapted from the CMC review.

3.1.1.1 Description of the Drug Product(s) and Drug Substance(s)

Palifermin is the USAN name for Amgen's Keratinocyte Growth Factor-1 (KGF-1), a member of the Fibroblast Growth Factor (FGF) Family within which KGF-1 is also known as FGF-7. Palifermin is manufactured via recombinant DNA technology in *E. coli*, [ ] drug substance (DS) that begins at the N-terminal amino acid #24 of native Human Keratinocyte Growth Factor. The palifermin DS is [ ] as a lyophilized drug product (DP) for refrigerated storage.

Palifermin is an N-terminal 23 amino acid truncation of native human KGF. KGF was originally identified as a growth factor for epithelial cells (Rubin and Osada et al.1989). KGF is a paracrine protein growth factor produced by mesenchymal cells, particularly sub-epithelial fibroblasts, and binds Fibroblast Growth Factor Receptor (FGFR) FGFR-4, which is a splice variant of FGFR IIIb expressed in many epithelial cells. After binding FGFR-4, KGF initiates epithelial cell proliferation, migration and up-regulates expression of numerous protective cell functions. As listed in the Palifermin Package Insert, native human KGF has trophic effects on many types of epithelial surfaces and tissues including tongue, buccal mucosa, esophagus, stomach, intestine, salivary gland, lung, liver, pancreas, kidney, bladder, mammary gland, and skin (hair follicles and sebaceous gland), and the lens of the eye. The KGF receptor is not present in cells of the hematopoietic lineage.

3.1.1.2 Description of How the Drug Product is Intended to be Used

At the bedside, Palifermin DP is reconstituted in water for injection for intravenous bolus injection as an adjunctive treatment of adult hematological malignancies to decrease the incidence and duration of severe mucositis attendant to myeloablative therapy with radiation and chemotherapy.

3.1.1.3 Basis for Approvability or Not-Approval Recommendation

Approvability is based on the submission of fully adequate Biochemistry, Manufacturing and Control documentation for this recombinant form of human KGF. This includes thorough information and data on manufacturing controls, methods and process validation, product

characterization (purity and product and non-product related impurities), consistency of manufacture (comparability of pilot, clinical and commercial lots of palifermin), specifications, and stability data.

Palifermin is a highly purified and well-characterized product with release specifications that will ensure lot-to-lot consistency. The manufacturing process is under control and has been satisfactorily validated. The clinical and conformance lots of drug substance and drug product were comparable. The product has a high degree of stability in the liquid form, and the low extent instability of the lyophilized and reconstituted drug product has been carefully examined, and will remain within specifications if stored as recommended during the assigned shelf life of [ ] for drug substance and 18 months for lyophilized drug product.

Immunogenicity does not appear to be a concern for this product. Patients receiving palifermin treatment showed a low incidence [ ] of antibody detection without development of neutralizing antibodies. KGF is protein within the 22-member FGF family of growth factor; consequently, with this high redundancy, patients developing antibodies would not be expected to experience long term or severe side effects.

3.2 Animal Pharmacology/Toxicology

3.2.1 Animal Pharmacology

This section is adapted from the Executive Summary of the Pharmacology/Toxicology Review - Animal Pharmacology.

3.2.1.1 Brief overview of nonclinical findings

Pharmacodynamic studies were conducted in mice and rats. These studies demonstrated that palifermin promoted epithelial cell regeneration in the salivary gland, tongue, esophagus and gastrointestinal tract when given before and/or after cytotoxic therapy. The enhancement of epithelial cell proliferation was shown by increased BrdU incorporation into cells, Ki67 immunostaining and increased target tissue(s) thickness.

The pharmacokinetics of palifermin in mice, rats, wethers and monkeys were linear and dose dependent. Terminal half-life in all these species was 1-3 hours. There was no accumulation of product (i.e., no increase in systemic exposure) with multiple dosing up to 7 days. The serum profile of palifermin in the monkey was different from the rodent; there was a plateau or "hump" effect 1-4 hours after intravenously (IV) dosing in the monkey. This effect was attributed to redistribution subsequent to rapid intravascular absorption. (The plateau effect is also seen in humans.) When given IV, volume of distribution was 50-100 ml/kg in rats, 1000-5000 ml/kg in monkeys and 2300-4000 ml/kg in wethers suggesting extensive extravascular exposure in larger species. Clearance averaged 50-165 ml/hr/kg, 450-1770 ml/hr/kg, and 800-1000 ml/hr/kg in the rat, monkey, and wether, respectively, with IV administration.

Absorption, distribution, metabolism and excretion studies demonstrated that palifermin was primarily metabolized and excreted by the kidney. A rat model showed minimal first-pass extraction of the product by the liver. In wethers, 45% of palifermin was absorbed by the lymphatic system after subcutaneously (SC) administration. Twenty-four hours after a radioactive IV injection of palifermin there was no significant accumulation in rodent tissues. Tissues with highest uptake of radioactive product over 24 hours were adrenal glands, intestine, kidneys, liver, ovaries, spleen, stomach, and trachea.

3.2.1.2 Pharmacologic activity

The product, palifermin, stimulates the growth of epithelial cells by binding to the keratinocyte growth factor (KGF) receptor. This receptor is found in a wide variety of tissues. KGF is a member of the fibroblast growth factor (FGF) family (specifically, FGF-7). Endogenous KGF is synthesized and released by fibroblasts and other mesenchymal cells. Endogenous KGF promotes epithelial cell healing subsequent to injury.

3.2.1.3 Nonclinical safety issues relevant to clinical use

It is not known if the product will enhance the growth of existing tumors, promote the growth of new tumors or protect tumors against cytotoxic therapies.

3.2.2 Animal Toxicology

This summary is adapted from the Executive Summary of the Pharmacology/Toxicology Review – Animal Toxicology

3.2.2.1 Brief overview of nonclinical findings

Non-clinical single-and repeat-dose toxicology studies were performed to evaluate the potential toxic effects of palifermin in a variety of animal models. The species studied included athymic nude mice, rats, rhesus and cynomolgus monkeys. Single doses were administered up to 30,000 ug/kg in rats and 50,000 ug/kg in monkeys. Repeated doses of up to 1000 ug/kg daily for up to 28 days were administered to rats and doses of 300 ug/kg daily for up to 28 days were administered to monkeys. The toxic effects observed were primarily extensions of the known pharmacologic activity of palifermin and included goblet cell hyperplasia, acanthosis and hyperkeratosis of the skin of various body regions and tongue in all species as well as involution of the thymus characterized as lymphoid depletion. Rats showed what appeared to be a higher sensitivity to the palifermin exposure with glomerulonephritis (rated mild to moderate), centrilobular apoptosis of the liver and increased thyroid follicular size and number. In rats, doses of up to 1000 ug/kg, IV or SC, were administered daily for up to 28 days. Dose dependent effects included acanthosis of the skin, hyperplastic and hypertrophic changes in the GI tract epithelium and urinary bladder. Goblet cell hyperplasia was observed in all regions of the GI tract in the higher dose groups. Effects of the study drug on the kidney included mild to moderate increases in organ weight, mild to moderate glomerulonephritis and glomerulosclerosis

accompanied by protein casts and thickening of the mesangial matrix at doses greater than 300 ug/kg.

Also observed in a dose dependent pattern was thymus gland involution and lymphoid depletion. Liver enlargement was also observed for the higher dose groups with increases in cholesterol, triglycerides, albumin, globulin and total protein. Microscopic changes of centrilobular necrosis were observed in the high dose group. Study drug effects were also seen in the thyroid of rats. Increases in the size and number of follicles were reported accompanied by periglandular fibrosis in some animals at doses 100 ug/kg.

The effects on the liver and kidney remained apparent, though at a lesser incidence and severity, at the end of the recovery period. The effects on the thyroid were observed with increased incidence after the recovery period.

In monkeys receiving doses of palifermin up to 300 ug/kg either SC or IV daily for 28 days, study drug related findings included acanthosis and hyperkeratosis of the skin (scalp, mammary area, gluteal region), hyperplasia of the mucosa of the tongue and esophagus, hyperplasia of goblet cells in all regions of the GI tract. One high dose monkey was sacrificed moribund. This animal showed significant weight loss and severe reduction in food consumption. Slight weight loss was noted for the surviving high dose mid-study but returned to amounts similar to control by the end of dosing. A decrease in mean RBC counts, hematocrit, and hemoglobin were noted at doses of $\leq$ 100 µg/kg/day. Slight decreases in hematocrit and hemoglobin were noted in females treated with 30 µg/kg/day. No treatment-related changes in hematology parameters were noted in groups treated with $\leq$ 10 µg/kg/day. The observed hematology changes were not apparent at the end of recovery.

Increased organ weight of the submandibular gland accompanied by elevation of serum amylase and hypertrophy of the acinar cells (rated slight) was noted for the high dose group. Involution of the thymus was also noted and did not resolve after the recovery period. These findings are thought to be primarily due to the pharmacological activity of the study drug and appeared to be largely reversible in the monkeys.

The toxicokinetic analysis showed that serum concentration time profiles of palifermin displayed an initial rapid decline followed by a plateau between 1 and 3 hours post-dose. The incidence of anti-drug antibodies increased with dose and dosing duration and appeared to increase with palifermin serum concentration.

Studies to assess the potential for palifermin to induce genetic abnormalities were performed. The following assays were conducted: microchromosome reverse mutation assay, Salmonella/Escherichia coli Mutagenicity Assay, CHO/HGPRT Mutation Assay, Micronucleus genetic assay in mice. No genotoxic effects of palifermin were observed under the conditions of these studies.

Studies to evaluate the potential for palifermin to promote tumor growth were conducted in vitro and in vivo. A series of human tumor cell lines were studied to determine the presence and

relative levels of the KGF receptor expression. In addition, xenograft models of tumor promotion were studied with human tumor cells implanted subcutaneously followed by treatment with palifermin or vehicle. The interpretation of the data is subject to debate. : One tumor type [redacted] showed a statistically significant growth enhancement in a dose dependent manner when exposed to increasing doses of palifermin. The results also showed growth of one additional tumor cell line [redacted] to be enhanced by palifermin treatment. However, the sponsor states that this study did not show statistical significance. No toxicokinetics were performed to confirm exposure. Palifermin at higher doses appeared to inhibit growth of some cell lines.

A series of reproductive toxicology studies were performed in rats and rabbits to support this application covering segments one and two only. To determine potential effect of palifermin exposure on fertility parameters, doses of up to 1000 ug/kg/day were administered IV to male rats for two weeks prior to mating. For female fertility assessment, doses of up to 1000 ug/kg/day were administered IV for one week prior to mating and continued through gestational day 7. The results indicate that palifermin exposure at the high dose levels (1000 ug/kg/day) can have an adverse effect on fertility parameters including fertility reduction of pregnancy rate (the number of pregnant rats/number of rats in cohabitation). Female rats treated with 1000 µg/kg/day rHuKGF also had significant reductions in the litter averages for corpora lutea and implantations. An increase in embryonic deaths was noted at doses ≥ 300 ug/kg/day. For male rats, reductions in sperm counts were noted for rats receiving doses ≥ 300 ug/kg/day. Dose dependent microscopic changes related to male fertility included hyperplasia of the tubular epithelium in 100% of rats in the high dose group, necrotic germ cells and/or hypospermia in the epididymal tubules and signs of reduced secretory activity in the seminal vesicles and prostate

To address potential effects on embryo/fetal development, palifermin was administered IV during gestation in doses of up to 1000 ug/kg/day in rats and up to 500 ug/kg/day in rabbits. Dose dependent reduction in body weight gain was observed in rats with doses greater than 300 ug/kg/day and for in rabbits with doses ≥ 150 ug/kg/day. These dose groups also showed increased resorption of the conceptuses in these dose groups. In the rabbit study, increased postimplantation loss and a corresponding decrease in viable litter size were also noted in the 150 µg/kg/day group. Intrauterine growth and survival were unaffected by treatment with doses ≤ 50 µg/kg/day.

In rats, the 300 and 1000 ug/kg/day doses of the test article were associated with increases in embryo deaths evident as significant increases in nonviable embryos and percent nonviable embryos, significant reductions in the litter averages for viable embryos and litter sizes (the sum of viable and nonviable embryos) and increases in the number of dams with nonviable embryos. In animals receiving 1000 µg/kg/day, mean fetal body weight was reduced and postimplantation loss was increased. No effects on embryo/fetal development were observed at doses up to 300 µg/kg/day in rats. For rabbits, no effects on reproductive parameters were noted at doses of 60 ug/kg/day or lower.

Toxicokinetic evaluation of palifermin in pregnant rats was performed. Doses of up to 1000 ug/kg IV were administered. Negligible amounts of palifermin were detected in fetal serum or amniotic fluid.

3.2.2.2 Pharmacologic activity

Keratinocyte growth factor is an endogenously secreted protein that binds to the keratinocyte growth factor receptor (FGFR2IIIb, a splice variant of the FGFR2 receptor). Binding of KGF to its receptor results in proliferation, differentiation, and upregulation of cytoprotective mechanisms (e.g, induction of antioxidant enzymes). The endogenous KGF is produced by mesenchymal cells and is upregulated in response to epithelial tissue injury.

In animal models, KGF receptor binding results in enhanced proliferation of epithelial cells in many tissues, including the tongue, buccal mucosa, and gastrointestinal tract. Of significance to this BLA, KGF can cause hyperplasia of the goblet cell population in the GI epithelium providing increased mucous secretion.

Nonclinical safety issues relevant to clinical use
In rats treated with palifermin at high doses daily for 28 days, findings were noted in liver, kidney and thyroid. These findings did not resolve completely after the recovery period. The thyroid findings actually increased after the recovery period. These toxicities were discussed with the clinical reviewer and no clinical correlations were noted. The dose levels and dosing duration used that resulted in the toxicities are significantly greater than the expected human exposure. Similar toxicities were not observed in monkeys receiving up to 300 ug/kg/day for 28-days.

There is some concern that exposure to palifermin may promote growth of non-hematologic tumors. This concern will be addressed in tumor promotion studies to be performed as part of a post-marketing commitment.

3.2.2.3 Comment clincal reviewer

COMMENT: *The finding of glomerulonephritis and glomerulosclerosis in the rat model with chronic exposure was assessed in the evaluation of clinical safety by reviewing hypertension and proteinuria in the safety data sets (see Section 7.1.4, Other Search Strategies). There is some evidence of a dose dependent increase in hypertension. The evaluation of proteinuria in Colorectal Cancer Studies detected an increased risk of proteinura in paliferimin treated subjects whose baseline urine was negative for protein. This analysis was incomplete because the compliance in collecting urinalyses was poor, and the data collected was only dipsick evaluation of urine without microscopic evaluation.*

There was no evidence of hepatic or thyroid toxicity in the clinical safety data reviewed (See Section 7.1.4 Other Search Strategies).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The information for this submission was submitted electronically in eCTD format. The application was supported by trials conducted by Amgen. The 120-Day Safety Report also contained limited information on results from an investigator-sponsored trial under IND 8783. The following reports and documents were submitted and reviewed for each of these trials in the June 15, 2004 submission. Schemas for the clinical trials are included in Appendix 10.4 Protocol Schemas.

Table 4-1 Documents and Data to Support Licensure of Palifermin by Amgen

Table 4.1 Documents and Data to Support Licensure of Palifermin by Amgen							
Study	Description of Study[1]	Clinical study report	Case report forms[2]	SAS (XPT) Files			Comment
				PK	Safety	Efficacy	
Hematologic Malignancy Peripheral Blood Progenitor Cell (PBPC) Transplantation							
20000162	Ph3 Cy/VPTBI	Final	All 214		X	X	Pivotal study
980231	Ph2 Cy/VP/TBI	Final	38/169		X	X	Support efficacy, safety
960189	Ph1 BEAM	Final	58/264	X	X	X	Safety, efficacy, PK, PRO
20010182	Ph1 TBI/VP/Cy	Final	1/13	X	X		PK and Safety
960226	Long term study	Interim	0		X		Safety
Solid Tumor[3]							
990119	Ph2 Head & Neck	Final	60/101		X	X	Safety
970149	Ph1 Head & Neck	Final	44/60		X	X	Safety
990123	Long term study HN	Interim	0		X		Safety
950225	Ph1 Colorectal	Final	38/149		X	X	Safety
950275	Ph1 Colorectal	Final	38/48		X	X	Safety
950226	Long term study CR	Final	0		X		Safety
Healthy Volunteer Studies							
950170	Subcutaneous	Synopsis	0/28	X	X		Safety, PK, PD
960136	Dose range IV	Synopsis	2/61	X	X		Safety, PK, PD
970276	Dose range IV	Final	4/18	X	X		Safety, PK, PD
970136	Dose range IV	Synopsis	0/24	X			Safety, PK
970290	Repeat testing	Synopsis	0/4	X			Evaluate possible error
20010192	Dose range IV	Final	10/84	X	X		Safety, PK, PD
120 day Safety report Investigator IND Study in Allogeneic transplant setting							
IND 8783	Ph1&2 dose schedule allogeneic	Report	No		X	X	Summary and tables

[1]For full titles of study see table Summary of Clinical Studies below
[2]Case report forms for all patients on pivotal study were submitted; in addition case report forms were submitted on all patients with serious adverse events and for subjects that discontinued treatment for any reason including death.
[3]Studies in solid tumor setting were reviewed for safety, not efficacy.

In addition to the individual study material, the submission includes integrated reports of efficacy in the transplant setting, and integrated reports of safety.

4.2 Tables of Clinical Studies

Table 4-2 Summary of Clinical Studies

Table 4.2 Summary of Clinical Studies		
20000162	A Phase 3, Randomized, Double-blind, Placebo-controlled Trial of Recombinant Human Keratinocyte Growth Factor for Reduction of Mucositis in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation and High-dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell Transplantation.	This is the pivotal trial that supports this application.
980231	A Phase 2, Randomized, Double-blind, Placebo controlled Trial of Recombinant Human Keratinocyte Growth Factor in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation and High-dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell Transplantation.	Provides supportive data for efficacy in the 86 patients treated with rHuKGF on the same schedule as pivotal trial & contributes 169 patients to safety evaluation.
960189	A Phase 1-2 Randomized, Double Blind, Placebo Controlled, Dose Escalation Trial of the Safety of Recombinant Human Keratinocyte Growth Factor in Hodgkin's Disease and Non-Hodgkin's Lymphoma Patients Undergoing High Dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell Transplantation	Provides safety data in transplant patients
20010182	An open-Label Study of the Pharmacokinetics (PK) of Recombinant Human Keratinocyte Growth Factor in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation and High-Dose Chemotherapy Followed by Peripheral Blood Progenitor Cell Transplantation.	Provides PK data using dose and schedule used in transplant setting & safety data in transplant patients
960226	A Long-term Follow-up Study of Patients With Hematologic Malignancies Who Were Previously Enrolled in Amgen-sponsored Clinical Trials Using Recombinant Human Keratinocyte Growth Factor	Long term follow up safety (especially focused on tumor control and promotion)
990119	A Phase 2 Study of Recombinant Keratinocyte Growth Factor in Head and Neck Cancer Patients Receiving Concurrent Chemotherapy with Standard or Hyperfractionated Radiation Therapy	Provides safety data
970149	A Phase 1-2 Study of Escalating Doses of Recombinant Keratinocyte Growth Factor in Head and Neck Cancer Patients Undergoing Chemoradiotherapy	Provides safety data
990123	A Long-term Follow-up Study of Head and Neck Cancer Study Subjects Previously Enrolled in Amgen sponsored Clinical Trials with Recombinant Human Keratinocyte Growth Factor	Long term follow up safety (especially tumor control and promotion)
950225	Randomized, Double-blind, Placebo controlled, Phase 1 Trial of Intravenously Administered Recombinant Human Keratinocyte Growth Factor in Colorectal Carcinoma Patients Treated with 5-Fluorouracil and Leucovorin: rHuKGF Dosing Before Chemotherapy	Provides safety data
950275	Open-label Study of Intravenously Administered Recombinant Human Keratinocyte Growth Factor in Colorectal Carcinoma Patients Treated With 5-Fluorouracil and Leucovorin: Cycle 2 Through 7	Provides safety data
950226	A Long-term Follow-up Study of Colorectal Carcinoma Patients Who Were Previously Enrolled in Amgen sponsored Clinical Trials Using Recombinant Human Keratinocyte Growth Factor	Long term follow up safety (especially tumor control and promotion)
950170	Randomized, Double-blind, Placebo-controlled Tolerability and Pharmacokinetic Trial of Recombinant Human Keratinocyte Growth Factor in Normal Volunteers	Safety, tolerability, pharmaco-kinetics when given subcutaneously – concluded subcutaneous administration not ideal
960136	Randomized, Double-blind, Placebo-controlled Tolerability and Pharmacokinetic Trial of Intravenously Administered Recombinant Human Keratinocyte Growth Factor in Normal Volunteers	Safety, tolerability, pharmacokinetics when given IV
970276	Randomized, Double-blind, Placebo-controlled, Safety, Biologic Activity and Pharmacokinetic Trial of Recombinant Human Keratinocyte Growth Factor in Normal Volunteers	Pharmacodynamic, safety, tolerability, and pharmacokinetics when given IV
970136	Safety and Pharmacokinetics of AMJ-9701 by Single Intravenous Injection in Healthy Volunteers	Japanese Study - safety, tolerability, and pharmacokinetics IV single dose
970290	Pharmacokinetics of AMJ-9701 by Single Intravenous Injection of 10 µg/kg in Healthy Volunteers	Japanese Study - evaluate outliers in 970136
20010192	A Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic of Recombinant Human Keratinocyte Growth Factor (rHuKGF) After Intravenous Administration to Healthy Volunteers	Pharmacodynamic, safety, tolerability, and pharmacokinetics when given IV single dose

4.3 Review Strategy

The efficacy review focused on the data submitted for Study 20000162 (the pivotal study) and Study 980231 (a supporting clinical trial). The data from the subset of patients in Study 980231 who were treated with a dose and administration schedule identical to that of Study 20000162 were reviewed as data supporting the results of the pivotal study. Safety information regarding palifermin in the transplant setting also included data from Studies 960189, 20010182, and 960226. Additional safety data was obtained from 6 additional studies in the solid tumor setting and 6 studies in healthy donors.

4.4 Data Quality and Integrity

For the efficacy review of Study 20000162 the following analyses were done:

1. Review to determine if the results of the primary endpoint, duration of WHO grade 3 and 4 oral mucositis, were similar in the individual centers and if the randomization of patients was balanced in the individual centers. Treatment 1 is palifermin and treatment 0 is placebo. See figure 4.1 and table 4.3 below:

Figure 4-1 Median Duration Grade 3 and 4 WHO Mucositis by Treatment Center

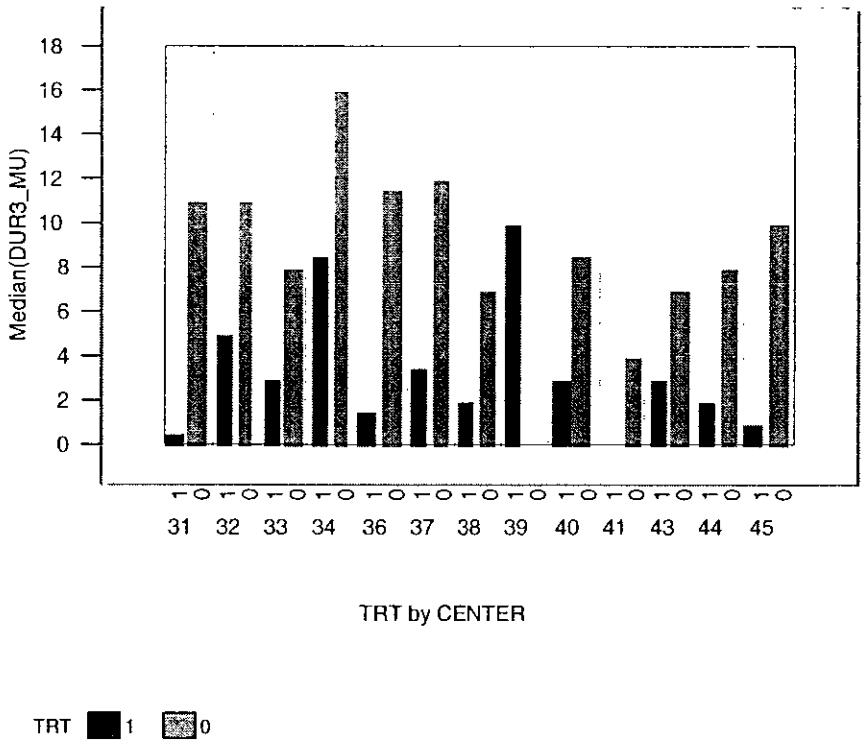


Table 4-3 Distribution of Randomization by Treatment Center

Table 4.3 Distribution of Randomization by Treatment Center													
Center	31	32	33	34	36	37	38	39	40	41	43	44	45
Total Subjects	29	40	30	13	8	10	25	1	6	5	17	17	11
KGF	14	19	15	6	4	6	13	1	4	3	8	8	6
Placebo	15	21	15	7	4	4	12	0	2	2	9	9	5

Comment: *Centers 31 and 32 were chosen as audit sites because they contributed the most patients and a change in data from center 31 was most likely to change the ultimate results.*

2. Review the data in the XPT file (endpt.xpt) for duration of WHO grade 3 and 4 mucositis (DUR3_MU), the measurement of the primary endpoint, was compared with data obtained directly from the clinical report forms (CRF). All CRF's for 20000162 were reviewed and the result compared with Amgen's result. There were 16 discrepancies, which favored Amgen's conclusion, and 16 discrepancies that weakened Amgen's conclusion. The table below compares the reviewer's analysis and Amgen's analysis of the mean duration of grade 3 or greater mucositis.

Table 4-4 Comparison of Reviewer Assessment of Primary Endpoint to Amgen's Assessment

Table 4.4 Comparison of Reviewer Assessment of Primary Endpoint to Amgen's Assessment					
Treatment	**Number of Subjects**	**Days grade 3+ WHO mucositis (Reviewer)**		**Days grade 3+ WHO mucositis (Amgen)**	
		Mean	**Median**	**Mean**	**Median**
Placebo	106	10.5	9	10.4	9
KGF	106	3.9	3	3.7	3

COMMENT: *The major difference in this caluculation of duration is a difference in method used by Amgen and the reviewer to calculate the duration of oral mucositis. Amgen counted the number of days a patient was classified as 3 or 4. Using this method if the WHO grade of oral mucositis was 3, then 2, then 3 again the duration is 2 days. The reviewer counted the duration from the first designation of WHO grade 3 or 4 oral mucositis until there were no additional days of grade 3 or 4 mucositis, in the example above the duration would be 3 days. In the Statistical Analysis Plan for Study 20000162 Amgen specified the method used in this application (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 907). The reviewer's method defines the length of time a patient would be experiencing this level of mucositis until it had resolved. The discrepancies in number of days of mucositis are minor and do not affect the conclusion.*

3. Review the data in the XPT file (endpt.xpt) for morphine equivalents of parenteral opioid analgesic (DOSE_OA), the measurement of cumulative parenteral opioid, was compared with data obtained directly from the clinical report forms (CRF). All CRF's for 20000162 were reviewed and the result compared with Amgen's result.

Table 4-5 Comparison of Reviewer Assessment of Opioid Requirement to Amgen's Assessment

Table 4.5 Comparison of Reviewer Assessment of Opioid Requirement to Amgen's Assessment					
Treatment	**Number of Subjects**	**Morphine Equivalents mg (Reviewer)**		**Morphine Equivalents mg (Amgen)**	
		Mean	**Median**	**Mean**	**Median**
Placebo	106	947.0	527.8	1146.5	534.9
KGF	106	545.2	226.5	699.5	211.6

Discrepancies were discussed with Amgen on a conference call 10/25/04. One major factor responsible for the discrepancy is that Amgen counted the day a fentanyl patch was placed and the day it was removed as a 24 hour exposure. These patches deliver fentanyl for a 72-hour period. By using this method of counting, the dose of fentanyl calculated from a single patch was equivalent to a 96-hour exposure. This was a systematic error since it was applied in the same manner to all subjects who were treated with patches. Overall, however, there were 20 placebo subjects and 14 palifermin subjects treated with fentanyl patches, and the mean dose of morphine equivalents in the placebo arm was inflated to a greater extent than in the palifermin arm. This error has less of an effect on the median dose of morphine equivalents. At the reviewer's request, Amgen recalculated this data using a half-day exposure for each patch on the days patches overlapped. This does not completely correct the error as shown in the table below:

Table 4-6 Amgen's Revised Assessment of Opioid Requirement Compared to Original

Table 4.6 Amgen's Revised Assessment of Opioid Requirement Compared to Original					
Treatment	**Number of Subjects**	**Morphine Equivalents mg (Original)**		**Morphine Equivaients mg (Revised)**	
		Mean	Median	Mean	Median
Placebo	106	1146.5	534.9	1143.5	534.9
KGF	106	699.5	211.6	699.0	210.0

The second reason for the discrepancy is imputation of missing data. If the missing dose did not have two adjacent values the dose was imputed using the highest dose that any subject with the same underlying malignancy required. This was the major factor in the difference in the reviewer's calculated mean compared to Amgen. The third type of discrepancy noted was that Amgen counted only opioid analgesics that were designated as having been given for mouth and throat soreness. This is not the method outlined in the statistical analysis plan for Study 20000162 (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 904) which stipulates recording the "Use of parenteral or transdermal opioid analgesics (in mg morphine equivalents) over the study period". Amgen's analysis was limited to opioid analgesics designated as being administered for mouth and throat soreness.

Amgen has submitted an additional analysis of the median dose of morphine equivalents in which doses were included irrespective of the reason for administration. The analysis of median mg dose of morphine equivalents for subjects without missing data was also included. These analyses do not substantially affect the difference in the medians of these two groups as is presented in the table below:

Table 4-7 Amgen's Additional Analysis of Opioid Analgesic Use

Table 4.7 Amgen's Additional Analysis of Opioid Analgesic Use				
	All Indications		Oral Mucositis Dysphagia	
	Placebo	Palifermin	Placebo	Palifermin
Incidence	103/106 (97%)	92/106 (87%)	103/106 (97%)	83/106 (78%)
Missing doses Imputed				
Median dose mg	535	236	535	212
Median dose mg (subjects who received opioids)	567	297	565	291
Subjects without missing dose information				
Number	103	101	103	103
Median dose mg	532	215	522	199

COMMENT: *These analyses demonstrate that the difference in the method of determination of the morphine equivalents by Amgen and the reviewer does not affect the conclusion that the requirement for parenteral opioid analgesics is less in the palifermin treated subjects.*

4. The Adverse event page of the CRF's was reviewed for every subject enrolled on Study 20000162. The Adverse event pages of the CRF's from the approximately 20% of subjects from Studies 9600189 and 980231 that were submitted were also reviewed. The adverse events reported were of the types and severity that would be expected in the transplant setting.

5. Division of Scientific Investigations (DSI) audited two sites. These included City of Hope National Medical Center, CA (designated site 32) and Cardinal Bernadin Cancer Center, IL (designated site 31).

A summary of outcome of these inspections derived from the DSI report is presented in the table below:

Table 4-8 Summary of DSI Inspections of Selected Study 20000162 Sites

Table 4.8 Summary of DSI Inspections of Selected Study 20000162 Sites				
Clinical Investigator	Location	Inspection Date	EIR Received	Classification[1]
Ricardo Spielberger, M.D.	City of Hope National Medical Center, California	Aug 2-17, 2004	Aug 24, 2004	VAI
Patrick J. Stiff, M.D.	Cardinal Bernadin Cancer Center, Illinois	Aug 31- Sep 10, 2004	Sep 28, 2004	VAI

[1]Key to Classifications: NAI = No deviation from regulations. Data acceptable; VAI = Minor deviation(s) from regulations. Data acceptable; OAI = Significant deviations from regulations. Data unreliable; Pending = Inspection not completed

Overall conclusion

There were several instances of protocol deviations. In general, for the two clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects existed,

fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. Overall, data from the clinical sites inspected appear acceptable for use in support of this BLA.

4.5 Compliance with Good Clinical Practices

The cover page of each of the study reports and synopses (eCTD M5.3.5) included the following declaration: "Good Clinical Practice: This study was conducted in accordance with the Principles of Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) regulations/guidelines.
Essential documents will be retained in accordance with ICH GCP."

4.6 Financial Disclosures

Financial disclosure information was submitted for the following studies in human subjects included in the application to establish the safety and efficacy of palifermin in subjects with hematologic malignancies undergoing myelotoxic therapy requiring hematopoietic stem cell support (eCTD M1.3.4):

- 20000162 A Phase 3, Randomized, Double-blind, Placebo-controlled Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) for Reduction of Mucositis in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation (TBI) and High-dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell (PBPC) Transplantation.

- 980231 A Randomized, Double-blind, Placebo controlled Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation (TBI) and High-dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell (PBPC) Transplantation.

- 20010182 An open-Label Study of the Pharmacokinetics (PK) of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation and High-Dose Chemotherapy Followed by Peripheral Blood Progenitor Cell (PBPC) Transplantation.

Amgen certified that all Principle Investigators participating in Studies 2000162, 980231 and 20010182 provided financial disclosure information. All Sub-investigators in Study 20010182 provided financial disclosure information. Two Sub-investigators Participating in Study 2000162 from one site, which provided 6 patients to the Study 2000162, did not provide financial disclosure information. Three Sub-investigators participating in Study 980231 did not provide financial disclosure information, one at a site that contributed 8 patients, one at a site that contributed no patients, and one at a site that contributed 10 patients.

Amgen certified that the clinical investigators outlined in the previous paragraph that provided disclosure information have certified to the absence of significant proprietary and or equity interests in either palifermin or Amgen Inc. As the sponsor of the submitted studies, Amgen Inc. also certified that it has not entered into any financial arrangements with the listed clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), and that these investigators were not recipients of significant payments of other sorts as defined in 21 CFR 54.2(f).

5 CLINICAL PHARMACOLOGY

This section is adapted from the Summary of Clinical Pharmacology and Biopharmaceutics Findings of BLA 125103 – Review PK PD.

5.1 Pharmacokinetics

In this license application, 8 clinical studies provide information about the pharmacokinetic properties of palifermin; 6 of which were conducted in healthy volunteers, and 2 studies were conducted in subjects with hematologic malignancies receiving high-dose cytotoxic therapy followed by PBPCT.

Table 5-1 Palifermin Studies that Provided Pharmacokinetic Information

Table 5.1 Palifermin Studies that Provided Pharmacokinetic Information				
Study #	**# Subjects Received Placebo**	**# Subjects Received Palifermin**	**Range of dose Route of Administration**	**# Dose/ subject**
Healthy Volunteers				
Study 950170[1]	3 4	9 12	1.0, 10, or 30 µg/kg, SC 1.0 or 10 µg/kg, SC	1 3
Study 960136[1]	5 10	16 30	0.2, 1, 5, 10 or 20 µg/kg, IV 0.2, 1, 5, 10 or 20 µg/kg/day, IV	1 3
Study 970136 (Japan)	6	18	5.0, 10, 20 µg/kg, IV	1
Study 970276[1]	6	12	20 or 40 µg/kg/day, IV	3
Study 970290 (Japan)	0	4	10 µg/kg, IV	1
Study 20010192[1]	16	63	60, 90, 120, 160, 210 or 250 µg/kg, IV	1
Study 20030142[2]	Renal impairment, ongoing			
Subjects with Hematologic Malignancies				
Study 960189[3]	4	13	60 µg/kg/day, IV	6
Study 20010182	0	13	60 µg/kg/day, IV	6

[1] These studies provided information on the pharmacodynamic properties of palifermin, buccal biopsies at baseline and at a single time point (either 48 hrs or 72 hrs) post-dose.
[2] A study in volunteers with renal impairment is ongoing and is not included in the BLA
[3] A phase 1/2 dose-escalation study in subjects with Hodgkin's disease and non-Hodgkin's lymphoma.

Mechanism of Action: Palifermin (recombinant human KGF, rHuKGF) stimulates the growth of epithelial cells from a wide variety of tissues but, due to the restricted expression of the keratinocyte growth factor (KGF) receptor, has no known direct effect on other cell types. Palifermin has been shown to substantially reduce injury to the oral and gastrointestinal (GI) tract mucosa and salivary glands in numerous models of radiation-induced and chemotherapy-induced GI injury. The protective activity of palifermin has been attributed not only to its mitogenic effect on mucosal epithelium, which can result in both increased epithelial thickness (when dosed prior to cytotoxic insult) and improved recovery (when dosed shortly after myelotoxic therapy, before overt ulceration occurred), but also to its impact on intercellular junctions (which may increase the physical integrity of the tissue) and on various cytoprotective mechanisms. Because of these properties, palifermin has the potential to prevent epithelial injury

caused by myelotoxic chemotherapy or radiation, and accelerates the healing process after the cytotoxic insult has occurred.

Single-Dose Pharmacokinetics: After single IV doses of 20 to 250 µg/kg (healthy subjects) and 60 µg/kg (cancer patients) of palifermin, serum drug concentrations declined rapidly (over 95% decrease) in the first 30 minutes postdose and a slight increase or plateau in concentration occurred at approximately 1- to 4-hours, followed by a terminal decline phase. Palifermin exhibited linear pharmacokinetics with extravascular distribution and an average terminal half-life ($t_{1/2}$) of 4.5 hours (3.3-5.7 hours). On average, total body clearance (CL) appeared to be 2- to 4-fold higher, and volume of distribution at steady state (Vss) to be 2-fold higher in cancer patients compared with healthy subjects after a 60 µg/kg single dose of palifermin.

Multiple-Dose Pharmacokinetics: Not surprisingly given the short elimination half-life, no accumulation of palifermin, as measured by area under the concentration-time curve (AUC), occurred after 3 consecutive daily doses to healthy subjects (20 and 40 mg/kg/day) or to patients with hematologic malignancies (60 mg/kg/day).

Binding Proteins: It is known that endogenous KGF is a heparin binding protein. Palifermin is a recombinant human KGF and it has been showed that palifermin binds to heparin *in vitro*. Consequently, for the labeled indication, a statement has been included in the physician information to ensure that IV lines utilizing heparin are rinsed with saline prior to administration of palifermin.

Distribution, Excretion and Elimination: Volume of distribution at steady state (Vss) for palifermin was greater than total body water volume, indicating extracellular distribution of palifermin after IV administration. This result is consistent with the KGF receptor's prevalence on all epithelial cells, and the binding of palifermin to this receptor.

Renal elimination plays a role in the clearance of radiolabeled palifermin in rats. Approximately 11% of a radioactive dose administered to rats was recovered in the urine as trichloro-acetic acid perceptible radioactivity over 24 hours, suggesting that some intact palifermin and/or smaller fragments may be excreted in the urine. Exposure to palifermin, as measured by AUC, increased by approximately 2-fold in bilaterally-nephrectomized rats compared to that observed in sham-operated rats, also suggesting that the kidneys play a role in the elimination of palifermin. It is possible that other organs may also participate in the elimination of palifermin through its binding to the KGF receptor and internalization/breakdown within epithelial cells.

Metabolism: The expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids, and the metabolic pathways are generally understood (ICH S6). As such, classical biotransformation studies as performed for pharmaceuticals are not conducted for biologic products. Because palifermin is a biologic molecule, no *in vitro* permeability, *in vitro* metabolism, or metabolic drug-drug interaction studies were performed for palifermin. However, palifermin has been shown to bind to heparin *in vitro* since KGF is a heparin-binding member of the fibroblast growth factor (FGF) family.

Drug-Drug Interactions: There were no formal in vivo nonclinical and clinical pharmacokinetic drug interaction studies conducted with palifermin but possibility was addressed as part of animal model evaluations. When granulocyte colony-stimulating factor (G-CSF), which is likely to be used in the indicated patient population, was used in combination with palifermin in murine and nonhuman primate chemotherapy/ radiotherapy models, there was no evidence of a drug interaction.

Pharmacokinetics in Special Populations: No formal studies were conducted to evaluate the effect of intrinsic or extrinsic factors on pharmacokinetics (PK) of palifermin except a study in subjects with renal impairment is ongoing, based on the observation of approximately 2-fold higher exposure in bilaterally-nephrectomized rats compared to sham-operated rats. The renal impairment study is not included in the BLA. The effects of age, weight, sex, and race/ethnicity on the PK of palifermin were explored using a combined dataset from studies in healthy subjects and another combined dataset from subjects with hematologic malignancies who participated in the two clinical studies. Neither weight nor sex appeared to have a notable effect on the PK of palifermin. Age did not appear to significantly alter the CL of palifermin, although the limited numbers of elderly patients preclude definitive conclusions. The effect of race/ethnicity on PK of palifermin was inconclusive because most of the subjects who provided the PK dataset were white; however, there is little rationale for race to influence the PK of palifermin.

Inter-Individual Variability in PK Data: Intersubject variability of approximately 40% has been observed for palifermin CL and up to 70% for Vss in the studies conducted in healthy subjects. A higher level of intersubject variability in palifermin CL and Vss was observed in patients with hematologic malignancies as evidenced by the wider range of parameter values. This higher variability could be related to underlying disease/treatment.

Rationale for Dose Selection: Early preclinical and clinical data in healthy subjects suggested that at the doses tested, 3 consecutive days of palifermin administration and 40 mg/kg/day were required to produce consistent biological activity on epithelial cells. In the phase 1/2 study, there were excess dose-limiting toxicities when 80 mg/kg/day was administered both before and after cytotoxic therapy. Based on these results, the dose of palifermin (60 mg/kg/day) was selected to use in the phase 2 and the phase 3 trials. Although a more recent pharmacology study in healthy subjects suggest that palifermin may be biologically active with higher single doses, the safety and efficacy of such a dosing strategy has not been investigated for the proposed indication.

5.2 Pharmacodynamics

Pharmacodynamic Findings: In buccal biopsies collected from healthy volunteers, a significant increase in Ki67 staining (a >200% increase in Ki67-stained area relative to baseline, a surrogate measure of epithelial cell proliferation) was observed up to 72 hours after intravenous administration of 3 consecutive daily doses of palifermin as low as 40 mg/kg/day or at single doses of 160 to 250 mg/kg. Of note, at 48 hours after dosing, the measured proliferation was highest but most of the quantifiable palifermin concentration values were less than twice the lower limit of quantification of the assay, indicating that the pharmacologic effect persists after active drug levels have dissipated.

5.3 Exposure-Response Relationships

Exposure-Response: The measurement of epithelial cell proliferation (as assessed by Ki67 staining) in the buccal mucosa before and after palifermin administration is a useful marker for palifermin's biologic activity. In a single dose study, analysis of epithelial cell proliferation demonstrated increased epithelial response with increased palifermin exposure at doses ranging from 60 to 250 mg/kg, with a plateau above 160 mg/kg. However, a clear correlation between exposure and efficacy/safety was not apparent.

5.4 Overall Summary of Pharmacology Review

Summary: Palifermin exhibits linear pharmacokinetics in the dose range of 10 to 250 mg/kg after single-dose administration to healthy volunteers. Palifermin exhibits extravascular distribution with an average terminal half-life of 4.9 hours in healthy subjects and 4.4 hours in subjects with hematologic malignancies. After a single IV dose, CL and Vss were higher in subjects with hematologic malignancies than in healthy subjects. No accumulation of palifermin occurred after multiple dosing to healthy subjects (3 consecutive daily doses of 10, 20, and 40 mg/kg) or to subjects with hematologic malignancies (3 consecutive daily doses of 60 mg/kg). No apparent differences were observed in the PK of palifermin between men and women (M/F ratio was 29/15 in healthy subjects and 13/9 in patients). In buccal biopsies taken from healthy subjects, increases in epithelial cell proliferation (a >200% increase in Ki67-stained area relative to baseline) were observed in at least 50% of subjects at doses of 40 mg/kg/day administered for 3 consecutive days and at single doses of 120 to 250 mg/kg. The proposed clinical dose (60 mg/kg/day for 3 consecutive days before and after high-dose chemotherapy with PBSCT) for patients with hematologic malignancies is within the range of doses that have shown biological activity.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication - ⊂ ⊐ decreasing the severity of mucositis

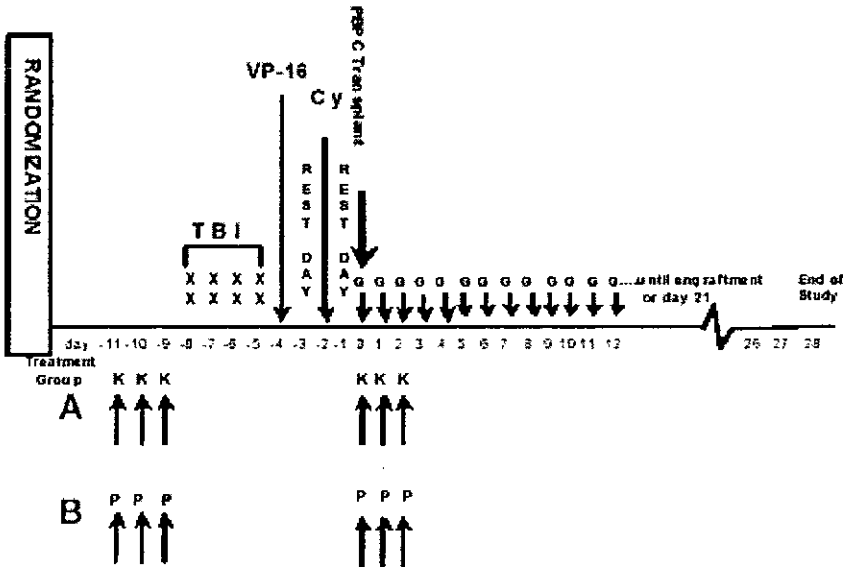
This license application is for the use of palifermin to decrease the incidence, duration, and severity of oral mucositis and related sequelae, and improve functioning in patients with hematologic malignancies receiving high-dose myelotoxic therapy requiring hematopoietic stem cell support.

6.1.1 Methods

6.1.1.1 Study 20000162

This approval is based on the results of Amgen Study 20000162 conducted between 3/23/01 and 10/23/02. This trial was a phase 3 double blind placebo (P) controlled evaluation of palifermin (K) given at a dose of 60μg/kg per day intravenously for 3 consecutive days prior to administration of a preparative regimen consisting of 1200 cGy fractionated total body irradiation, etoposide 60 mg/kg, and cyclophosphamide 100 mg/kg, and for 3 consecutive days after infusion of a minimum of 1.5 X 10^6 cryopreserved autologous CD 34 positive peripheral blood stem cells. Amgen's study schema is presented below (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 43):

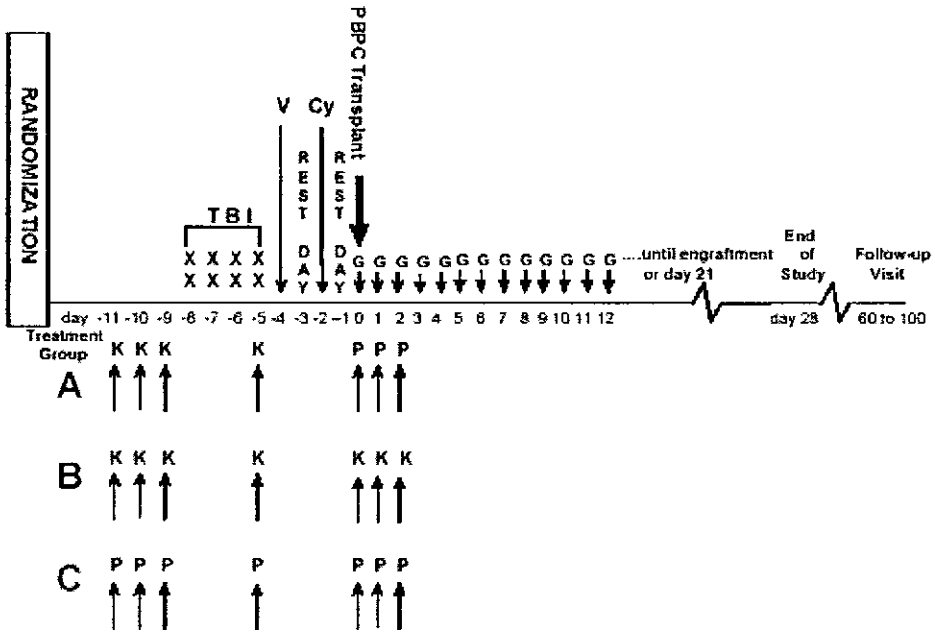
Figure 6-1 Schema of Trial Study 2000162



6.1.1.2 Study 980231

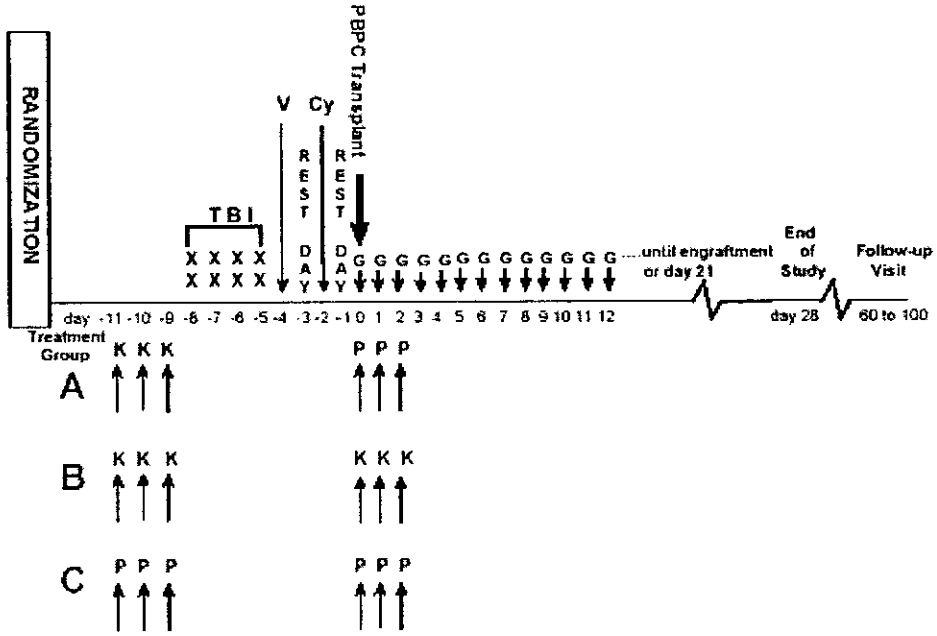
The second trial used to support the efficacy claims for palifermin is Amgen trial 980231. This trial was conducted between 2/23/99 to 7/24/00. This trial was the phase 2 double blind placebo controlled evaluation of palifermin in a transplant setting. The preparative regimen consisted of 1200 cGy fractionated total body irradiation, etoposide 60 mg/kg, and cyclophosphamide 75-100 mg/kg. The only significant difference in the preparative regimen compared to trial 20000162 was the range of dose for cyclophosphamide. A minimum of 1.5 X 10^6 cryopreserved autologous CD 34 positive peripheral blood stem cells were infused on day 0. In the initial phase of the trial patients were randomized in a 1:1:1 ratio to: (A.) palifermin (K) 4 doses and placebo (P) 3 doses; (B.) palifermin (K) 7 doses; or (C.) placebo (P) 7 doses on days –11, -10, -9, -5, 0, 1, 2. Amgen's study schema for this portion of the study is presented below (eCTD 5.3.5.1.3, Clinical Study Report 980231 page 63):

Figure 6-2 Schema of Original Trial in Study 980231



During the initial phase of this trial, analysis of subjects treated under the 7-dose schedule revealed no significant statistical or clinical difference in duration of oral mucositis between the palifermin and placebo groups. Furthermore, in the analyses of subjects who received all 7 doses, a negative although not statistically significant trend of increased duration of oral mucositis was observed for the palifermin 7-dose schedule group (B). As a consequence, the study was revised to omit the day –5 dose. Amgen's study schema for the amended study is presented below (eCTD 5.3.5.1.3, Clinical Study Report 980231 page 64):

Figure 6-3 Schema of Revised Trial in Study 980231



In this phase of the study, subjects treated on the palifermin arms demonstrated a decrease in the duration of severe mucositis. The results in subjects who received 6 doses of palifermin were marginally better than those in subjects who received 3 doses. As a result, the 6-dose schedule was chosen for Study 20000162 (the pivotal trial), and the subset of subjects treated with 6 doses on Study 980231 is used in this application to support the results of Study 20000162. This subset included 40 patients in the placebo group, and 46 patients in the palifermin group who received treatment identical to that used in the palifermin arm of Study 20000162.

6.1.2 General Discussion of Endpoints

Statistical Analysis Plans

6.1.2.1 Study 2000162

Amgen's Original Statistical Analysis Plan for Study 2000162 was dated 2/14/01, the second version with changes resulting from Amgen's internal review was dated 10/15/01 and submitted to the FDA 3/13/02 (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 903). The Statistical Analysis was reviewed by the FDA and comments forwarded to Amgen 9/3/02. The final version of the Statistical Analysis Plan version 4, was amended to incorporate changes to address FDA' s comments regarding imputation of data for subjects who die or withdraw from the study, inclusion of additional sensitivity analyses to address imputed data, and request for more details regarding the re-estimation of sample size. Version 4 dated 10/30/02 is the final version and is the version used to analyze trial 2000162.

The efficacy endpoints of this study outlined in the Statistical Analysis Plan dated 10/30/02 were:
Primary:

- The duration of severe mucositis is calculated as the number of days on which a subject's daily oral mucositis assessments are scored as WHO grade 3 or 4. If a subject does not experience any WHO grade 3 or 4 mucositis, his/her duration of severe mucositis will be 0 days. Where there are missing daily oral mucositis assessments bounded by two observed assessments before discharge, the missing assessment(s) will be assigned the larger boundary value and will be included in the primary endpoint calculation. This same rule will be applied to gaps after a subject is discharged with WHO grade 3 or 4 mucositis but the follow-up assessments are not done daily.

Secondary:
HRQOL and Clinical Sequelae Related to Oral Mucositis

- subject's self assessment of mouth and throat soreness as summarized by AUC of the daily VDS score (Question 2 in the HRQOL questionnaire) over the study
- use of parenteral or transdermal opioid analgesics (in mg morphine equivalents) over the study period

Oral Mucositis as Measured by Different Severity Grades of Interest and by Other Visual Assessment Scales

- incidence of WHO grade 4 oral mucositis
- duration (days) of WHO grade 2, 3, or 4 oral mucositis
- duration of WCCNR grades 2 or 3 oral mucositis on the Lesion sub-scale

6.1.2.2 Study 980231

The Statistical Analysis Plan describing the statistical methods used to analyze Study 980231 is dated 4/23/04 and is version 3 (eCTD M.5.3.5.1.3, Clinical Study Report 980231 page 1199). The original protocol for this study was dated November 17th, 1998. Subsequently, there were 2 amended protocols dated 5/27/99 and 8/17/99. The first amendment allowed for the inclusion of patients 12 years and older, patients with multiple myeloma, and patients with a tandem-transplant regimen. The second adopted a 6-dose treatment schedule by eliminating the 4th dose at day –5 of the blinded investigational product from the originally designed 7-dose schedule. Changes in version 3 of the Statistical Analysis Plan include:

- subjects with the 6-dose and the 7-dose schedules are analyzed separately
- a detailed statistical method on the imputation of daily oral mucositis assessment grades
- a nonparametric method (i.e., generalized Cochran-Mantel-Haenszel (CMH) test) to analyze the efficacy endpoints
- for duration type secondary endpoints, analyses are based on all treated subjects (ie, subjects who receive at least one dose of investigational product.) as well as subjects who had the events (affected subjects) during the study

The efficacy endpoints of this study outlined in the Statistical Analysis Plan dated 4/23/04 were:
Primary

- To evaluate the efficacy of palifermin in reducing the duration of severe oral mucositis (WHO grade 3 or 4) induced by total body irradiation (TBI) and high-dose chemotherapy in subjects with hematologic malignancies.

Secondary

- Improving PRO as measured by mouth and throat soreness and its sequelae
- Reducing clinical sequelae related to oral mucositis
- Reducing oral mucositis as measured by different severity grades of interest and by other visual assessment scales.
- Assess the feasibility, reliability and validity including sensitivity of the Oral Mucositis Daily Questionnaire (OMDQ)

Regulatory History of Efficacy Endpoints

The following are excerpts of portions of meeting minutes with Amgen during the development of palifermin for the transplant setting discussing efficacy endpoints:

DATE: September 30, 1999
SUBJECT: BB-IND [ ]End of Phase 2 Meeting
INTRODUCTION:
Amgen, Incorporated is investigating keratinocyte growth factor (human, recombinant, *E. coli*) as a treatment or preventative measure for oral mucositis resulting from chemotherapy and/or radiation therapy. The purpose of this meeting was to discuss key issues in the development of this product.

DISCUSSION: [regarding efficacy endpoints]
CBER[FDA] asked the sponsor to clarify how an assessor distinguishes grade 2 from grade 3 mucositis. For example, CBER asked how a patient would be graded if his/her mouth is sore but they can swallow. Amgen stated that the presence of ulcers would require a grade 2 mucositis rating. CBER asked what types of training assessors receive and which individuals perform the assessments. The sponsor stated they have been training the oncologist and the research nurse to do the assessments and they are providing training as well as photographs of examples of grades 1, 2, 3, and 4 mucositis. CBER asked that the sponsor submit the photographs and training material to the file. CBER asked if the sponsor had considered photographing the patients' mouth for each evaluation. The sponsor stated that good oral photographs are hard to obtain and patient cooperation may not be possible but they would consider other alternatives.

DISCUSSION ISSUES: [regarding efficacy endpoints]
Acceptability of WHO oral mucositis scale as an endpoint tool for measuring prevention and/or treatment of oral mucositis induced by chemotherapy.

CBER stated the WHO scale could potentially be used but the Agency needed to review the Phase 2 data and do additional research on the WHO scale. If the WHO scale is used, the Center wants to see clinical improvement in grades 3 and 4 mucositis. The sponsor asked what information would be acceptable if they wanted to use the WHO scale to evaluate grades 2, 3, and 4. CBER stated the sponsor would have to win on all grades. In addition, the sponsor needed to quantitate analgesic use with the WHO scale. CBER also recommended the sponsor provide data on different clinical sequelae and how they correlate with the WHO scale. CBER recommended that a blinded assessor be used, that assessments be made every 3 days either by phone or an oral exam, and that the sponsor should clearly describe what foods are classified as liquids (i.e. pureed versus Jell-O) and solids.

In summary, CBER emphasized that it was important for them to demonstrate an effect on the anatomic findings and the functional findings as well (e.g. ability to eat, pain). Improvements in grade 2 mucositis as defined by the WHO criteria may have little relevance for the quality of life of the patient whereas improvements in grade 3 and 4 would be significant. This also has to be coupled with the possible negative effect on the anti-tumor therapy if KGF turns out to interfere with efficacy. The assessments of mucositis must be frequent in order not to miss or lose data on the peak severity of mucositis and to get some idea of duration, since grade 3 mucositis of one day's duration is less concerning than grade 2 mucositis of 10 day's duration.

Amgen did not propose measures, in their pivotal trial, for conducting amylase and lipase studies where a proportion of patients may be unblinded due to clinical and laboratory pharmacological effects of rHuKGF.

CBER noted that it is not acceptable for the sponsor to refrain from routine testing for amylase and lipase elevations. They must continue to collect data on amylase and lipase levels on all patients in order to be able to fully assess the safety of the product. CBER suggested that the investigators be blinded to the amylase and lipase results, and the amylase and lipase be evaluated by a physician not involved in the patient's care, who would alert the investigator in case of a serious (e.g., grade 3-4) elevation. In addition, they should be trying to determine the source of the amylase.

DATE: December 17, 1999
SUBJECT: Phase 2 Minutes
INTRODUCTION:

Amgen is evaluating treating mucositis resulting from chemotherapy and/or radiation therapy with Keratinocyte Growth Factor under BB-IND [ ] This teleconference was held to gain advice on appropriate endpoints, to discuss the agencies minutes from the September 30, 1999, meeting, and to discuss information provided on sample size.

DISCUSSION ISSUES: [regarding efficacy endpoints]

Agency feedback from discussion with external experts on mucositis.

FDA informed the sponsor that the feedback from the mucositis experts is consistent with advice given during the September 30, 1999, meeting regarding the frequency of assessments, and the severity and duration of mucositis.

The agency informed the sponsor that although the WHO scale can be used it was not the scale preferred by the mucositis experts, and stated that the primary analysis should compare the

incidence of Grade 3 and 4 mucositis rather than Grades 2-4. The WHO scale was not the preferred scale because it is open to interpretation and will not provide enough details on the physical and anatomical findings in the mouth or details about the symptoms of the disease. The agency also informed the sponsor that there is an advantage to keeping the assessments focused, and an advisory committee may have issues with this scale depending on the results.

Appropriate Clinical Endpoints
Mean mucositis scores will not be acceptable. The data are categorical and the primary analysis should focus on Grade 3 and 4 mucositis; the duration of mucositis is an important secondary endpoint that will need to be supportive of the primary endpoint of proportion of patients with Grade 3 or 4 mucositis. The sponsor was informed that it would be problematic to look at mean scores in terms of the severity or duration. The agency asked the sponsor to submit the raw data by treatment groups.

DATE: September 5, 2000
SUBJECT: Pre-Phase 3 Minutes
INTRODUCTION:
Amgen is evaluating treating oral mucositis with Keratinocyte Growth Factor (KGF) under IND [redacted] This meeting was held to discuss a proposal for a Phase 3 trial and the results of the Phase 2 trial KGF 980213, which was designed to assess the effect of KGF on severe (i.e. Grade 3 and 4 by the WHO criteria) oral mucositis patients with hematologic malignancies who are receiving high-dose chemotherapy and radiation supported by autologous peripheral blood progenitor cell transplantation.

SEPCIFIC QUESITONS:[regarding efficacy endpoints]

Are the design, endpoints, and statistical analysis methods of the proposed Phase 3 study adequate to support licensure?

The median duration of Grade 3 and 4 mucositis may be driven by a decreased incidence independent of any change in duration. The agency advised the sponsor that any claim of improved duration of Grade 3 and 4 mucositis must also be apparent by examining only those patients who develop Grade 3 and 4 mucositis and determining whether or not that group of patients experiences a decreased duration or not. If the duration is the same then they may only be able to claim decreased incidence.

FDA suggested consideration of the two-part Model as a method for analyzing such an endpoint that zero response (no Grade 3 and 4 mucositis) accounts for more than 25 percent of the responses. The sponsor noted that they had used this model before and agreed to further explore the possibility of using this model as the primary analysis method in this trial. The statistical analysis methods for the Phase 3 trial will be discussed further between the agency's and the sponsors' statisticians.

The agency also noted that median duration of severe mucositis was the preferred descriptor of the data since many patients will be coded as zero. Outliers could be dealt with differently.

The agency asked the sponsor to capture information on the incidence and duration of Grade 2, 3, and 4 mucositis in the Phase 3 trial as a secondary endpoint.
On February 29, 2000 (Serial #076) Amgen submitted details regarding investigative-site oral mucositis assessment training for all rHuKGF studies either completed or in progress. Amgen proposed an expanded training program for the Phase 3 study. Is the proposed expanded training program adequate?

The agency informed the sponsor that the training materials are adequate, but encouraged the sponsor to use the RTOG and WHO criteria instead of the WCCNR nursing scale. The agency stated that the nursing scale does not provide adequate anatomical, detailed information on the state of the oral mucosa. The RTOG scale or one similar to it which assesses the anatomic state in greater detail should be included as a secondary endpoint in the trial. The Amgen consultant mentioned the difficulties associated with getting an anatomical assessment in some severe mucositis patients because it would be very painful; he also acknowledged that it is possible to do. FDA suggested increasing pain medication prior to an oral examination. The agency asked the sponsor to clearly specify the parts of the WHO scale that have been modified, and to explain the meaning of non-specific terms such as "extensive erythema".

Quality of Life:

The sponsor plans to request a Type C advice teleconference to discuss the Quality of Life assessment that will be used in the Phase 3 trial. The agency asked the sponsor to provide the following:

- details of the instrument used;
- validation of the instrument in the transplant setting:
- method of administering;
- method of measuring the data; and
- an analytical plan

The agency raised the concern of missing data in the Quality of Life assessment which would make the results of this assessment difficult to interpret. The sponsor stated that they have good compliance at Day 7 and 10 in the Phase 2 trial.

DATE: September 7, 2001
SUBJECT: Pre-Phase 3 Advice Minutes
INTRODUCTION:
The purpose of this teleconference is to reach agreement with the agency on the acceptability of the objectives of the Keratinocyte Growth Factor (rHuKGF) Health Related Quality of Life (HRQOL) clinical development program for subjects with hematologic malignancies undergoing total body irradiation (TBI) and high-dose chemotherapy prior to autologous peripheral blood progenitor cell transplantation (PBPCT).
The general objectives are to obtain agreement that:

- The questionnaires are valid and reliable

- The method for questionnaire administration is acceptable
- The statistical methods are acceptable
- The data for the HRQOL program is adequate for inclusion of its assessments as specified in the proposed clinical experience section of the package inset, assuming results are consistent with the proposed labeling claim in the clinical experience section (listed below)

Labeling Claim:

[redacted]

SPECIFIC QUESTIONS: [regarding endpoints]
Are the available literature and information sufficient to establish the validity and reliability of the HRQOL questionnaires in the PBPCT setting?

The agency informed the sponsor that additional information would be required before a decision can be made as to whether the HRQOL questionnaires are valid and reliable in the PBPCT setting. The agency asked the sponsor to submit the following information to address concerns raised regarding the HRQOL questionnaire:

- A description of how the HRQOL questionnaire was developed over time that includes an analysis of its validity and reliability before and after implementation of the revisions in this instrument as incorporated from Phase 1 through the present version.
- The reasons the number and order of questions were changed.
- A description of how discrepancies between the patients overall health and the answers on the questionnaire about mouth and throat soreness will handled in the analytical plan.

Is the method of administrating the HRQOL questionnaires in the proposed Phase 3 study acceptable?

The agency informed the sponsor that the method of administering the HRQOL questionnaires in the proposed Phase 3 study is acceptable. The sponsor was asked to include instructions for completing the questionnaire in the case report forms and to document the person completing the questionnaire when patients cannot complete them.

Are the statistical analysis methods for HRQOL data in the proposed Phase 3 study acceptable? Specifically,

a. are the methods proposed for handling missing data acceptable, and

The agency informed the sponsor that the method for handling missing data are acceptable except for the last observation carried forward method for patients with a sufficient number of daily assessments who die or withdraw from the study. The agency stated that it is not necessary to impute the values for this group of patients. The agency emphasized the importance of conducting sensitivity analyses for HRQOL endpoints and suggested using a mixed model and the raw outcome measures instead of AUC as one of the alternative analyses. The agency stressed the importance of having the questionnaires completed on the peak days, Days 5 through 7. The sponsor was informed that if there is a large amount of missing data the results might be difficult to interpret. The sponsor stated that they would insist on high compliance.

b. are the methods for analyzing multiple comparisons acceptable?

The agency informed the sponsor that the methods for analyzing multiple comparisons are acceptable. The agency asked the sponsor whether they are going to test the HRQOL endpoints if they do not win on the clinical primary endpoint. The sponsor confirmed that the HRQOL endpoints would be tested only if the primary clinical endpoint is significant. The order of analyses for the endpoints is Grade 3/4 mucositis, mouth and throat soreness, mucositis-related problems, and FACT-G.

Is the overall HRQOL program adequate to support the statements in the product label, assuming the results and the analyses are acceptable?

The agency informed the sponsor that it is too soon to comment on the wording of the label.

ADDITIONAL ISSUES DISCUSSED: [regarding endpoints]

- The agency suggested that the sponsor avoid collecting redundant data that does not provide additional information to the QOL.
- The agency informed the sponsor that information for the QOL should be based on patient's assessments rather than physicians.
- The agency reiterated very emphatically that if there were an inappropriate number of missing data points, then the entire analysis will be called into question and conclusions regarding HRQOL may not be able to be drawn. It is incumbent on the sponsor to ensure that data collection be complete as possible for all time points.

Summary regulatory history of efficacy endpoints

COMMENT: *Amgen has incorporated the following advice from meetings in Study 20000162:*

- *Grade 3 and 4 WHO mucositis the primary endpoint*
- *The endpoints are incidence and duration not the mean WHO 3 and 4 mucositis*
- *The RTOG and WCCNR scale are used as secondary endpoint to confirm the primary endpoint*
- *Captured grade 2 WHO oral mucositis*
- *Quantification of opioid requirement was included as a secondary endpoint*
- *Mucositis evaluations were collected daily*
- *Amylase and Lipase testing was done at a reference laboratory to minimize risk of inadvertent unblinding of investigators*

- *A comprehensive training program of mucositis evaluators was implemented and documented in the application*
- *Evaluation of duration of WHO 3 and 4 mucositis comparing duration in those subjects who experienced WHO 3 and 4 mucositis, excluding subjects with maximum WHO grade 2 or less*

Clinical Scales

In both studies, oral mucositis assessments were to be performed daily using the WHO oral toxicity rating scale. This scale measures both anatomical and functional components of oral mucositis. In addition The Western Consortium for Cancer Nursing Research (WCCNR) stomatitis staging system was used in both studies and the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria for mucous membranes was used in trial 20000162. These 2 scales measure only the anatomical changes associated with oral mucositis. A comparison of these scales is presented in the table below:

Table 6-1 Comparison of Mucositis Scales Used to Assess Severity of Mucositis

Table 6.1 Comparison of Mucositis Scales Used to Assess Severity of Mucositis					
Grade	**0**	**1**	**2**	**3**	**4**
WHO[1]	None	Soreness and erythema	Erythema, ulcers Patient can swallow solid diet	Ulcers, extensive erythema Cannot swallow solid diet	Mucositis to the extent that alimentation is not possible
RTOG[2]	None	Erythema of the mucosa	Patchy pseudo-membraneous reaction <1.5 cm in diameter, noncontiguous	Confluent pseudo-membraneous reaction >1.5 cm in diameter, contiguous	Necrosis or deep ulceration; may include bleeding not induced by trauma or abrasion
WCCNR[3]	Lesions: none Color: pink Bleeding: none	Lesions: 1-4 Color: slight red Bleeding: N/A	Lesions: > 4 Color: moderate red Bleeding: with eating and oral hygiene	Lesions:Coalescing Color: very red Bleeding: spontaneous	N/A

[1] World Health Organization- WHO handbook for reporting results of cancer treatment. Geneva: World Health Organization, 1979

[2] Radiation Therapy Oncology Group. Acute radiation morbidity scoring criteria. Available from UKL: http://www.rtog.org/members/toxicity.

[3] Western Consortium for Cancer Nursing Research. Development of a staging system for chemotherapy-induced stomatitis. Cancer Nurse. 1991;14:6-12.

COMMENT: *These scales are validated and appropriate measures of the chemotherapy radiotherapy induced mucositis. In the 12/17/99 meeting documented above, the FDA informed Amgen that the WHO oral mucositis scale was acceptable and that the RTOG and WCCNR scales should also be used as secondary efficacy endpoints.*

A centralized training program for mucositis evaluators was a mandatory component of study participation. For the phase 2 Study 980231, the clinical personnel responsible for oral mucositis

assessment were identified at each study center before study initiation, and all oral mucositis evaluators were trained.

For the phase 3 Study 20000162, training was more rigorous. [ ] provided this training. The instructors included oral medicine physicians and the training was given at the study initiation meeting and at each site's initiation meeting. In addition one-on-one training by an experienced oral evaluator on site to a new team member was provided when necessary. There was a training web site, and refresher training by the [ ]; site evaluator during visits at each site.

Comment: *The training program was comprehensive and included continual training and feedback to oral mucositis evaluators throughout the study. This was an adequate program to insure the grade of mucositis was measured appropriately.*

Ability to assess clinical benefit

COMMENT: *A decrease in the incidence and duration of severe chemotherapy and radiotherapy induced mucositis clearly constitutes a clinical benefit to patients undergoing transplantation. This side effect of transplantation is acknowledged to be burdensome for transplant recipients (Sonis and Elting et al. 2004). The untoward consequences of mucositis during transplantation include pain which is usually severe enough to require opioid analgesics, difficulty swallowing resulting in the requirement for parental nutrition, break down of mucosal barriers leading to a portal of entry for systemic infection, mucosal bleeding leading to increased requirement for transfusion of red cells to replace blood loss and platelets to minimize bleeding (Sonis and Oster 2001). Minimizing patient suffering, decreasing the requirement for use of opioid analgesics with their related side effects, minimizing the time patients are at risk of systemic invasion of infectious agents, minimizing time parenteral nutrition is required, and minimizing requirements for transfusion of blood products are the potential clinically significant benefits that reducing mucositis affords transplant patients.*

6.1.3 Study Design

Review of trials to determine if they are adequate and well designed

Studies 20000162 and 980231 were multi-center prospective double blind randomized placebo controlled studies. Each trial was analyzed using an FDA-reviewed statistical analytic plan. Amgen modified the statistical analytic plan in response to FDA comments.

The statistical analytic plan used to analyze Study 980231 was not prospective. This phase 2 trial was amended substantially as outlined above in section 6.1.1 Methods. The third version of the statistical analytic plan, submitted as part of the final study report for trial 980231, was used to analyze the original protocol as well as the subsequent amendment (eCTD 5.3.5.1.3, Clinical Study Report 980231 page 1199). Changes in the statistical analytic plan included 1) analyzing subjects with the 6-dose and the 7-dose schedules separately; 2) a detailed statistical method on

the imputation of daily oral mucositis assessment grades; 3) use of generalized Cochran-Mantel-Haenszel (CMH) test) to analyze the efficacy endpoints; 4) amended definition of analysis of duration type secondary endpoints, defining the analyzed subjects to be all treated subjects and analyzing subjects who experienced events (affected subjects) during the study. Although this analysis plan was not prospective, the changes allow analysis of the subset of interest, and allow better comparison with the results of Study 20000162. This analysis plan is acceptable.

For Study 20000162, in addition to the endpoints Amgen identified prospectively (see Section 6.1.2 General Discussion of Endpoints), the application contains exploratory endpoints intended to support the assessment of clinical benefit (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 80). These include the following:

- incidence of total parenteral nutrition use
- incidence of severe neutropenia (ANC < 500 x 10^6/L)
- incidence of febrile neutropenia (defined as ANC < 500 x 10^6/L and fever ≥ 38.5°C)
- incidence of clinically significant infections (bacteremia, infection bacterial,
- pneumonia, sepsis, sepsis bacterial, septic shock)
- incidence of intubations

COMMENT: *Because these endpoints were not prospectively identified, the ability of the results of these analyses to support label claims is limited.*

Although the Study 20000162 trial design is double blind, the physiologic effects of palifermin on the skin and oral mucosa may have allowed subjects and investigators to guess which arm the subject received. Because of this physiologic effect, there is no way to completely blind investigators. To account for this potential bias, Amgen evaluated the efficacy outcome removing palifermin subjects with reported skin and oral adverse events (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 103).

Table 6-2 Recalculation of Primary Endpoint Excluding Subjects with Pre- irradiation Skin and Oral Adverse Events Study 20000162

Table 6.2 Recalculation of Primary Endpoint Excluding Subjects with Pre-irradiation Skin and Oral Adverse Events Study 20000162			
	Number subjects	Mean duration WHO grade 3 +	Median duration WHO grade 3 +
Recalculated			
Placebo	101	10.6	9
Palifermin	81	4.0	3
Original			
Placebo	106	10.4	9
Palifermin	106	3.7	3

Because only 30 subjects (1.4%, 5 in placebo group and 25 in the palifermin group) in Study 20000162 developed skin or oral adverse events during this period, the FDA Statistician determined this analysis was inconclusive.

Another possible source of unblinding was elevations of amylase and lipase. In order to minimize the possibility of unblinding of investigators based on knowledge of elevated amylase and lipase in Study 20000162, amylase and lipase testing was done by an outside reference laboratory.

The randomization was stratified by study center and type of hematologic malignancy (4 categories: NHL, Hodgkin's disease, multiple myeloma, or any acute or chronic leukemia). Within a particular stratum (defined by study center and hematologic malignancy type), the allocation ratio was 1:1 rHuKGF: placebo. The stratification by study center is summarized in the table below:

Table 6-3 Distribution of Randomization by Treatment Center

Table 6.3 Distribution of Randomization by Treatment Center													
Center	**31**	**32**	**33**	**34**	**36**	**37**	**38**	**39**	**40**	**41**	**43**	**44**	**45**
Total subjects	29	40	30	13	8	10	25	1	6	5	17	17	11
Palifermin	14	19	15	6	4	6	13	1	4	3	8	8	6
Placebo	15	21	15	7	4	4	12	0	2	2	9	9	5

The stratification by type of hematologic malignancy is summarized in the table below:

Table 6-4 Distribution of Randomization by Disease

Table 6.4 Distribution of Randomization by Disease				
Disease	**Hodgkin's Disease**	**Lymphoma**	**Multiple Myeloma**	**Leukemia**
Total	44	142	21	7
Palifermin	21	72	12	2
Placebo	23	70	9	5

Review of application to determine if benefit was demonstrated

In the controlled studies that support this application the duration of observation of subjects was appropriate. The period of risk for mucositis is within the first month after transplant, and mucositis was monitored daily starting from day –7 to 28 of the transplant.

The Inclusion and Exclusion criteria were (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 825):
Inclusion Criteria
Disease-Related

1. Patients with: non-Hodgkin's lymphoma, Hodgkin's disease, acute myelogenous leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, or multiple myeloma
2. Eligible for fractionated total body irradiation (fTBI) plus high-dose chemotherapy followed by autologous PBPC [peripheral blood progenitor cell] support.

Demographic

3. 18 years of age or older
4. Karnofsky performance status $\geq$ 70%

Laboratory

5. Minimum of 1.5 x 10^6 CD34+ cells/kg cryopreserved and to be transplanted

Ethical

6. Before any study specific procedure including subject registration is done, the subject or legally acceptable representative must give informed consent for participation in the study.

Exclusion Criteria

Disease-related

1. History of or concurrent cancer other than non-Hodgkin's lymphoma, Hodgkin's disease, acute myelogenous leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, or multiple myeloma
Exception: Adequately treated basal cell carcinoma of the skin.
2. Prior bone marrow or peripheral blood stem cell transplantation.
Exception: subjects who are scheduled to undergo the second transplantation of a tandem transplantation regimen if in the investigator's opinion they tolerated the first transplantation without major complications
3. Negatively selected (purged) stem cell product
4. Currently active infection or oral mucositis
5. Congestive heart failure (New York Heart Association class III or IV)

Laboratory:

6. Serum creatinine > 1.5x upper limit of institutional normal range
7. Direct bilirubin > 1.5x upper limit of institutional normal range
Note: If total bilirubin result at screening is within the normal range, then no direct bilirubin test is needed; if the screening total bilirubin result is elevated, then a direct bilirubin test must be done and checked for exclusionary limits.
8. Transaminases (aspartate transaminase (AST) and/or alanine transaminase (ALT) > 3x upper limit of institutional normal range
9. Inadequate pulmonary function as measured by a corrected DLCO [diffusion capacity of carbon monoxide] < 50% of predicted

General

10. Subject is currently enrolled in, or has not yet completed at least 30 days since ending other investigational device or drug trial(s) or is receiving other investigational agent(s).
11. Subject is pregnant (eg, positive human chorionic gonadotropin (HCG) test) or is breastfeeding.
12. Subject refuses to use adequate contraceptive precautions.
13. Subject has known hypersensitivity to any of the products to be administered during dosing, including *Escherichia coli*-derived products.
14. Subject is compromised in his/her ability to give a truly informed consent.

COMMENT: *The inclusion and exclusion criteria were appropriate for the indication sought in this application. The disease categories chosen were appropriate for a transplant done in the autologous setting. Autologous transplant was a good choice for the type of transplant to study, because there are less transplant complications associated with autologous transplant compared to allogeneic transplant. This simplifies the assessment of adverse events. During the evaluation*

of a supportive care agent in the transplant setting, the majority of adverse events are related to the transplant not the investigational agent.

Allogeneic transplant is associated with more complications than autologous transplant. In particular, allogeneic transplant is associated with graft versus host disease, and a major manifestation of graft versus host disease is skin rashes. The determination of the etiology of adverse events associated with palifermin would have been more complicated if these trials had been done in the allogeneic setting. The exclusion criteria included are standard requirements for transplant subjects. The indication for palifermin is in the setting of transplant, therefore the exclusion criteria of this protocol should not affect the ability to generalize the results to the intended population.

The indication for pallifermin this application supports is to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support. This indication does not make a distinction about the source of stem cells. Because mucositis is the consequence of the preparative regimen, the same benefit would be expected in the allogeneic setting.

Adequacy of dose finding in phase 2

The treatment dose and schedule developed in phase 2 and used in Study 20000162 was effective and well tolerated. Amgen continues to evaluate the dose and schedule. Study 20010182 is investigating the pharmacokinetics of delivering the same cumulative dose of palifermin administered on 2 days (- 11 and 0). If the pharmacokinetics are comparable, such a schedule would simplify administration of palifermin.

6.1.4 Efficacy Findings

6.1.4.1 Study 20000162

Trial design: Schema presented in Section 6.1.1 Methods

Demographics:
The demographic characteristics of the modified intent to treat population of Study 20000162 are presented in the table below derived from Amgen's table (eCTD 5.3.5.1.1, Clinical Study report 20000162 page 173):

Table 6-5 Demographics Study 20000162

Table 6.5 Demographics Study 20000162		
	Placebo N=106	Palifermin N=106
Sex - n(%)		
Male	72 (68)	59 (56)
Female	34 (32)	47(44)
Race - n(%)		
Caucasian	89 (84)	78 (74)
Black	7 (7)	11 (10)
Hispanic	7 (7)	11 (10)
Asian	1 (1)	4 (4)
Other	2 (2)	2 (2)
Age (years) - n(%)		
18-30	13 (12)	12 (11)
31-40	18 (17)	22 (21)
41-50	29 (27)	28 (26)
51-60	39 (37)	37 (35)
61-64	2 (2)	4 (4)
65-70	5 (5)	3 (3)
Age (years)		
Mean	46	46
Median	49	48
Karnofksy Performance Status (%) – n(%)		
70	1 (1)	3 (3)
80	19 (18)	15 (14)
90	58 (55)	59 (56)
100	28 (26)	29 (27)

COMMENT: *The distribution of all demographic characteristics (gender, race, age, height, weight, Karnofsky Performance Status) appears to be uniform. The overall study population includes more men than women.*

Baseline Characteristics:

The baseline characteristics of the modified intent to treat population of Study 20000162 are presented in the table below derived from Amgen's table (eCTD 5.3.5.1.1, Clinical Study report 20000162 page 176):

Table 6-6 Subject Baseline Disease Characteristics Study 20000162 Modified Intent to Treat (mITT)

Table 6.6 Subject Baseline Disease Characteristics Study 20000162 Modified Intent to Treat (mITT)		
	Placebo N = 106	Palifermin N = 106
Type of Diagnosis -n(%)		
Hodgkin's Disease	23 (22)	21 (20)
Non-Hodgkin's Lymphoma	69 (65)	72 (68)
Multiple Myeloma	9 (8)	11 (10)
Leukemia	5 (5)	2 (2)
Mobilization -n(%)		
Cytokines only	30 (28)	26 (25)
Chemotherapy only	0 (0)	1 (1)
Cytokines and Chemotherapy	76 (72)	79 (75)
Total Number of CD34+ Cells (10^6/kg)		
n	106	106
Mean	7.0	8.6
SD	7.8	12
Median	5.0	5.2
Q1, Q3	3.1, 7.3	3.4, 7.4
Min, Max	1.5, 41	1.8, 87
Reason for PBPC Transplantation -n(%)		
Consolidation	9 (8)	4 (4)
First complete remission	22 (21)	15 (14)
Second complete remission	2 (2)	3 (3)
First partial remission	12 (11)	19 (18)
Chemotherapy sensitive relapse	33 (31)	39 (37)
Induction failure	0 (0)	4 (4)
Primary refractory disease	24 (23)	20 (19)
Other	4 (4)	2 (2)

COMMENT: *Most of the baseline characteristics also seem to be uniformly distributed. The majority of patients had non-Hodgkin's lymphoma (65% and 68% for the placebo and palifermin group, respectively). CD34+ cells were mobilized with cytokines and chemotherapy for over 70% of the patients. The indication for transplantation for most subjects was a chemotherapy sensitive relapse (31% and 37% for the placebo and palifermin group, respectively). All subjects had prior chemotherapy; over 85% of the subjects did not receive prior radiotherapy.*

Inclusion and exclusions criteria:
Outlined in Section 6.1.3 Study Design

Pre-specified Efficacy Endpoints:
Outlined in Section 6.1.2 General Discussion of Endpoints

Enrollment:
There were 245 subjects screened, and 214 subjects were randomized 107 to each arm. Two subjects one from each arm did not receive investigational agent. In the placebo arm 103 subjects completed the study, 3 discontinued the study; in the palifermin arm 104 subjects completed study, 2 discontinued the study.

Protocol Deviations:

Eligibility Criteria

- Eligibility criteria violations in placebo subjects included a history of melanoma, and elevated ALT; in palifermin subjects, inadequate number of CD34+ cells prior to enrollment, and inadequate DCLO (2 subjects).
  The palifermin subject who did not have an adequate number of stem cells received 3 doses of investigational agent before additional stem cells were harvested. TBI was started 15 days after the last dose of investigational agent. (The duration of WHO grade 3 or 4 oral mucositis was 6 days)

Exposure to palifermin

- One subject received the Day –11 dose but did not receive Day –10 and – 9 doses due to an upper respiratory infection. TBI was delayed to 6 days after the Day –11 dose. (The duration of grade 3 + WHO mucositis was 13 days)
- One subject received Day –11 and – 10 doses but did not receive additional doses due to skin rash. (The duration of grade 3 + WHO mucositis was 6 days)
- One subject missed the day –9 dose with no reason given. (The duration of grade 3 + WHO mucositis was 0 days)
- One subject received Day –11, -10, -9 doses only, subject requested no additional doses be administered. (The duration of grade 3 + WHO mucositis was 8 days)
- One subject had no documentation of a Day – 9 dose. (The duration of grade 3 + WHO mucositis was 0 days)

Table 6-7 Exposure to Investigational agent Study 20000162

Table 6.7 Exposure to Investigational agent Study 20000162		
Total Doses	**Placebo N = 106**	**Palifermin N = 106**
6	103	101
5	1	2
4	1	1
3	1	1
2	0	1

Exposure to Chemotherapy:

There were many deviations in calculations of chemotherapy. The formulas for dosing of cyclophosphamide and etoposide required calculation of ideal body weight. There was no formula given in the protocol to calculate ideal body weight. Individual centers may have used different methods to determine a subject's ideal body weight. The reviewer requested Amgen supply a formula to calculate ideal body weight (Robinson and Lupklewicz et al.1983); this was used to calculate the protocol-specified dose of chemotherapy. This dose was compared to the dose documented in the xpt data file (eCTD 5.3.5.1.1, Study 20000162, chemo.xpt).

The protocol-specified dose of etoposide was 60 mg/kg. The protocol specified the dose be modified for obesisty. If the subject's weight was greater than 135% of the ideal body weight then ideal body weight was to be used to calculate etoposide dose.

The dose of cyclophophamide was calculated by ideal body weight. The protocol-specified dose was 100 mg/kg of ideal body weight. However if the subject was underweight, defined as less than 95% of the ideal body weight, the dose was to be calculated using the subject's actual weight.

The table below summarizes the number of subjects who received a dose that was not within 15% of the correct dose.

Table 6-8 Number of Subjects with Chemotherapy Doses Not Within 15% of Correct Dose Specified in Study 2000162

Table 6.8 Number of Subjects with Chemotherapy Doses Not Within 15% of Correct Dose Specified in Study 2000162				
	Placebo < 85%	Palifermin < 85%	Placebo > 115%	Palifermin > 115%
Women				
Etoposide	3	1	11	14
Cyclophosphamide	2	0	0	3
Men				
Etoposide	0	0	20	15
Cyclophospahmide	0	1	3	0

To determine if higher dose of chemotherapy increased mucositis in placebo subjects or a lower dose of chemotherapy diminished mucositis in the palifermin, the mean and median duration of WHO grade 3 or 4 oral mucositis was recalculated. Placebo subjects who received a dose of chemotherapy greater than 115% of the protocol specified dose and palifermin subjects who received a dose of chemotherapy less than 85% of the protocol specified dose were excluded.

Table 6-9 Recalculation of Primary Endpoint of Subjects Whose Preparative Regimen Could Have Diminished Efficacy Result in Study 20000162

Table 6.9 Recalculation of Primary Endpoint of Subjects Whose Preparative Regimen Could Have Diminished Efficacy Result in Study 20000162			
	Number subjects	Mean duration WHO grade 3 +	Median duration WHO grade 3 +
Recalculated			
Placebo	75	10.1	9
Palifermin	104	3.6	3
Original			
Placebo	106	10.4	9
Palifermin	106	3.7	3

COMMENT: *The results did not change substantially.*

Exposure to Total Body Irradiation:

The protocol specified dose of total body irradiation was 1200cGy. There were 2 subjects who received greater or less than 15% of the correct dose. A placebo subject received 600cGy and a palifermin subject received a dose to the head lower than the recommended dose.

COMMENT: *These deviations do not effect the interpretation of the efficacy endpoints.*

Use of proscribed medications:

Table 6-10 Use of Proscribed Medications in Study 20000162

Table 6.10 Use of Proscribed Medications in Study 20000162		
	Placebo N = 106	Palifermin N = 106
Hydrogen peroxide	0	1
"Magic Mouthwash"	6	4
Beclovent	4	2
Sucralfate Suspension	3	0
Chlorhexidine	1	2

COMMENT: *The use of proscribed medication was balanced equally between placebo and palifermin subjects. None of these agents are effective in decreasing the severity or duration of mucositis (Rubenstein and Peterson et al. 2004). Therefore the use of these agents was not likely to affect the efficacy endpoint.*

Laboratory assessments:

Twenty-two subjects (11 in each arm) had missing laboratory assessments.

COMMENT: *These missing data do not affect efficacy results.*

Analysis of endpoints:

See section 4.4 Data Quality and Integrity for review of primary data source and data in database.

Missing efficacy endpoint evaluation:

For the primary efficacy endpoint, the imputation scheme was indicated in the analysis plan. If a subject did not experience any WHO grade 3 or 4 oral mucositis, the duration of severe oral mucositis was assigned as 0 days.

If a subject's mucositis was not resolved upon early withdrawal or death, the subject was given the mean duration of severe mucositis (WHO grade 3 or 4) among subjects who experience at least the same duration of severe mucositis as this subject.

When there was a gap between 2 observed grades, the missing grades were assigned the larger adjacent grade. The same rule was applied to gaps after a patient is discharged with WHO grade 3 or 4 mucositis (but the follow-up assessments were not done daily).

In addition, the sponsor also conducted a "worst case" analysis to demonstrate the robustness of the results. In the "worst case" analysis, the missing grades were replaced with the higher

adjacent value in the palifermin group, and the missing grades in the placebo group were replaced with the lower adjacent values.

The following figure is a table from Amgen summarizing the number of missing efficacy data points (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 98):

Figure 6-4 Amgen's Table of Summary of Missed Efficacy Evaluations 20000162 Study

Table 9-4. Summary of Missed Visits for Oral Mucositis

	Placebo (n = 106)	rHuKGF Pre-Post (60 µg/kg/day) (n = 106)	Total
Number of subjects with missed visits requiring imputation of WHO grades 3 or 4	25	7	32
Potential days of oral evaluation	2921 (100%)	2803 (100%)	5724 (100%)
Number of missed visits requiring imputation of WHO grades 3 or 4	110 (4%)	14 (0.5%)	124 (2%)
Number of missed visits requiring imputation of any WHO grades	150 (5%)	32 (1.1%)	182 (3%)

COMMENT: *Very little data for the analysis of the primary efficacy endpoint is missing. Amgen conducted a "worst case" sensitivity analysis for missing data assigning better adjacent score to placebo subjects and worse adjacent score to palifermin subjects. The mean (median) duration grade 3 and 4 WHO mucositis was 9.4 (8.0) days for placebo and 3.7 (4) days for palifermin.*

Analysis of Efficacy endpoints:

The following table summarizes the results of the analysis of endpoints of the 20000162 trial excluding the patient reported outcome endpoint which will be discussed separately:

Table 6-11 Amgen's Evaluation of Pre-specified Efficacy Endpoints Study 20000162

Table 6.11 Amgen's Evaluation of Pre-specified Efficacy Endpoints Study 20000162		
Primary Endpoint		
	Placebo N = 106	**Palifermin N = 106**
Duration days WHO 3 + Mucositis	Mean 10.4 - SD 6.2 Median 9.0 - Q1,Q3 6.0,13.0	Mean 3.7 - SD 4.1 Median 3.0 - Q1,Q3 0,6.0
Secondary Endpoints		
Incidence WHO 4 Mucositis	62.2%	19.8%
Duration days WHO 2 + Mucositis	Mean 15.7 SD 7.8 Median 14.3 - Q1,Q3 11.0, 19.0	Mean 8.4 SD 5.8 Median 8.0 - Q1,Q3 4.0, 12.0
Duration days WCCNR 2 + Mucositis	Mean 9.9 - SD 9.3 Median 6.0 - Q1,Q3 3.0, 11.0	Mean 3.2 SD 5.2 Median 1.0 - Q1,Q3 0, 5.0
Duration days RTOG 3 + Mucositis	Mean 8.1 SD 8.5 Median 6.0 - Q1,Q3 3.0, 11.0	Mean 2.1 SD 3.5 Median 0 - Q1,Q3 0, 4.0
Parenteral or transdermal opioid (mg)	Mean 1146.5 - SD 1702.1 Median 534.9 - Q1,Q3 268.7, 1429.0	Mean 699.5 - SD 1747.8 Median 211.6 - Q1,Q3 3.0, 558.4

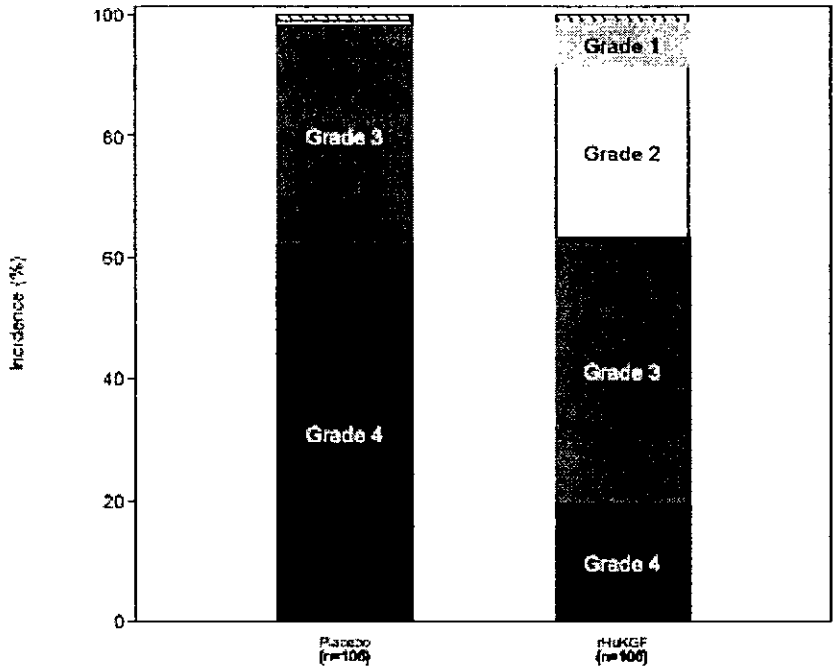
The sponsor's summary of the cumulative dose of opioid analgesic use for mucositis demonstrates a statistically significant difference in opioid analgesic doses. The placebo treated group had higher total dose of opioid analgesic use (median = 534.9 mg) as compared with the palifermin treated group (median = 211.6 mg). The placebo treated group also had longer duration of analgesic use for mucositis (median days on analgesic for mucositis is 14.3 days for placebo group and 8 days for the palifermin group).

The sponsor's summary of duration of WHO Grade 2, 3 or 4 mucositis indicates the palifermin group had shorter duration of milder mucositis, as well as a decrease in incidence and duration of WHO Grade 4 oral mucositis as compared to the placebo group. The primary endpoint was supported by the decrease in duration of RTOG grades 3 and 4 oral mucositis and of WCCNR grade 2 and 3 oral mucositis.

Amgen's Bar Graph of the incidence of the maximum WHO grade of oral mucositis in Study 20000162 is presented below (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 98):

Figure 6-5 Amgen's Figure of Incidence of Maximum Mucositis by WHO Grade

Figure 9-9. Incidence of Oral Mucositis Toxicity By WHO Grade (mITT Population)



COMMENT: *The primary endpoint of decrease in the duration in WHO grade 3 and 4 oral mucositis was statistically significant. The results of secondary endpoints using alternative assessment scales, such as incidence of WHO grade 4 oral mucositis and duration of oral mucositis as determined by RTOG and WCCNR scales were all supportive of the primary endpoint. Analysis of the efficacy endpoints evaluating the duration of mucositis comparing only those subjects experiencing oral mucositis supported these results.*

Use of parenteral or transdermal opioid analgesics was also a pre-specified secondary endpoint. In the results included in table 6.11, Amgen calculated doses of opioid analgesics that were administered to treat mouth and throat soreness. The statistical analysis plan for this trial indicated the endpoint would be: "Use of parenteral or transdermal opioid analgesics (in mg morphine equivalents) over the study period", not just opioid analgesics designated as being administered for mouth and throat soreness (eCTD M.5.3.5.1.1, Clinical Study Report 20000162 page 903). See section 4.4 Data Quality and integrity for a review of this issue.

COMMENT: *The conclusion based on the review in Section 4.4 is that evaluation of all opioid analgesics or evaluation limited to opioid analgesics administered for mucositis and throat pain provides similar results. Palifermin treated subjects required less parenteral opioid analgesics.*

Secondary Efficacy Endpoint - Patient-Reported Outcome

Amgen's analysis of the patient reported outcome endpoint mouth and throat soreness is contained in eCTD 2.7, Summary of Clinical Efficacy – Mucositis page 30.

Table 6-12 Amgen's Evaluation of Patient Reported Mouth and Throat Soreness in Study 20000162

Table 6.12 Amgen's Evaluation of Patient Reported Mouth and Throat Soreness in Study 20000162		
	Placebo N = 106	**Palifermin N = 106**
Patient-reported Mouth and Throat Soreness, VDS[1] Scale (AUC[2])	Mean 52.5 -SD 22.4 Median 46.8	Mean 32.6 – SD 20.8 Median 29.0

[1] VDS = verbal descriptive scale; a Likert-type scale. (0 = no soreness; 4 = extreme soreness).
[2]AUC = Area under the curve; Patient-reported assessments of mouth and throat soreness and its limitations on daily activities were evaluated as area-under-the-curve scores (AUCs) over the duration of the study (from day -12 to day 28). Mean AUCs were compared between subjects who received palifermin and subjects who received placebo. Subjects' AUCs could vary from 0 (no soreness over the entire study period) to a theoretical maximum of 160 (severe soreness every day for 41 days). However, scores rarely were above 80 (i.e., severe mouth and throat soreness for 20 days). The generalized CMH test for the mouth and throat soreness and impact on related activities AUCs was conducted at the 0.05 level

Amgen's statistical analysis of this endpoint yielded $p < 0.001$.

For a comprehensive review of the Patient-reported outcome validation of the questionnaire, please see the statistical review of Dr. Lisa Kammerman, Ph.D. The analysis concludes there were serious flaws in the methodology of validating the questionnaire used to measure the secondary endpoint "subject's self assessment of mouth and throat soreness as summarized by AUC of the daily VDS score (Question 2 in the HRQOL questionnaire) over the study."

COMMENT: *Based on this analysis of the validation of the questionnaire, the result of the analysis of mouth and throat soreness must be interpreted with caution. The evaluation of the analysis of mouth ant throat soreness supports a statement in the label: "Compared with placebo-treated subjects, palifermin-treated subjects reported less mouth and throat soreness."*

Exploratory Endpoints Analyses:

Amgen' analysis of exploratory endpoints (eCTD M.5.3.5.1.1, Clinical Study Report 20000162 page 127) is summarized in the table below:

Table 6-13 Amgen's Evaluation of Exploratory Efficacy Endpoints in Study 20000162

Table 6.13 Amgen's Evaluation of Exploratory Efficacy Endpoints in Study 20000162		
	Placebo N = 106	**Palifermin N = 106**
Incidence fever and neutropenia	91.5%	74.5%
Incidence significant infections	24.5%	15.1%
Incidence of Intubations	3.7%	0.9%
Incidence Requirement parenteral nutrition	54.5%	31.1%
Incidence of parenteral nutrition due to mucositis	43.3%	11.3%

Fever and neutropenia was defined in the protocol as an absolute neutrophil count less than 500/UL with a concurrent temperature of at least 38.5°C. Significant infections were defined as bloodborne infections including the following preferred terms: bacteremia, infection bacteria, pneumonia, pneumonia lobar, sepsis, septic bacterial, septic shock.

Information about subject intubations for mechanical ventilation was analyzed from the subset of subjects who missed at least 3 oral assessments (potentially with WHO grade 3 or 4) or who terminated the study early without resolution of WHO grade 3 and 4 oral mucositis. There were 13 (12 placebo, 1 palifermin) subjects who met these criteria. Four subjects in the placebo group and 1 subject in the palifermin group were intubated during the study.

Review of effectiveness of palifermin in demographic subsets

The following table shows the results of the primary endpoint analyzed by demographic subset:

Table 6-14 Analysis of Duration WHO grade 3 and 4 Oral Mucositis Study 20000162 by Demographic Group

Table 6.14 Analysis of Duration WHO grade 3 and 4 Oral Mucositis Study 20000162 by Demographic Group		
	Placebo N = 106	**Palifermin N = 106**
Male N = 131	N = 72 Mean 10.5 Median 10	N = 59 Mean 3.7 Median 3
Female N = 81	N = 34 Mean 10.2 Median 8	N = 47 Mean 3.7 Median 3
Age 65 years and greater N = 8	N = 5 Mean 14.6 Median 18	N =3 Mean 3.3 Median 0
Age less than 65 N = 204	N = 101 Mean 10.2 Median 9	N = 103 Mean 3.7 Median 3
Caucasians N = 167	N = 89 Mean 10.3 Median 9	N = 78 Mean 3.5 Median 3
Black N = 18	N = 7 Mean 12.8 Median 12	N = 11 Mean 3.09 Median 1
Hispanic N = 18	N = 7 Mean 7.7 Median 7	N = 11 Mean 5.4 Median 6
All non-Caucasians N = 45	N = 17 Mean 11.0 Median 10	N = 28 Mean 4.2 Median 5

COMMENTS: *All demographic subgroups demonstrated shorter duration of grade 3 or greater WHO mucositis. This difference was the least pronounced in the Hispanic subjects.*

6.1.4.2 Study 980231

Trial Design

See section 6.1.1 Methods.

Demographics:

The subset of subjects from Study 980231 treated with the identical dose and schedule of investigational agent was used to support the efficacy results of Study 20000162. The demographic characteristics of these subjects are presented in the table below derived from Amgen's table (eCTD 5.3.5.1.3, Clinical Study Report 980231 page 270):

Table 6-15 Demographics of the Subset of Subjects from Study 980231 Used to Support Efficacy

Table 6.15 Demographics of the Subset of Subjects from Study 980231 Used to Support Efficacy		
	Placebo (N=40)	Palifermin (N=46)
Sex - n (%)		
Male	20 (50)	26 (57)
Female	20 (50)	20 (43)
Race - n (%)		
Caucasian	30 (75)	33 (72)
Black	5 (13)	4 (9)
Hispanic	4 (10)	7 (15)
Asian	1 (3)	1 (2)
Other	0 (0)	1 (2)
Age (years) - n (%)		
18-30	11 (28)	7 (15)
31-40	40 8 (20)	13 (28)
41-50	7 (18)	11 (24)
51-60	11 (28)	11 (24)
61-64	3 (8)	4 (9)
65-70	0 (0)	0 (0)
Age (years)		
Mean	42	44
Median	44	44
ECOG Performance Status –n (%)		
0	28 (70)	27 (59)
1	12 (30)	18 (39)
2	0 (0)	0 (0)
Unknown	0 (0)	1 (2)

COMMENT: *Most of the demographic data appears to be balanced between treatment groups, except that placebo group seems to have better ECOG status at baseline (70% of placebo treated subjectsts had ECOG status 0, while 59% of palifermin treated subjects had ECOG).*

Baseline characteristics:

The baseline characteristics of the subjects used to support efficacy from Study 980231 are presented in the table below derived from Amgen's table (eCTD 5.3.5.1.3, Clinical Study Report 980231 page 277):

Table 6-16 Subject Baseline Disease Characteristics of the Subset of Subjects from Study 980231 Used to Support Efficacy

Table 6.16 Subject Baseline Disease Characteristics of the Subset of Subjects from Study 980231 Used to Support Efficacy		
	Placebo N = 40	Palifermin N = 46
Type of Diagnosis -n (%)		
Hodgkin's Disease	14 (35)	8 (17)
Non-Hodgkin's Lymphoma	18 (45)	28 (61)
Multiple Myeloma	5 (13)	1 (2)
Leukemia	3 (7)	9 (19)
Mobilization -n (%)		
Cytokines only	2 (5)	10 (22)
Cytokines and Chemotherapy	38 (95)	36 (78)
Reason for PBPC Transplantation -n (%)		
Consolidation	18 (45)	19 (41)
Chemotherapy sensitive relapse	18 (45)	21 (46)
Induction failure	4 (10)	6 (13)
Subjects with Prior Chemotherapy -n (%)		
Yes	40 (100)	46 (100)
Subjects with Prior Mediastinal Radiotherapy -n (%)		
Yes	0 (0)	1 (2)
No	40 (100)	45 (98)
Subjects with prior Radiotherapy -n (%)		
Yes	4 (10)	6 (13)
No	35 (88)	40 (87)
Unknown	1 (3)	0 (0)

COMMENT: *The baseline characteristics do not seem to be balanced between treatment groups. The palifermin group included more non-Hodgkin's Lymphoma (61% for the palifermin group) as compared with the placebo group (45%), while the placebo group had more Hodgkin's disease (35%) as compared with the palifermin groups (17%). CD34+ cells were mobilized with cytokines and chemotherapy forthe majority of patients; however, cytokines and chemotherapy were utilized more frequently in the placebo group (98%) than in the palifermin group (78%). A majority of patients did not have prior mediastinal radiotherapy or prior radiotherapy.*

Inclusion and exclusion criteria:

The inclusion and exclusion criteria were the same as in trial 20000162 with the following exceptions: age eligibility was between 12 to 65 years, the criteria for minimum absolute neutrophil count and platelet count were 1000/uL and 50,000/uL, repectively; subjects with insulin-requiring diabetes mellitus were excluded; and known HIV positive patients were excluded.

Efficacy endpoints:

The modified efficacy endpoints were identified in the statistical analysis plan dated 4/23/04 in section 6.1.1 Methods (eCTD M.5.3.5.1.3, Clinical Study Report 980231 page 1199).

Enrollment

After the amendment to modify the dose schedule of palifermin to eliminate the day – 5 dose (6-Dose Schedule), 134 subjects were randomized. Forty were randomized to placebo, 46 to palifermin 3 doses on days –11, -10 and – 9 (palifermin pre only), and 48 were randomized to 6 doses of palifermin (palifermin pre and post). (See Section 6.1.1 Methods for schedule.) Five subjects did not receive investigational agent three in the palifermin pre group and two in the palifermin pre-post group. In the placebo arm all 40 subjects completed the study; in the palifermin pre arm one subjected discontinued the study; and in then palifermin pre-post arm three subjects discontinued the study.

Protocol Deviations of Note in the Placebo and Palifermin Pre-post Groups:

Eligibility criteria:

- three subjects in the palifermin group had mucositis at screening

Exposure to investigational agent:

- one subject in palifermin missed day 2 dose
- one subject in palifermin group missed doses day 0, 1, 2

Exposure to Chemotherapy

Table 6-17 Number of Subjects with Chemotherapy Doses Not Within 15% of Correct Dose as Specified in Study 980231

Table 6.17 Number of Subjects with Chemotherapy Doses Not Within 15% of Correct Dose as Specified in Study 980231				
	Placebo N = 40	Palifermin N = 46	Placebo N = 40	Palifermin N = 46
	< 85%	< 85%	> 115%	> 115%
Etoposide	3	2	0	0
Cyclophosphamide	0	1	2	4

Exposure to Total Body Irradiation:
One palifermin subject received a dose to the head lower than the recommended dose.

Proscribed mediations:
Use of proscribed medications was equally distributed.

Laboratory assessments:
Instances of missing laboratory assessments were equally distributed between placebo and palifermin subjects and do not interfere with the efficacy assessment.

Missing efficacy endpoint evaluation:
For the primary efficacy endpoint, the imputation scheme was indicated in the analysis plan. If a subject did not experience any WHO grade 3 or 4 oral mucositis, the duration of severe oral mucositis was assigned as 0 days.

If a subject's mucositis is not resolved upon early withdrawal or death, he/she was given the mean duration of severe mucositis (WHO grade 3 or 4) among subjects who experience at least the same duration of severe mucositis as this subject.

When there was a gap between 2 observed grades, the missing grades were assigned the higher adjacent grade. The same rule was applied to gaps after a patient is discharged with WHO grade 3 or 4 mucositis (but the follow-up assessments were not done daily).

In addition to the imputation scheme, the sponsor also conducted a "worst case" analysis to demonstrate the robustness of the results. In the "worst case" analysis, the missing grades were replaced with the higher adjacent value in the palifermin group, and the missing grades were replaced with the lower adjacent values in the placebo group.

The following Figure is a table from Amgen summarizing the number of missing efficacy data points (eCTD 5.3.5.1.3, Clinical Study Report 980231 page 145):

Figure 6-6 Amgen's Table of Missing Efficacy Evaluations 980231 Study

Table 9-12. Summary of Missed Visits for Oral Mucositis - 6-dose Schedule

		rHuKGF (60 µg/kg/day)	
	Placebo (N=40)	Pre (N=43)	Pre-Post (N=46)
Number of subjects with missed visits requiring imputation of WHO grades 3 or 4	15	11	12
Potential days of oral evaluation	1015(100%)	1080(100%)	1161(100%)
Number of missed visits requiring imputation of WHO grades 3 or 4	56(6%)	25(2%)	41(4%)
Number of missed visits requiring imputation of any WHO Grades	129(13%)	65(6%)	95(8%)

COMMENT: *Although there is more data missing for the analysis of the primary efficacy endpoint in this study than in Study 20000162, the amount of data that has been captured allows a reasonable expectation that conclusions drawn are reliable.*

Analysis of Efficacy Endpoints:

The following tables summarize the results of the analysis of endpoints for the subjects from Study 980231 used to support efficacy:

Table 6-18 Amgen's Evaluation of the Pre-specified Efficacy Endpoints from Study 20000162 in the Subjects in the Supportive Subset of Study 980231

Table 6.18 Amgen's Evaluation of the Pre-specified Efficacy Endpoints from Study 20000162 in the Subjects in the Supportive Subset of Study 980231				
Primary Endpoint				
	Placebo N = 40		**Palifermin N = 46**	
Duration days WHO 3 + Mucositis	Mean 8.6	Median 6.0	Mean 4.7	Median 4.0
Secondary Endpoints				
Incidence WHO 4 Mucositis	50.0%		26.1%	
Duration days WHO 2 + Mucositis	Mean 17.7	Median 12.5	Mean 11.1	Median 9.0
Duration days WCCNR 2 + Mucositis	Mean 8.8	Median 6.0	Mean 2.9	Median 0
Parenteral or transdermal opioid (mg)	Mean 1163	Median 523.9	Mean 514.4	Median 204.9

Table 6-19 Amgen's Evaluation of Supportive Efficacy Endpoints Study 980231

Table 6.19 Amgen's Evaluation of Supportive Efficacy Endpoints Study 980231				
	Placebo N = 40		**Palifermin N = 46**	
Incidence WHO 3+ Mucositis	80.0%		67.3%	
Duration days WHO 3+ Mucositis affected subjects	Mean 10.8	Median 8.5	Mean 6.9	Median 6.0
Incidence WHO 2+ Mucositis	97.5%		84.7%	
Duration WHO 2+ Mucositis affected subjects	Mean 18.2	Median 13.0	Mean 12.8	Median 10.0
Duration WHO 4 Mucositis mITT	Mean 2.6	Median 0.5	Mean 1.5	Median 0
Duration WHO 4 Mucositis affected subjects	Mean 5.1	Median 4.5	Mean 5.5	Median 3.0
Incidence opioid use	95.0%		80.4%	
Use parenteral or transdermal opioid affected subjects	Mean 1223.8	Median 526.4	Mean 639.5	Median 300.0

COMMENT: *Amgen's primary efficacy analysis results for the 6-dose schedule indicated a significant longer duration of WHO Grade 3 or 4 mucositis for the placebo group (median 6 days) than the duration for the palifermin group (median 4 days). The trend of a longer duration of mucositis in placebo group was consistent in the subgroup of patients who developed WHO Grade 3 and 4 mucositis. The primary analysis results were also similar in Amgen's "worst-case" analysis.*

Since Amgen did not pre-specify the decision rule for the secondary endpoints, the following analyses are more exploratory in nature. The nominally significant results (nominal p-value $<$ 0.05) that might provide supporting information for Study 20000162 are the duration of WHO grade 2, 3 and 4 mucositis, incidence and duration of WHO grade 4 mucositis. The duration of WHO grade 3 and 4 mucositis results were further supported by the duration of WCCNR grade 2 and 3 results.

The results from the sponsor's analysis of the cumulative dose of opioid analgesic administered for mucositis showed a nominally significant lower total dose of analgesic administered in the palifermin group as compare to the placebo group. Similarly, the palifermin group seems to have shorter duration of analgesic use for mucositis as compared with the placebo group.

6.1.5 Clinical Microbiology

Palifermin is not an antimicrobial therefore this not applicable.

6.1.6 Efficacy Conclusions

COMMENT: *Amgen has demonstrated, that palifermin admistered in the schedule and dose used in Study 20000162 reduces the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support. Because mucositis is the consequence of the preparative regimen, similar benefit might*

be expected in the allogeneic setting. Extrapolation to the transplant setting with other preparative regimens should be done cautiously, as the timing of administration of palifermin in relation to the preparative regimen is critical. Palifermin should not be administered within 24 hours of chemotherapy.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety evaluation was done by reviewing safety in the hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support setting (Hematologic Malignancy Studies), the solid tumor setting, and in normal volunteers. Because palifermin is a growth factor that stimulates epithelial cells, tumor promotion of epithelial derived cancers expressing Keratinocyte Growth Factor (KGF) receptors, is an important concern. Hematologic cells do not express KGF receptors, therefore tumor promotion of the underlying malignancy is not a concern for the indication sought. However, patients who undergo myeloablative therapy with stem cell rescue are at risk for the development of secondary cancers. In some cases these may be of epithelial origin. Therefore, the safety evaluation of this study also focuses on the long-term follow up of subjects, in particular monitoring the incidence of secondary malignancies.

The following studies were included in the submission to support the safety evaluation:

Hematologic Malignancy Studies:

- 20000162 A Phase 3, Randomized, Double-blind, Placebo-controlled Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) for Reduction of Mucositis in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation (TBI) and High-dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell (PBPC) Transplantation.

- 980231 A Randomized, Double blind, Placebo controlled Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation (TBI) and High-dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell (PBPC) Transplantation.

- 960189 A Randomized, Double Blind, Placebo Controlled, Dose Escalation Trial of the Safety of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Hodgkin's Disease and Non-Hodgkin's Lymphoma Patients Undergoing High Dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell Transplantation

- 20010182 An open-Label Study of the Pharmacokinetics (PK) of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation and High-Dose Chemotherapy Followed by Peripheral Blood Progenitor Cell (PBPC) Transplantation.

- 960226 A Long-term Follow-up Study of Patients With Hematologic Malignancies Who Were Previously Enrolled in Amgen-sponsored Clinical Trials Using Recombinant Human Keratinocyte Growth Factor (rHuKGF)

Solid Tumor Studies:

- 990199 A Phase 2 Study of Recombinant Keratinocyte Growth Factor (rHuKGF) in Head and Neck Cancer Patients Receiving Concurrent Chemotherapy with Standard or Hyperfractionated Radiation Therapy Investigational Product: recombinant human keratinocyte growth factor (rHuKGF; palifermin)

- 970149 A Phase 1-2 Study of Escalating Doses of Recombinant Keratinocyte Growth Factor (rHuKGF) in Head and Neck Cancer Patients Undergoing Chemoradiotherapy

- 990123 A Long-term Follow-up Study of Head and Neck Cancer Study Subjects Previously Enrolled in Amgen sponsored Clinical Trials with Recombinant Human Keratinocyte Growth Factor (rHuKGF)

- 950225: Randomized, Double-blind, Placebo controlled, Phase 1 Trial of Intravenously Administered Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Colorectal Carcinoma Patients Treated with 5-Fluorouracil and Leucovorin: rHuKGF Dosing Before Chemotherapy

- 950275: Extension Study to KGF 950225: Open-label Study of Intravenously Administered Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Colorectal Carcinoma Patients Treated With 5-Fluorouracil and Leucovorin: Cycle 2 Through 7 - rHuKGF Dosing Before Chemotherapy

- 950226 A Long-term Follow-up Study of Colorectal Carcinoma Patients Who Were Previously Enrolled in Amgen sponsored Clinical Trials Using Recombinant Human Keratinocyte Growth Factor (rHuKGF)

Healthy Volunteer Studies:

- 950170 Randomized, Double-blind, Placebo-controlled Tolerability and Pharmacokinetic Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Normal Volunteers

- 960136 Randomized, Double-blind, Placebo-controlled Tolerability and Pharmacokinetic Trial of Intravenously Administered Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Normal Volunteers

- 970276 Randomized, Double-blind, Placebo-controlled, Safety, Biologic Activity and Pharmacokinetic Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Normal Volunteers

- 970136 Safety and Pharmacokinetics of AMJ-9701 by Single Intravenous Injection in Healthy Volunteers

- 970290 Pharmacokinetics of AMJ-9701 by Single Intravenous Injection of 10 μg/kg in Healthy Volunteers

- 20010192 A Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Recombinant Human Keratinocyte Growth Factor (rHuKGF) After Intravenous Administration to Healthy Volunteers

The following type of safety data was supplied for these individual studies:

Table 7-1 Safety Data Supplied for Individual Studies

Table 7.1 Safety Data Supplied for Individual Studies				
Study	**Description of Study**	**Clinical study report**	**Case report forms[1]**	**SAS (XPT) Files**
Hematologic Malignancy Studies				
20000162	Ph3 Cy/VPTBI	Final	All 214	X
980231	Ph2 Cy/VP/TBI	Final	38/169	X
960189	Ph1 BEAM	Final	58/264	X
20010182	Ph1 TBI/VP/Cy	Final	1/13	X
960226	Long term study	Interim	0	X
Solid Tumor Studies				
990119	Ph2 Head & Neck	Final	60/101	X
970149	Ph1 Head & Neck	Final	44/60	X
990123	Long term study HN	Interim	0	X
950225	Ph1 Colorectal	Final	38/149	X
950275	Ph1 Colorectal	Final	38/48	X
950226	Long term study CR	Final	0	X
Healthy Volunteer Studies				
950170	Subcutaneous	Synopsis	0/28	X
960136	Dose range IV	Synopsis	2/61	X
970276	Dose range IV	Final	4/18	X
970136	Dose range IV	Synopsis	0/24	
970290	Repeat testing	Synopsis	0/4	
20010192	Dose range IV	Final	10/79	X

[1]Case report forms for all patients on pivotal study were submitted; in addition case report forms were submitted on all patients with serious adverse events and for subjects that discontinued treatment for any reason including death.

The submission also included an integrated safety analysis. There were 6 groups evaluated in this integrated analysis:

- Safety Pool A
  Subject Sample: This subset consists of all subjects in the primary efficacy pool, it includes the subjects who received 60 μg/kg/day palifermin or placebo for 3 consecutive days before (pre) the conditioning regimen (Total Body Irradiation, Etoposide, and Cyclophosphamide) and 3 consecutive days after (post) the initiation of hematopoietic stem cell infusion (on days 0-2, where day 0 is the first day of the hematopoieitic stem cell transplant). This set includes all treated subjects in Study 20000162, and the subjects in Study 980231 who received the same dose and schedule of investigational agent administered in Study 20000162.

- Safety Pool B (Primary Safety Pool)
  Subject Sample: This safety subset includes all subjects with hematologic malignancies who received at least one dose of investigational product in Studies 960189, 980231, 20000162 or 20010182. There are 650 subjects included in this subset: 241 placebo and 409 palifermin.

- Safety Pool C (Transplantation Long-Term Follow-up)
  Subject Sample: This safety subset consists of survival and tumor outcome data collected in the 4 parent studies 960189, 980231, 20000162 and 20010182. The long-term study evaluating these patients is Study 960226. There are 537 subjects included in this subset: 198 placebo and 339 palifermin.

- Safety Pool D Head and Neck Cancer Studies
  Subject Sample: This safety subset includes all subjects with advanced head and neck cancer who received at least one dose of investigational product in Studies 970149 or 990119. There are 159 subjects included in this subset: 46 placebo and 113 palifermin.

- Safety Pool E (Head and Neck Cancer Long-Term Follow-up)
  Subject Sample: This safety subset consists of survival and tumor outcome data in Studies 970149 and 990119 (Safety Pool D). The long-term study evaluating these patients is 990123. There are 159 subjects included in this subset: 46 placebo and 113 palifermin.

- Safety Pool F
  Subject Sample: This safety subset includes all subjects with advanced colorectal cancer who received at least one dose of investigational product in Study 950225. Some of these subjects subsequently continued into the extension Study 950275 and/or the long-term follow-up Study 950226. There were 145 subjects included in Study 950225, 63 placebo and 82 palifermin. Study 950275 was an open label continuation study. In this study, 19 subjects who received placebo and 29 subjects who received palifermin on Study 950225 received palifermin. Overall, in safety pool F, 44 subjects received placebo and 101 subjects received palifermin. There are 132 subjects in the long-term follow-up cohort: 39 placebo and 93 palifermin.

7.1.1 Deaths

Hematologic Malignancy Studies:

The following table summarizes the subjects who died on study; it also includes a subject who developed the fatal adverse event on study but died after the study period was complete. The case report forms for these subjects were reviewed.

Table 7-2 Deaths on Study - Hematologic Malignancy Safety Pool B

Table 7.2 Deaths on Study - Hematologic Malignancy Safety Pool B			
Study	**Treatment Arm**	**Day of Study**	**Cause of Death**
20000162	Placebo	Day 12 post Transplant	Gram Negative Sepsis
20000162	Palifermin	Day 31 post Transplant	Veno-occlusive Disease of the Liver
980231	Placebo	Day 16 post Transplant	Adult Respiratory Distress Syndrome
960189	Placebo	Day – 4	Respiratory Failure
960189	Palifermin 5µg/kg X 3 pre	Day 16 post Transplant	Pneumonia Septic Shock Multi-organ Failure
960189	Palifermin 80µg/kg X 3 pre/post	Day 41 Death occurred after study ended	Developed Interstitial Pneumonia presumed CMV day 3; Incubated day 17 Died respiratory failure

COMMENT: *The use of myeloablative chemotherapy with stem cell rescue to treat hematologic malignancies is associated with a significant risk of treatment-related mortality. Five deaths among 650 patients enrolled in transplant setting within the first month of therapy are within the expected incidence. Of the 5 deaths, which occurred on study in the transplantation setting, 3 were among the 241 (1.2%) subjects who received placebo. One palifermin-treated subject died after the study period, the cause of death was interstitial pneumonia, which had developed on day 3 post transplant. There were 2 deaths among the 409 (0.5%) palifermin-treated subjects. One death in the palifermin-treated patients was due to veno-occlusive disease of the liver, a well described transplant related complication; the second was due to pneumonia and septic shock, also an expected complication in the early post transplant period. Based on these data, there is no indication that treatment with palifermin in the autologous transplant setting increases the risk of mortality.*

Mortality in the first 100 days post transplant is a standard transplant benchmark. Twenty percent mortality in the first 100 days is generally considered acceptable. In safety pool A (subjects who received investigational agent at the dose and schedule used to demonstrate the efficacy of palifermin in the autologous hematologic transplant setting), there were 16 deaths among 152 subjects (10%) in the palifermin arm and 21 deaths among 146 subjects (14%) in the placebo arm. In safety pool B (all transplant subjects), there were 86 deaths among 408 palifermin subjects (21%) compared to 49 deaths among 214 placebo subjects (20%). Based on these data, there is no indication of increased mortality in the palifermin treated subjects in the first 100 days post transplant.

Solid Tumor Studies:

Table 7-3 Deaths on Study - Solid Tumor Studies

Table 7.3 Deaths on Study - Solid Tumor Studies			
Study	**Treatment Arm**	**Study Day**	**Cause of Death**
Head and Neck Cancer Safety Pool D			
970149	Placebo	Day 57	Unknown - Died after recent discharge s/p emergency tracheostomy for respiratory compromise.
970149	Palifermin 60µg/kg X 3	Day 45	Sepsis during chemotherapy induced neutropenia
990119	Palifermin 60µg/kg X 3	Day 25	Sepsis during chemotherapy induced neutropenia
990119	Palifermin 60µg/kg X 3	Day 48	Aspiration pneumonia due to feeding tube
990119	Palifermin 60µg/kg X 3	Day 143	Unknown died at site distant from treatment center
990119	Placebo	Day 57	Pneumonia respiratory failure subsequent multiorgan failure
990119	Placebo	Day 49	Respiratory failure after hemorrhage into the throat.
990119	Palifermin 60µg/kg X 3	Day 23	Myocardial Infarction
Colorectal Cancer Safety Pool D			
950225	Placebo	Day 22	Intestinal obstruction progressive disease
950225	Palifermin 80µg/kg X 3	Day 23	Arrhythmia Patient off study due to disease progression
950225	Palifermin 40µg/kg X 3	Day 44	Progressive Disease
950275	Palifermin 60µg/kg X 3	Day 7 of 2nd cycle	Intestinal complication including abscess, necrosis, and perforation

COMMENT: *In the head and neck cancer trials of palifermin there were 8 (5.0%) deaths among 159 subjects; 3 (6.5%) among 46 subjects treated with placebo and 5 (4.4%) among 113 subjects treated with palifermin. This frequency of deaths and the observed etiologies could be expected in this population.*

In subjects with colorectal cancer there were 4 (2.7%) deaths among 145 patients who received investigational product; 3 (3.6%) among 82 patients in the palifermin group and 1 (1.5%) among 63 patients who received placebo. In 1 placebo and 2 palifermin in cases, the subject had progressive cancer. One patient treated with palifermin died of post-operative complications. There was no obvious role of palifermin in these deaths; they are expected outcomes in the patient population included in this study. Tumor promotion in solid tumors is a concern; however, these studies in colorectal cancer were not designed to evaluate the possible role of palifermin in tumor promotion. Tumor promotion will be evaluated in long-term follow-up studies.

Healthy Volunteer Studies:

There were no deaths in the healthy volunteer studies.

7.1.2 Other Serious Adverse Events

Hematologic Malignancy Studies:
Palifermin is intended for use in patients at risk to develop severe mucositis. The efficacy can only be determined in patients who have received a sufficient dose of chemo-radiotherapy to predictably cause severe mucositis. At the required doses of chemo-radiotherapy, multiple severe side effects are inevitable. Therefore, the majority of studies Amgen has conducted in support of this license application have randomized palifermin with placebo to facilitate identifying side effects related to palifermin in contrast to those resulting from the chemo-radiotherapy.

In the hematologic malignancy studies, palifermin was most commonly administered 3 days prior to the beginning of the preparative regimen and 3 days after infusion of stem cells. In this application the evaluation of toxicity was reported in two phases, pre chemotherapy and post chemotherapy. The table below summarizes the serious adverse events reported:

Table 7-4 Summary of Serious Adverse Events in Hematologic Malignancy Safety Pool B

Table 7.4 Summary of Serious Adverse Events in Hematologic Malignancy Safety Pool B				
Subjects n (%) 650 Total 241 Placebo 409 Palifermin	**Serious Adverse Event**	**Grade 3&4 Adverse Event**	**Serious Treatment Related Adverse Event**	**Grade 3 + Treatment Related Adverse Event**
Pre chemo				
Placebo	6 (2%)	21 (9%)	0	0
Palifermin	10 (2%)	29 (7%)	1	0
Post chemo				
Placebo	47 (20%)	84 (35%)	2 (1%)	2 (1%)
Palifermin	77 (19%)	156 (38%)	7 (2.7%)	6 (1%)
Total				
Placebo	52 (22%)	91 (38%)	2 (1%)	2 (1%)
Palifermin	85 (20%)	165 (40%)	8 (2%)	6 (1%)

COMMENT: *The incidence of Serious and Grade and Grade 3 and 4 toxicity was similar in the placebo and palifermin subjects in the pre-chemotherapy period. There were slightly more grade 3 and 4 adverse events in the palifermin subjects during the post-chemotherapy period. There were no specific events identified that accounted for this slightly higher incidence other than the events identified as treatment-related below.*

Significant toxicities either classified as serious or graded as 3,4, or 5 that were identified as related to therapy are summarized in the table below:

Table 7-5 Significant Adverse Events Attributed by Investigator to Be Related to Investigational Agent in Hematologic Malignancy Safety Pool B

Table 7.5 Significant Adverse Events Attributed by Investigator to Be Related to Investigational Agent in Hematologic Malignancy Safety Pool B			
Adverse event	**Treatment Arm (Period Occurred)**	**Designated Serious**	**Designated Grade 3 +**
Rash	Palifermin (pre)	yes	no
Severe Renal Insufficiency	Placebo (post)	yes	Yes (grade 3)
Hypotension	Placebo (post)	yes	yes (grade 4)
Fever and Respiratory Insufficiency	Palifermin (post)	yes	Yes (grade 3)
Bilateral Interstitial Pneumonia Fatal (see chart Deaths)	Palifermin (post)	yes	Yes (grade 5)
Bronchial Stenosis Oral Bronchial Fungal Infections	Palifermin (post)	yes	Yes (grade 4)
Skin Rash Hands and feet	Palifermin (post)	yes	Yes (grade 3)
Acute Renal Failure	Palifermin (post)	yes	Yes (grade 4)
Skin Toxicity Pain Excoriation	Palifermin (post)	yes	Yes (grade 3)
Generalized Rash	Palifermin (post)	yes	no
Abdominal Pain	Palifermin (post)	no	Yes (grade 3)
Erythema	Palifermin (post)	no	Yes (grade 3)
Swollen Neck, Throat Tightness	Palifermin (post)	no	Yes (grade 3)
Edema Face and Neck	Palifermin (post)	no	Yes (grade 3)
Dry Mouth	Placebo (post)	no	Yes (grade 3)
Itching Hands and Back	Placebo (pre)	no	Yes (grade 3)
Rash Trunk Extremity	Palifermin (post)	no	Yes (grade 3)
Pruritis	Placebo (pre)	no	Yes (grade 3)
Rash Chest Arms	Palifermin (pre)	no	Yes (grade 3)
Rash Face Neck Chest Back	Palifermin (post)	no	Yes (grade 3)
Rash Trunk Arms	Placebo (post)	no	Yes (grade 3)
Rash Face Neck Upper Back Chest	Placebo (post)	no	Yes (grade 3)

COMMENT: *The majority of serious adverse events designated as related to investigational agent were identified in the palifermin group (8 of 10). Four of these were rashes and skin toxicity. There were 12 additional subjects with grade 3 adverse events designated as treatment related that were not designated as serious, predominantly skin and oral toxicity.*

One episode of renal insufficiency was identified in the placebo group and one was identified in the palifermin group. The two additional serious adverse events identified as treatment related were fatal interstitial pneumonitis and oral respiratory fungal infections. These are known transplant complications, and each was only seen in a single patient. The etiologic role of palifermin is unlikely.

Solid Tumor Studies:

The table below summarizes all serious adverse events reported in solid tumor studies, comparing placebo-treated subjects to palifermin-treated subjects:

Table 7-6 Summary of Adverse Events in Solid Tumor Studies

Table 7.6 Summary of Adverse Events in Solid Tumor Studies					
Subjects n (%)	**Serious Adverse Event**	**Grade 3&4 Adverse Event**	**Treatment Related Adverse Event**	**Serious Treatment Related Adverse Event**	**Grade 3 + Treatment Related Adverse Event**
Head and Neck Cancer 159 total, 113 palifermin, 46 placebo					
Placebo	22 (48%)	28 (61%)	7 (15%)	0	0
Palifermin	64 (57%)	68 (61%)	35 (31%)	2 (2%)	5 (4%)
Colorectal Cancer 145 total, 82 palifermin, 63 placebo					
Placebo	16 (25%)	26 (40%)	31 (49%)	0	2 (3%)
Palifermin	15 (18%)	32 (39%)	50 (60%)	0	1 (1%)
Colorectal Cancer 950275 48 total 19 prior placebo and 29 prior palifermin on 950225					
Palifermin	13 (27%)	31 (64%)	37 (77%)	0	4 (8%)

Head and Neck Cancer

COMMENT: *In the head and neck population, there were more serious adverse events reported in the palifermin group. The notable serious adverse events reported more frequently in the palifermin subjects included severe neutropenia (palifermin-treated subjects 35% compared to placebo-treated subjects 22%) and skin and oral toxicity (palifermin-treated subjects 38% compared to the placebo-treated subjects 30%). The role of palifermin in the excess neutropenia is unclear. In the current hematologic malignancy transplant studies, neutropenia is not a significant issue as there was no evidence of delayed engraftment in the palifermin treated subjects. Skin and oral toxicity is the most common side effect of palifermin.*

Colorectal Cancer

COMMENT: *In the colorectal cancer population, the overall incidence of adverse events designated serious, and adverse events graded as 3, 4, or 5 was the same or less in the palifermin group compared to the placebo group. The incidence of treatment related adverse event was greater in the palifermin group compared to the placebo group (60 v 49%). The majority of the treatment related adverse events that were identified at an increased incidence in the palifermin-treated subjects were side effects known to be associated with palifermin. These were predominantly skin and oral toxicity.*

In the continuation study 950275, all subjects received palifermin, the majority of adverse events that were identified as treatment related were the side effects known to be associated with palifermin, predominantly skin and oral toxicity. The adverse events reported in four subjects as treatment related ≥ grade 3 were grade 3 arthralgia, rash and 2 subjects with taste perversion.

The table below summarizes toxicities occurring in solid tumor subjects, classified either as serious or graded as 3 or 4, and attributed by the Investigator to investigational agent:

Table 7-7 Serious or Grade 3 and 4 Adverse Events Attributed by Investigator to Investigational Agent in Solid Tumor Studies

Table 7.7 Serious or Grade 3 and 4 Adverse Events Attributed by Investigator to Investigational Agent in Solid Tumor Studies			
Adverse event	**Treatment Arm**	**Designated Serious**	**Designated Grade 3 or 4**
Head and Neck Cancer			
Pancreatitis, abdominal pain	Palifermin	yes	No (grade 2)
Hypersalivation, dehydration, pain, dysphagia, fatigue	Palifermin	yes	Yes (grade 3)
Hypersalivation	Palifermin	no	Yes (grade 3)
Erythema, rash	Palifermin	no	Yes (grade 3)
Nausea, vomiting	Palifermin	no	Yes (grade 3)
Fatigue	Palifermin	no	Yes (grade 3)
Colorectal Cancer			
Fatigue	Placebo	no	Yes (grade 3)
Elevated Bilirubin	Placebo	no	Yes (grade 3)
Edema and erythema of face, pruritis	Palifermin	no	Yes (grade 3)

Head and Neck Cancer:

In the Head and Neck Cancer Safety Pool D, the serious or ≥ grade 3 toxicities included 2 subjects with hypersalivation, 1 subject with nausea and vomiting, 1 subject with fatigue, and 1 subject with grade 2 pancreatitis.

Amgen's further analysis of the episode of pancreatitis follows (eCTD 5.3.5.4.4, Clinical Study Report 990119 page 148):
"This subject was a 51-year-old woman with nasopharyngeal cancer. The subject had a 5-day history of nausea, vomiting, and right lower quadrant pain that started after chemoradiotherapy and after the second weekly dose of palifermin. The subject was hospitalized for acute epigastric pain; presenting symptoms included nonradiating pain, worse when supine, with movement and after eating. Amylase (894 U/L) and lipase (58 U/L) values were elevated from normal baseline. The subject was treated with intravenous fluids and pain medication and palifermin was discontinued. Symptoms resolved within 3 days and amylase/lipase values returned to baseline. Approximately 4 days after hospital discharge, the subject was readmitted with febrile neutropenia and diarrhea; stool culture was positive for Clonorchis, Opisthorchis, Heterophyes, and Metagonimus eggs. The hospital reported that the organisms were present before the subject began receiving chemotherapy and that immune suppression would make a flare of these organisms more likely to occur. Also, the Clonorchis would cause symptoms consistent with early pancreatitis."

COMMENT: *In the Head and Neck Cancer Safety Pool D, all the adverse events designated as serious or graded as grade 3 were in the palifermin group. The majority of these adverse events were skin or oral symptoms.*

Colorectal Cancer:

COMMENT: *In the Colorectal Cancer Safety Pool F, all of the 3 adverse events designated as serious were grade 3. Two were in the placebo group, and 1 was in the palifermin group. The adverse events reported in the palifermin subject were edema and erythema of the face and pruritis.*

Healthy Volunteer Studies:

No subject experienced a serious adverse event. There was one adverse event Amgen reported as being notable (eCTD 5.3.3.1.3, Clinical Study Report 20010192 page 83). This occurred in a 19-year-old woman enrolled in Study 20010192. The subject experienced severe abdominal pain coincident with her mid-menstrual cycle after a single administration of palifermin at a dose of 60 µg/kg. The event resolved without sequelae.

7.1.3 Dropouts and Other Significant Adverse Event

7.1.3.1 Overall profile of dropouts

Hematological Malignancy Studies:

The overall disposition of subjects in safety pool B is summarized in the table below derived from Amgen Table 2.1.b (eCTD 5.3.5.3.2.1, Integrated Safety Analysis page 49):

Table 7-8 Overall Disposition of Subjects Hematologic Malignancy Safety Pool B

Table 7.8 Overall Disposition of Subjects Hematologic Malignancy Safety Pool B		
Number of Subjects (%)	**Placebo (N=241)**	**Palifermin (N=409)**
Subject Received Investigational Product	409(100)	241(100)
Subject Who Completed Study	234(97)	397(97)
Subject Who Discontinued Study	7(3)	12(3)
Adverse Event	2(1)	2(0)
Consent Withdrawn	0(0)	3(1)
Unrelated Medical Condition	0(0)	1(0)
Disease Progression While on Study	1(0)	1(0)
Administrative / Investigator Decision	0(0)	2(0)
Lost to Follow-up	0(0)	1(0)
Death on Study	3(1)	1(0)
Other	1(0)	1(0)

The details regarding the six patients who were removed from studies after adverse events are summarized in the table below. Amgen provided each subject's CRFs and these were reviewed.

Table 7-9 Adverse Events Leading to Removal from Study - Hematologic Malignancy Safety Pool B

Table 7.9 Adverse Events Leading to Removal from Study - Hematologic Malignancy Safety Pool B					
Study Investigational Agent	**Adverse Event**	**Day of transplant Adverse Event Occurred**	**Protocol Treatment Administered**	**Investigator Attribution to Investigational Agent**	**Comments**
960189 Palifermin 5µg/kg	Subject developed illeus required surgery, illeus related to tumor	Day -8	Subject received Palifermin 2 of 3 planned doses	Not related	Off study prior to receiving preparative regimen
960189 Palifermin 60µg/kg	Developed Oral and Bronchial fungal Infection requiring mechanical ventilation	Day +8	Subject received 3 of 3 planned doses palifermin and the preparative regimen	Related	Subject and investigator decided subject would terminate study day 18
960189 Palifermin 80µg/kg	Central venous catheter thrombosis	Day -8	Subject received 2 of 3 planned doses palifermin	Not related	Off study prior to receiving preparative regimen
960189 Placebo	Perirectal abscess	Day -8	Subject received 1 of 6 planned doses of placebo	Not related	Off study prior to receiving preparative regimen
980231 Palifermin 60µg/kg	Myocardial infarction	Day +1	Subject received 4 of 4 planned doses palifermin and the preparative regimen	Not related	Subject and investigator decided subject would terminate study day 28
20000162 Placebo	Severe rash with severe pruritis	Day -1	Subject received 3 of 6 planned doses of placebo and the preparative regimen	Related	Subject decided to terminate study on day 0, rash itching with after initial 3 doses intolerable

The adverse events that led to discontinuation of investigational agent are summarized in the table below:

Table 7-10 Adverse Events Leading to Discontinuation of the Study Agent – Hematologic Malignancy Safety Pool B

Table 7.10 Adverse Events Leading to Discontinuation of the Study Agent – Hematologic Malignancy Safety Pool B				
Study Investigational Agent	**Adverse Event**	**Day of transplant Adverse Event Occurred**	**Protocol Treatment Administered**	**Attribution to Investigational Agent**
960189 Palifermin 80µg/kg	Severe Erythematous rash, edema and burning extremities	Day –7	Subject received 2 of 6 planned doses of palifermin	Related
960189 Palifermin 80µg/kg	Severe Erythematous rash, and edema	Day +1	Subject received 4 of 6 planned doses of palifermin	Related
980231 Palifermin 60µg/kg	Diffuse Maculopapular rash	Day +1	Subject received 5 of 6 doses of palifermin	Related
980231 Palifermin 60µg/kg	Maculopapular rash on head and upper arms	Day -9	Subject received 3 of 6 doses of palifermin	Related
20000162 Placebo	Severe rash with severe pruritis	Day -1	Subject received 3 of 6 planned doses	Related
20000162 Palifermin 60µg/kg	Lobar Pneumonia requiring mechanical ventilation	Day -10	Subject received 1 of 6 doses of palifermin transplant delayed	Not related
20000162 Placebo	Severe rash with severe pruritis	Day -1	Subject received 3 of 6 planned doses of placebo	Related
20000162 Placebo	Hypotension	Day 0	Subject received 4 of 6 planned doses of placebo	Related
20000162 Palifermin 60µg/kg	Severe rash and flushing	Day -10	Subject received 2 of 6 planned doses	Related
20000162 Palifermin 60µg/kg	Upper respiratory infection symptoms	Day -10	Subject received 5 of 6 planned doses day –10 (2nd dose) held	Not related

Solid Tumor Studies:

The overall disposition of subjects in safety pool D is summarized in the table below derived from Amgen Table 14-2 and Table 14-1.3.1 (eCTD 5.3.5.4.3, Clinical Study Report 970149 page 128; eCTD 5.3.5.4.4, Clinical Study Report 990119 page 166):

Table 7-11 Overall Disposition of Subjects with Head and Neck Cancer Safety Pool D

Table 7.11 Overall Disposition of Subjects with Head and Neck Cancer Safety Pool D				
Number of Subjects (%)	Study 970149 End of Active Treatment Phase (Week 11)		Study 990119 End of Study (Week 20)	
	Placebo	Palifermin	Placebo	Palifermin
Subject Received Investigational Product	14(100)	46(100)	32(100)	67(100)
Completed	12(86)	39(85)	28(88)	50(75)
Discontinued	2(14)	7(15)	4(13)	17(25)
Consent Withdrawn	0(0)	1(2)	1(3)	4(6)
Administrative / Investigator Decision	1(7)	5(11)	0(0)	7(10)
Lost to Follow-up	0(0)	0(0)	1(3)	0(0)
Death	1(7)	1(2)	2(6)	4(6)
Other			0(0)	2(3)

The overall disposition of subjects in Colorectal Cancer Safety Pool F is summarized in the table below derived from Amgen Table 14-1.2c and Table 14-1.2d (eCTD 5.3.5.4.3, Clinical Study Report 950225 and 950275 pages 274 and 275):

Table 7-12 Overall Disposition of Subjects with Colorectal Cancer Safety Pool F

Table 7.12 Overall Disposition of Subjects with Colorectal Cancer Safety Pool F				
Number of Subjects (%)	Study 950225		950275 Continuation Study of 950225	
	Placebo	Palifermin	Placebo	Palifermin
Subject Randomized	64	85	19	29
Did not receive Investigational Product	1 (2)	3 (4)		
Completed	55 (86)	76 (89)	5 (26)	9 (31))
Discontinued	9 (14)	9 (11)	14 (74)	20 (69)
Consent Withdrawn	2 (3)	0 (0)	0 (0)	1 (3)
Intolerable Adverse Event Unrelated to Investigational Agent			1 (5)	1(3)
Administrative / Investigator Decision	0 (0)	1 (1)	4 (21)	2 (7)
Protocol Violation	2 (3)	0 (0)		
Disease Progression	2 (3)	2 (2)	8 (42)	14 (48)
Death	1 (2)	1 (1)	0 (0)	1 (3)
Unrelated Medical Condition	0 (0)	1 (1)		
Other	2 (3)	4 (5)	1 (5)	1 (3)

Tables summarizing adverse events that led to study removal and discontinuation of investigational agent for solid tumor subjects follow below:

Table 7-13 Adverse Events Leading to Removal from Study Head and Neck Cancer Safety Pool D

Table 7.13 Adverse Events Leading to Removal from Study Head and Neck Cancer Safety Pool D		
Study Investigational Agent	**Adverse Event**	**Attribution to Investigational Agent**
970149 Palifermin 80µg/kg	Motor Vehicle Accident	Not related
970149 Palifermin 60µg/kg	Severe back pain secondary to compression fracture L3	Not related

Table 7-14 Adverse Events Leading to Discontinuation of the Study Agent Head and Neck Cancer Safety Pool D

Table 7.14 Adverse Events Leading to Discontinuation of the Study Agent Head and Neck Cancer Safety Pool D		
Study Investigational Agent	**Adverse Event**	**Attribution to Investigational Agent**
970149 Palifermin 20µg/kg	Sepsis ultimately fatal	Not related
970149 Palifermin 40µg/kg	Liver failure Renal failure	Not related
970149 Placebo	Fever	Not related
990119 Palifermin 60µg/kg	Cerebrovascular accident	Not related
990119 Palifermin 60µg/kg	Diarrhea, nausea and vomiting Aspiration Pneumonia	Not related
990119 Palifermin 60µg/kg	Erythema face/neck & Conjunctivitis R facial nerve palsy Sepsis ultimately fatal	Not related
990119 Palifermin 60µg/kg	Aspiration Pneumonia	Not related
990119 Palifermin 60µg/kg	Stroke ultimately fatal	Not related
990119 Placebo	Pneumonia Multi-organ failure	Not related
990119 Palifermin 60µg/kg	Pancreatitis	Related
990119 Palifermin 60µg/kg	Jaundice	Not related
990119 Palifermin 60µg/kg	Excessive salivation Dehydration	Related
990119 Palifermin 60µg/kg	Pulmonary Embolism	Not related

Table 7-15 Adverse Events Leading to Removal from Study Colorectal Cancer Safety Pool F

Table 7.15 Adverse Events Leading to Removal from Study Colorectal Cancer Safety Pool F		
Study Investigational Agent	**Adverse Event**	**Attribution to Investigational Agent**
950275 Palifermin 10µg/kg	Hyperbilirubinemia	Not Related
950275 Palifermin 80µg/kg	Edema and Rash	Related
950275 Palifermin 60µg/kg	Small Bowel Necrosis and Abdominal perforation	Not Related

Table 7-16 Adverse Events Leading to Discontinuation of Investigational Agent in Colorectal Cancer Safety Pool F

Table 7.16 Adverse Events Leading to Discontinuation of Investigational Agent in Colorectal Cancer Safety Pool F		
Study Investigational Agent	**Adverse Event**	**Attribution to Investigational Agent**
950225 Palifermin 60µg/kg	Edema face Erythema Chest and Buttock	Definite
950275 Palifermin 80µg/kg	Septic Shock	Not related
950275 Placebo	Erythema base of back Excoriations	Not related

7.1.3.2 Adverse events associated with dropouts

Hematologic Malignancy Studies:

In the Hematologic Malignancy Safety Pool B the majority of study dropouts were not related to the investigational agent. There were 6 subjects who withdrew from studies. In 3 subjects, a contraindication to transplantation was identified prior to starting the preparative regimen and the transplant was cancelled.

One subject who withdrew received placebo. Two patients who received palifermin developed severe medical complications (oral and bronchial fungal infection requiring mechanical ventilation and myocardial infarction) and withdrew. In these cases, the subject and investigators decided to halt study participation. The investigator caring for the subject with the oral and bronchial fungal infection indicated that the adverse event was related to the investigational agent. It is unlikely this attribution is correct. There is no indication that palifermin promotes fungal infections, and review of the subjects pre-therapy physical exam identifies a Candida skin rash was present prior to starting treatment.

Among patients identified as having study agent discontinued due to adverse events, there was an additional patient who did not undergo transplant due to a medical contraindication. There

were 7 patients who did not receive the planned number of doses of palifermin due to skin and oral toxicity.

COMMENT: *Skin and oral toxicity is the most common adverse event that directly interfered with the ability use palifermin in clinical trials.*

Solid Tumor Studies:

In both the Head and Neck Cancer Safety Pool D and the Colorectal Cancer Safety Pool F the majority of dropouts were not related to the investigational agent, but were related to the underlying disease or to the anticancer therapy.

In the Head and Neck Cancer Studies, one subject discontinued investigational agent due to excessive salivation resultin in dehydration, and a second subject discontinued investigational agent due to pancreatitis. The excessive salivation is notable because palifermin in known to induce elevated levels of amylase and lipase. These enzymes are predominantly salivary gland in origin. Because of these enzyme elevations, the risk of pancreatitis has been carefully monitored in palifermin trials. The subject with pancreatitis in Head and Neck Cancer Safety Pool D is the only subject treated with palifermin in Safety Pool B, D or F experiencing pancreatitis as an adverse event. (See section 7.1.2 Other Serious Events for clinical details.) In Hematologic Malignancy Safety Pool B, two subjects who received placebo experienced pancreatitis.

In the Colorectal Cancer Safety Pool F, one subject on Study 950225 discontinued investigational agent due to skin toxicity.

COMMENT: *Skin and oral toxicity is the most common adverse event that directly interfered with the ability use palifermin in clinical trials.*

Healthy Volunteer Studies:

One subject was withdrawn from the study due to an adverse event. In Study 960136, a subject in the 5-µg/kg/day, palifermin multiple-dose cohort developed mild periorbital and conjunctival petechiae after receiving 2 of 3 doses (cumulative total dose 10 µg/kg) and was withdrawn from study.

7.1.3.3 Other significant adverse events

Laboratory abnormalities not meeting the definition of serious:

Elevated Amylase and Lipase – Potential Risk of Pancreatitis
In preclinical toxicology studies, it was determined that palifermin caused elevations of lipase and amylase. Pancreatic ductal and glandular cells express KGF receptors. Based on this

preclinical information, the clinical trails of palifermin were designed to monitor subjects carefully for for clinical pancreatitis and elevations in serum amylase and lipase levels. In palifermin clinical trials elevation of serum amylase and lipase was common. Fractionation of serum amylase in subjects with elevated levels determined that the major source of amylase was salivary, although a minor fraction was pancreatic in origin.

Hematologic Malignancy Patient Population:

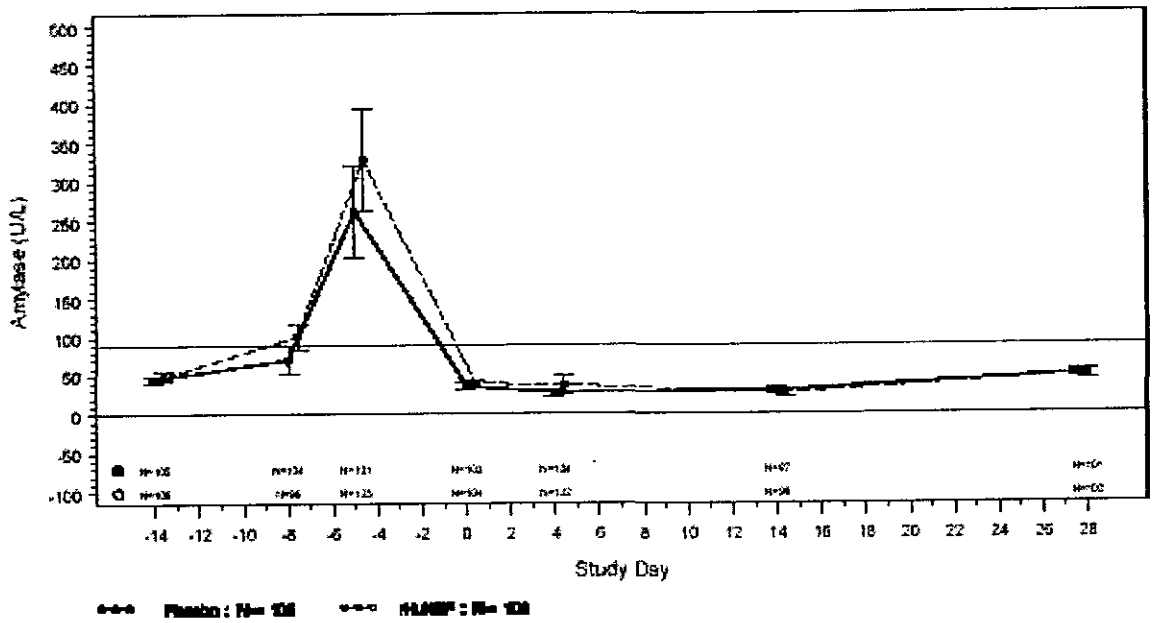
Inflammation of the salivary glands is a well-described complication of total body irradiation used as part of the preparative regimen of transplantation. Review of amylase determinations in Hematologic Malignancy Safety Pool B demonstrated amylase was elevated in the majority of patients. This elevation was reversible. Amylase was elevated in 56% of subjects tested in the Hematologic Malignancy Safety Pool B: 55% placebo and 60% palifermin. In Hematologic Malignancy Safety Pool A, the subjects treated with a TBI containing regimen, the overall incidence of elevated amylase was 70%: 64% placebo and 74% palifermin. In both placebo and palifermin subjects, the peak amylase occurred between transplant day –5 to day 0. Elevated amylase occurred after the palifermin administration on day –11, -10, -9 only. A similar peak was not seen after the administration of palifermin on days 0, 1, and 2.

The analysis of lipase was similar, although the overall incidence of elevated lipase was lower. Lipase was elevated in 30% patients tested in the transplant Safety pool B: 27% placebo and 32% palifermin.

In the modified intent to treat population of Study 20000162, Amgen analyzed the time course of the elevation of the serum amylase, comparing the palifermin and placebo subjects. See Amgen Figure below (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 149).

Figure 7-1 Amgen's Graph of Mean Amylase Levels by Day of Study

Figure 11-1. Mean Amylase Levels by Study Day (mITT Population)



As can be seen from the graph, the mean serum amylase peaked at day -5 and was slightly greater in the palifermin (dotted line) subjects, but returned to normal by day 0 in both groups. There were no clinical manifestations associated with these elevated levels. Two subjects in the Hematologic Malignancy Safety Pool B experienced pancreatitis; both of these subjects received placebo.

In order to evaluate possibility of undiagnosed pancreatitis, subjects in Safety Pool A with an adverse event coded as Pain Abdominal or Pain Back were evaluated to determine if they also had increased amylase. Sixty-one subjects with abdominal and or back pain had an elevated amylase. Among these, there were 9 subjects identified in whom the symptom and elevated amylase may have overlapped. The case report forms for 8 subjects were reviewed. In no case was the information regarding the clinical course of the subject suggestive of pancreatitis.

Solid Tumor Setting:

In Head and Neck Cancer Safety Pool D and Colorectal Cancer Safety Pool F the serum amylase and lipase values were commonly elevated, predominantly in the palifermin treated subjects. See table below:

Table 7-17 Incidence of Elevated Amylase and Lipase in Solid Tumor Studies

Table 7.17 Incidence of Elevated Amylase and Lipase in Solid Tumor Studies			
	Overall	Placebo	Palifermin
Head and Neck Cancer Safety Pool D			
Amylase	28/144 (19%)	5/42 (12%)	23/102 (23%)
Lipase	37/149 (25%)	6/44 (14%)	31/105 (30%)
Colorectal Cancer Safety Pool F			
Amylase	21/144 (15%)	3/62 (5%)	15/82 (18%)
Lipase	72/144 (50%)	22/62 (35%)	50/82 (63%)

One patient in the Study 990119 palifermin group experienced pancreatitis. The clinical evidence suggests the pancreatitis in this subject was related to a parasitic infection not palifermin. (See section 7.1.2 Other Serious Adverse Events for details.)

There were no other cases of pancreatitis identified in the solid tumor safety pools. The observed laboratory abnormalities did not have any clinical manifestations.

Healthy Volunteer Studies:

Elevations of amylase and lipase were seen in the healthy volunteer population. The subjects with elevated levels of amylase did not report abdominal pain or exhibit other signs of pancreatitis, although 3 women on Study 970276 who reported back pain and had elevated amylase levels.

Maximum total amylase and lipase values obtained in the volunteer clinical trials and in the subset of subjects enrolled on these trials who received a cumulative dose of ≥120 µg/kg are described in the table below (derived from Table 41 and 42, eCTD 2.7.4, Summary of Clinical Safety pages 182 and 183):

Table 7-18 Maximum Level Amylase in Healthy Volunteer Studies

Table 7.18 Maximum Level Amylase in Healthy Volunteer Studies				
	All Subjects		Subjects with dose > or = 120µg/kg	
	Placebo (N=50)	Palifermin (N=160)	Placebo (N=11)	Palifermin (N=38)
Maximum CTC grade Total Amylase				
Below normal range	1 (2)	1 (1)	0 (0)	0 (0)
0 (Within normal limits)	47 (94)	138 (86)	11 (100)	28 (74)
1 (>1.0 - 1.5 x ULN)	2 (4)	18 (11)	0 (0)	8 (21)
2 (>1.5 - 2.0 x ULN)	0 (0)	2 (1)	0 (0)	1 (3)
3 (>2.0 - 5.0 x ULN)	0 (0)	1 (1)	0 (0)	1 (3)
4 (>5.0 x ULN)	0 (0)	0 (0)	0 (0)	0 (0)
Maximum CTC grade Lipase				
Below normal range	1 (2)	1 (1)	1 (9)	0 (0)
0 (Within normal limits)	41 (82)	124 (78)	10 (91)	29 (76)
1 (>1.0 - 1.5 x ULN)	1 (2)	7 (4)	0 (0)	1 (3)
2 (>1.5 - 2.0 x ULN)	1 (2)	6 (4)	0 (0)	5 (13)
3 (>2.0 - 5.0 x ULN)	0 (0)	4 (3)	0 (0)	3 (8)
4 (>5.0 x ULN)	0 (0)	0 (0)	0 (0)	0 (0)

COMMENT: *The increased incidence in the subset that received a palifermin cumulative dose of ≥120 µg/kg suggests that the incidence of elevated amylase and lipase may be dose related.*

7.1.4 Other Search Strategies

7.1.4.1 Infusional toxicity

In order to evaluate possible infusion related toxicity, adverse events that occurred within 24 hours of the first 3 days of investigational drug infusion were evaluated. Specifically, fever, skin toxicity, low blood pressure, pulmonary symptoms, and cardiac symptoms in the Safety Pool B subjects were evaluated. The following preferred term categorizes were reviewed: allergic reaction, dizziness, dyspnea, edema, erythema, fever, pain, pruritis, rash, respiratory insufficiency, rigors, syncopy, tachycardia, and vaso-vagal reaction. Using these terms, there were 60 adverse reactions identified during this time period, 20 in 241 placebo subjects and 40 in 409 palifermin subjects. The adverse event data files and available case report forms were reviewed for these advese reactions. The following events were notable:

- Allergic reaction (1 incident: palifermin): Study 960189 subject 11302. The incident began 1 ½ hours after medication and consisted of tingling around lips and radiating to left cheek and left eye. Left eye was watery and pruritic. It occurred with first dose and was less pronounced after dose 2 and 3.
- Edema (10 incidents: 4 placebo, 6 palifermin): The duration of edema was prolonged in 7 instances from 6 to 30 days after the last dose of investigational agent. In two cases it occurred prior to the first dose of investigational agent. In a placebo subject it occurred on the day of the first dose and did not recur with subsequent doses.

- Skin toxicity (8 incidents: 3 placebo, 5 palifermin): These were identified under preferred terms pruritis, erythema and rash. Additional verbatim terms associated with the preferred terms were: erythema – palms, neck, cheeks, axilla, scalp itching, and rash, erythematous. In the palifermin subjects the terms used were: facial erythema, rash, erythema – palms, neck, cheeks, axilla, and scalp itching. The duration and timing of these events were not consistent with infusional toxicity; these terms are descriptive of the skin toxicity associate with palifermin.
- Flushing (2 incidents: palifermin): This seems to be a variation of the skin toxicity and appears to be drug related.
- Fever (9 incidents: 2 placebo, 7 palifermin): All subjects identified with fever during this time period were enrolled on 960189. Four of the palifermin subjects developed fever the day prior to the palifermin. The remaining 3 palifermin subjects developed the fever on the first day of administration. Overall, fever was determined to occur more frequently in the palifermin subjects, but the time period when this was most pronounced was the post chemotherapy period.
- Hypotension, Vaso-vagal episode, Syncope (1 each: all palifermin): The episode of hypotension was prolonged with a duration of 14 days. The vasovagal episode and the episode of syncope occurred with the first dose and may have been related to palifermin.
- Pain (20 incidents: 6 placebo, 14 palifermin): In nine subjects pain was present prior to first dose of investigational agent or was determined to be tumor related. There was no single characteristic verbatim description of pain reported in the palifermin subjects; the verbatim descriptions included: abdominal pain (3), back pain, chest pain non cardiac, burning left abdomen, and burning sensation chest. No specific pattern of pain was obvious, and the overall incidence was similar between placebo and palifermin subjects.

The verbatim terms for the events outlined above were also reviewed. There were no unusual or noteworthy terms identified.

There were 2 subjects identified with more than 1 of these possible infusion related adverse event starting after the first dose but within 24 hours of the first 3 doses of palifermin:

- Chest pain and syncope
- Facial flushing and Erythema – palms, neck, cheeks, axilla

The flushing and erythema are the typical palifermin-associated reactions, not an infusional reaction. It is possible that the chest pain and syncope were related and a form of infusional reaction.

COMMENT: *Based on the review above there does not seem to be an appreciable level of infusional toxicity associated with the administration of palifermin.*

7.1.4.2 Search based on preclinical toxicology findings

In rats receiving high, prolonged doses of palifermin in preclinical toxicology studies there were three histological findings of concern:

1. Centrolobular apotosis was seen in the liver histology. In order to evaluate this histologic finding, the clinical data was reviewed to determine if there was evidence of a greater degree of elevation of bilirubin, AST and ALT in the palifermin subjects. As seen in section 7.1.7. 3.1 Analyses Focused on Measures of Central Tendency, the mean and median of bilirubin, AST, ALT were comparable between the placebo and palifermin subjects. Also as seen in section 7.1.7.3.3 Marked Outliers and Dropouts, there was no indication that there were extreme abnormalities of bilirubin, AST, ALT in palifermin subjects.

2. Increased follicles were seen in the histology of thyroid tissue. In order to evaluate this histologic finding, clinical data was reviewed looking for abnormalities in thyroid testing. Thyroid test were conducted only in Study 950225 for colorectal cancer. Thyroid testing included T3, T4, and TSH. There were no abnormal thyroid tests in any palifermin subjects. One placebo subject was reported to have an elevated TSH as an adverse event.

3. There were protein casts, necrosis and regenerating tubules seen in kidney histology. In order to evaluate these in the clinical database the results of urinalyses were reviewed. Urinalyses were only collected in the Colorectal Cancer Safety Pool F. There were no placebo subjects who developed 2 + or greater proteinuria after treatment with investigational agent. There were 9 palifermin subjects with a baseline urinalysis negative for protein who subsequently developed 2+ or greater proteinuria after treatment. Microscopic urinalysis was not donein these trials, so the incidence of protein casts in urine is unknown. In healthy volunteer studies 20010192, 950170, 960136, 970290 and 970290, urinalysis was done as part of routine testing. In pharmacology trial 970276, data demonstrated that no subject developed proteinuia (eCTD 5.3.3.1.4, Clinical Study Report 970276 page 574).

A second item that was reviewed as a marker of renal toxicity was hypertension. Hypertension was reviewed in detail in section 7.1.8.3.Standard analyses and explorations of vital signs data. In Hematologic Malignancy Study 960189, the systolic and diastolic pressure increased from baseline in palifermin subjects and the increase was dose related.

COMMENT: *There were no clinical correlations to preclinical liver or thyroid histologic findings. Regarding the abnormal preclinical renal abnormalities, there was limited urinalysis data collected. Only one trial included urinalysis data in the laboratory data set. Nine palifermin-treated subjects in this trial who initially had urinalysis documenting no proteinuria developed 2+ proteinuria during the course of the study.*

In most clinical trials included in this application blood pressure was not documented in data sets. Generally, hypertension was only captured if it was identified as an adverse event. In the one studyin which blood pressure was captured in the data sets, a dose related increase from baseline was noted. Given the preclinical signal and the limited data available, information regarding the occurance of proteinuria and hypertension should be included in the label.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Palifermin is intended for use in patients at risk to develop severe mucositis. The efficacy can only be determined in patients who have received a sufficient dose of chemo-radiotherapy to predictably cause severe mucositis. At the required doses of chemo-radiotherapy, multiple severe side effects are inevitable. Therefore, the majority of studies Amgen has conducted in the support of this license have randomized palifermin with placebo to facilitate comparing side effects related to palifermin to those intrinsic to the chemo-radiotherapy.

The definition and protocol instructions used to elicit adverse events are summarized below for the randomized trials that comprise the safety population. This includes the schedules of evaluation tests and time points for the individual trials.

Hematologic Malignancy Studies:

The method outlined in Studies 20000162 (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 839), 980231, and 960189 to elicit adverse events was:

Amgen defined an adverse event as any new, undesirable medical occurrence or change (worsening) of an existing condition in a subject that occurs during treatment and within the study period up to the end-of-study visit on day 28 or within 10 days thereafter, whether or not considered to be product related.

Elective hospitalizations for administering the conditioning TBI and chemotherapy followed by PBPC transplantation were not adverse events. Abnormal laboratory findings were not considered adverse events, unless the lab abnormality was associated with a clinical event that would be considered an adverse event.

Mucositis-related toxicities to the oral cavity were not considered adverse events. Neutropenia, febrile neutropenia, thrombocytopenia, anemia, and diarrhea resulting from the TBI or chemotherapy were not considered adverse events, unless considered by the investigator to be outside the levels usually experienced in this setting. Specifically, expected events were neutropenia (WHO grade 4), thrombocytopenia (WHO grade 4), and anemia (WHO grade 4). Clinical sequelae of such toxicities such as hemorrhage or petechiae secondary to thrombocytopenia were recorded as adverse events. Hypokalemia, hyponatremia, hypocalcemia and hypophosphatemia due to vigorous IV hydration as part of the blood stem cell transplantation regimen were not considered adverse events.

A serious adverse event was defined as a significant hazard or side effect, regardless of the investigators or sponsor's opinion on the relationship to investigational product.
These include, but may not be limited to, any event that:

- is fatal;
- is life threatening (places the subject at immediate risk of death);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- is persistent and results in significant disability/incapacity; or
- is a congenital anomaly/birth defect

Important medical events that jeopardized the subject or required intervention to prevent one of the outcomes listed above, or resulted in urgent investigation, were considered serious.

In Study 2000162 the explicit instructions for assigning severity and relatedness were:
The severity of toxicities was assessed using the following scale: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = fatal.

Association or relatedness to study drug was assessed by a No / Yes question: Is there a reasonable possibility that the event may have been caused by the test article?

In trial 980231 instructions for assigning severity and relatedness were:

The severity of toxicities will be assessed on the following scale with appropriate clinical definitions: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = fatal. Association or relatedness to study drug will be graded as follows: 1 = unrelated, 2 = unlikely, 3 = possibly, 4 = probably, and 5 = definitely related.

In Study 960189 the severity of toxicity was graded using the WHO Adverse Event Grading Scale. There were not specific instructions in the protocol on how to assess relatedness but the same scale outlined for Study 980231 was included in the CRF.

The Schedule of Safety Evaluation in Study 20000162 was (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 858):

Table 7-19 Schedule of Safety Evaluation in Study 20000162

Table 7.19 Schedule of Safety Evaluation in Study 20000162																			
Day	Pre	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	4	7	14	21	28	60 - 100
PHYSICAL																				
Med. History/ PE	X																			
PS, Wt, VS	X																		X	
Slit Lamp, Ophth	X																		X	
AE Notation (1)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Temperture	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
LABORATORY																				
Amylase, Lipase	X				X			X					X		X		X		X	
CBC (3)	X							X	X	X	X	X	X	X	X	X	X	X	X	
Chem Panel (3)	X				X			X					X			X	X	X	X	
Anti-rHuKGF AB	X																		X	X

[1]Adverse Event Notation, Body Temperature daily while hospitalized
[2]CBC daily until ANC > 1000/μL
[3]Chemistry Panel -Na, K, Ca, Total Protein, Albumen, Creatinine, Uric Acid, Total Bilirubin, Glucose, Alkaline Phosphatase, Lactate Dehydrogenase, ALT,AST

The Schedule of Safety Evaluation in Study 980231 was (eCTD 5.3.5.1.3, Clinical Study Report 980231 page 1146):

Table 7-20 Schedule of Safety Evaluation in Study 980231

Table 7.20 Schedule of Safety Evaluation Study in 980231																				
Day	Pre	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	4	7	14	21	28	60 - 100
PHYSICAL																				
Med. History/ PE	X																			
PS, Wt, VS	X																		X	
AE Notation (1)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Temperature	X																		X	
LABORATORY																				
Amylase, Lipase	X				X								X				X		X	
CBC (2)	X							X	X	X	X	X	X	X	X	X	X	X	X	
Chem Panel (3)	X							X					X			X	X	X	X	
Anti-rHuKGF AB	X																		X	X
Intest Perm Study	X													X		X	X	X		

[1]Adverse Event Notation, Body Temperature daily while hospitalized
[2]CBC daily until ANC > 1000/μL
[3]Chemistry Panel -Na, K, Ca, Total Protein, Albumen, Creatinine, Uric Acid, Total Bilirubin, Glucose, Alkaline Phosphatase, Lactate Dehydrogenase, ALT,AST

The Schedules of Safety Evaluation in Study 960189 were (eCTD 5.3.5.1.2, Clinical Study Report 960189 page 1307):

Table 7-21 Schedules of Safety Evaluation in Study 960189 Schedule of Assessments For Cohorts 1-10

Table 7.21 Schedules of Safety Evaluation in Study 960189 Schedule of Assessments For Cohorts 1-10				
Assessment	**Pre Study**	**Daily from Day-9**	**End of Study**	**Follow-up**
Med. History/ Phys.	X			
Vital signs	X	X	X	
CBC/Diff/Platelets	X	X	X	X
Chemistry Panel[1]	X	weekly	X	X
Adverse Event Assessment	**Continuous Assessment**			

[1]Chemistry Panel -Na, K, Ca, Total Protein, Albumen, Creatinine, Uric Acid, Total Bilirubin, Glucose, Alkaline Phosphatase, Lactate Dehydrogenase, ALT,AST, BUN, CO2, PO4, Cl

Table 7-22 Schedules of Safety Evaluation in Study 960189 Schedule of Assessments For Cohorts 11

Table 7.22 Schedules of Safety Evaluation in Study 960189 Schedule of Assessments For Cohorts 11				
Assessment	**Pre Study**	**Daily from Day-11**	**End of Study**	**Follow-up**
Med. History/ Phys.	X			
Vital signs	X	X	X	
CBC/Diff/Platelets	X	Daily until recovery	X	X
Chemistry Panel[1]	X	weekly	X	X
Amylase/ Lipase	X	Daily –11 to-2 daily normal and day 4	X	X
Adverse Event Assessment	**Continuous Assessment**			

[1]Chemistry Panel -Na, K, Ca, Total Protein, Albumen, Creatinine, Uric Acid, Total Bilirubin, Glucose, Alkaline Phosphatase, Lactate Dehydrogenase, ALT,AST, BUN, CO2, PO4, Cl

Solid Tumor Studies:
Head and Neck Cancer

The Method outlined in Studies 970149 and 990119 to elicit adverse events was (eCTD 5.3.5.4.3, Clinical Study Report 970149 page 1307):

Amgen defined an adverse event as any new, undesirable medical occurrence or change of an existing condition in a subject, which occurs during or after treatment, whether or not considered to be product-related. In general, abnormal laboratory findings should not be recorded as adverse events; however, any associated clinical sequelae will be reported as adverse events.

In this study, the loco-regional toxicities related to chemo-radiotherapy in the Head and Neck area and all oral cavity infections that occur should not be listed as an Adverse Event. Systemic effects such as dehydration or renal toxicity should be recorded as an Adverse Event. A subject's hospitalization for the delivery of chemo-radiotherapy should not be considered an adverse event.
A serious adverse event is any experience that suggests a significant hazard and includes any event that:

- is fatal;
- is life threatening (places the subject at immediate risk of death);
- requires or prolongs in-patient hospitalization

- is permanently disabling or incapacitating
- is a new malignancy
- is a congenital anomaly

Important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

In Study 970149 the explicit instructions for assigning severity and relatedness were:

The severity of toxicities will be assessed on the following scale with appropriate clinical definitions: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = fatal. Association or relatedness to study drug will be graded as follows: 1 = unrelated, 2 = unlikely, 3 = possibly, 4 = probably, and 5 = definitely related.

In Study 990119 the explicit instructions for assigning severity and relatedness were (eCTD 5.3.5.4.4, Clinical Study Report 990119 page 1989):

The severity of adverse events will be graded on the following scale: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = fatal. Association or relatedness to study drug will be assessed by a NO/YES question: Is there a reasonable possibility that the event may have been caused by test article?

In Study 990119 the explicit instructions for assigning severity and relatedness were (eCTD 5.3.5.4.4, Clinical Study Report 990119 page 1989):

Table 7-23 Schedules of Safety Evaluation in Study 970149

Table 7.23 Schedules of Safety Evaluation in Study 970149													
Week	**Pre**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Med. History/ PE	X												
PS, Wt, VS	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Notation	X	X	X	X	X	X	X	X	X	X	X	X	X
Xerostomia	X											X	X
Amylase, Lipase	X				X							X	
CBC	X	X	X	X	X	X	X	X				X	
Chem Panel (1)	X				X							X	
Anti-rHuKGF AB	X											X	X
Creatinine Clearance Repeat q 4 wk if Cr > 2	X				X								

[1]Chemistry Panel -Na, K, Cl, CO2, Ca, Total Protein, Albumen, Creatinine, Uric Acid, Total Bilirubin, Glucose, Alkaline Phosphatase, Lactate Dehydrogenase, ALT, AST, BUN, PO4, Cholesterol

The Schedules of Safety Evaluation in Study 990119 were (eCTD 5.3.5.4.4, Clinical Study Report 990119 page 1989):

Table 7-24 Schedules of Safety Evaluation in Study 990119

Table 7.24 Schedules of Safety Evaluation in Study 990119														
Week	**Pre**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**20**
PHYSICAL														
Med. History/ PE	X													
Tumor Eval	X													X
PS, Wt, VS	X	X	X	X	X	X	X	X	X		X		X	
AE Notation	X	X	X	X	X	X	X	X	X	X	X	X	X	
LABORATORY														
Amylase, Lipase, Isoamylase	X	X				X						X		
CBC	X	X	X	X	X	X	X	X				X		
Chem Panel (1)	X				X							X		
Anti-rHuKGF AB	X												X	
Creatinine Clearance Repeat q 4 wk if Cr > 2 OR > 60 Year	X				X									

[1]Chemistry Panel -Na, K, Cl, CO2, Ca, Total Protein, Albumen, Creatinine, Uric Acid, Total Bilirubin, Glucose, Alkaline Phosphatase, Lactate Dehydrogenase, ALT, AST, BUN, PO4, Cholesterol

Colorectal Cancer

The Method outlined in Studies 950225 and 950275 (extension study) (eCTD 5.3.5.4.1, Clinical Study Report 950225 and 950275 page 2381): to elicit adverse events was:

Amgen defined an adverse event as any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered related to study material. Abnormal laboratory findings considered by the reporting physician to be clinically significant (e.g., those that are unusual or unusually severe for the population being studied) should be recorded as adverse events.

A serious adverse event is any experience that suggests a significant hazard and includes any event that:

- is fatal;
- is life threatening (places the subject at immediate risk of death);
- requires or prolongs hospitalization
- is permanently disabling
- is a (new) malignancy
- is a congenital anomaly
- is a known or suspected overdose

In Study 950225 the instructions for assigning severity and relatedness were:

Adverse Events Standard Grading Score

0 = NONE
1 = MILD - aware of sign or symptom, but easily tolerated
2 = MODERATE - discomfort enough to cause interference with usual activity
3 = SEVERE - incapacitating with inability to work or do usual activity
4 = LIFE-THREATENING or DEBILITATING

5 = FATAL

Adverse Events Categories for Determining Relationship To Test Drug

1 = UNRELATED

This category is applicable to those adverse events which, after careful medical consideration at the time of evaluation, are Judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under UNLIKELY, POSSIBLE, OR PROBABLE.

2 = UNLIKELY

In general, this category is applicable to those adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be unlikely related to the test drug. An adverse event may be considered UNLIKELY if, or when for example:

1. It does not follow a reasonable temporal sequence from administration of the drug.
2. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It does not follow known response pattern to the suspected drug.
4. It does not reappear or worsen when the drug is re-administered.

3 = POSSIBLE

This category applies to those adverse events in which, after careful medical consideration at the time they are evaluated, the connection with the test drug administration appears unlikely, but cannot be ruled out with certainty. An adverse event may be considered POSSIBLE if, or when;

1. It follows a reasonable temporal sequence from administration of the drug.
2. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
3. It follows a known response pattern to the suspected drug.

4 = PROBABLE

This category applies to those adverse events which, after "careful medical consideration at the time they are evaluated, are considered, with a high degree of certainty, to be related to the test drug. An adverse event may be considered probable if, for example:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It could hot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
3. It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g.
   (1) bone marrow depression,
   (2) fixed drug eruptions, and
   (3) tardive dysknesias.
4. It follows a known pattern or response to the suspected drug.

5 =DEFINITE

Investigator is completely certain that the study medication caused the adverse event.

The Schedules of Safety Evaluation in Study 950225 were (eCTD 5.3.5.4.1, Clinical Study Report 950225 and 950275 page 2399):

Table 7-25 Schedules of Safety Evaluation in Study 950225

Table 7.25 Schedules of Safety Evaluation in Study 950225																
	BASELINE	STUDY DAY														
		1	2	3	4	5	6	7	8	10	12	15	18	22	26	31
Physical Examination	X				X				X			X		X		X
Weight	X				X				X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X				X			X		X		X
Chemistry panel	X	X	X	X	X				X			X		X		X
Stool Hemoccult	X				X											
Thyroid function	X		X		X							X				X
Special Tests[2]	X		X		X							X				X
Coagulation tests	X		X		X							X				X
Urinalysis	X	X	X		X							X				X
CBC/Diff/Platelets	X	X	X	X	X				X			X		X		X
Chest X-ray	X															X
KGF Antibody Sample	X				X											X
ECG	X															X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

The Schedules of Safety Evaluation in Study 950275 (extension study) were (eCTD 5.3.5.4.2, Clinical Study Report 950225 and 950275 page 2493):

Table 7-26 Schedules of Safety Evaluation in Study 950275

Table 7.26 Schedules of Safety Evaluation in Study 950275			
	BASELINE	CYCLE 2-7	END OF STUDY
Physical Examination	X	X	X
Vital Signs	X	X	X
CBC Chemistry panel[1]	X	X days 4, & day (18-20)	X
KGF antibody sample		X	
Adverse Events		X	X

[1]Chemistry Panel -Na, K, Cl, CO2, Ca, Total Protein, Albumen, Creatinine, Uric Acid, Total Bilirubin(total/direct), Glucose, Alkaline Phosphatase, Lactate Dehydrogenase, ALT,AST, BUN, PO4, Cholesterol Triglycerides
[2]Special Tests Insulin, C-peptide, Creatinine phosphokinase, Amylase, Lipase, Creatinine clearance

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Amgen modified WHOART dictionary was used to code the adverse event verbatim terms. Verbatim adverse events that were associated to a fatal event or led to dropout were identified. These were compared to the preferred term and the body class term as shown in the tables below:

Table 7-27 Comparison of Verbatim Term with Preferred Term Amgen's WHOART Modified Dictionary and Body Class Term Deaths on Study

Table 7.27 Comparison of Verbatim Term with Preferred Term Amgen's WHOART Modified Dictionary and Body Class Term Deaths on Study		
Verbatim term	**Preferred term**	**Body Class Term**
Hematologic Malignancy Safety Pool B		
1 SEPSIS 2 MULTIORGAN FAILURE 3 PNEUMONIA, LEFT LOWER LOBE 4 MYOCARDIAL INFRACTION	1 SEPSIS 2 MULTI ORGAN FAILURE 3 PNEUMONIA LOBAR 4 MYOCARDIAL INFARCTION	1 RESISTANCE MECHANISM 2 BODY AS A WHOLE 3 RESPIRATORY 4 MYO/ENDO/PERICARDIAL
WORSENING VOD	VENOUS OCCLUSION	VASCULAR DISORDERS
ADULT RESPIRATORY DISTRESS SYNDROME	ADULT RESP DISTRESS SYNDROME	RESPIRATORY
RESPIRATORY FAILURE	RESPIRATORY INSUFFICIENCY	RESPIRATORY
1,2 3 SEPTIC SHOCK/ PULMONARY FAILURE/ RENAL FAILURE	1 SEPTIC SHOCK 2 RESPIRATORY INSUFFICIENCY 3 RENAL FAILURE	1 RESISTANCE MECHANISM 2 RESPIRATORY 3 URINARY DISORDERS
PULMONARY INFILTRATION	RESPIRATORY	RESPIRATORY
Head and Neck Cancer Safety Pool D		
SEPSIS	SEPSIS	RESISTANCE MECHANISM
DEATH, CAUSE UNKNOWN	DEATH CAUSE UNKNOWN	BODY AS A WHOLE
RESPIRATORY FAILURE	RESPIRATORY INSUFFICIENCY	RESPIRATORY
MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION	MYO/ENDO/PERICARDIAL
PULMONARY FAILURE	RESPIRATORY INSUFFICIENCY	RESPIRATORY
SEPSIS	SEPSIS	RESISTANCE MECHANISM
STROKE	CEREBROVASCULAR DISORDER	CNS/PNS
Colorectal Cancer Safety Pool F		
SM BOWEL OBSTRUCTION	INTESTINAL OBSTRUCTION	GASTROINTESTINAL
CARDIAC ARRYTHMIA	ARRHYTHMIA	HEART RATE/RHYTHM
LIVER FAILURE SECONDARY TO PROGRESSIVE DISEASE	HEPATIC FAILURE	LIVER AND BILIARY
DEATH DUE TO PROGRESSIVE DISEASE (COLORECTAL CANCER)	RECTAL CARCINOMA	GASTROINTESTINAL

Table 7-28 Comparison of Verbatim Term with Preferred Term Amgen's WHOART Modified Dictionary and Body Class Term In Drop Out Subjects Hematologic Malignancy Safety Pool B

Table 7.28 Comparison of Verbatim Term with Preferred Term Amgen's WHOART Modified Dictionary and Body Class Term In Drop Out Subjects Hematologic Malignancy Safety Pool B		
Verbatim term	**Preferred term**	**Body Class Term**
RASH BILATERAL HANDS, CHEST BACK	RASH	SKIN AND APPENDAGES
1 RASH CHEST, ARMS, BACK AXILLA 2 FLUSHING ENTIRE BODY	1 RASH 2 FLUSHING	1 SKIN AND APPENDAGES 2 SKIN AND APPENDAGES
URI	INFECTION UPPER RESPIRATORY	RESPIRATORY
SKIN ERYTHEMA GENERALIZED CHEST, ABDOMEN	ERYTHEMA	SKIN AND APPENDAGES
DIFFUSE MACULAR PAPULAR RASH IN TRUNK	RASH MACULO-PAPULAR	SKIN AND APPENDAGES
MACULAR PAPULAR RASH ON HEAD, UPPER ARMS	RASH MACULO-PAPULAR	SKIN AND APPENDAGES
MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION	MYO/ENDO/PERICARDIAL
1 SKIN REDDENED 2 PAINFUL BURNING SENSATION IN FEET 3 SWOOLEN HANDS/FINGERS	1 ERYTHEMA 2 PAIN LIMB 3 EDEMA PERIPHERAL	1 SKIN AND APPENDAGES 2 MUSCULO-SKELETAL 3 BODY AS A WHOLE
GENERALISED PAIN	PAIN	BODY AS A WHOLE
1 UPPER BACK, NECK, UPPER TRUNK FACIAL ERYTHEMA 2 EDEMA / FACE, NECK	1 ERYTHEMA 2 EDEMA FACE	1 SKIN AND APPENDAGES 2 BODY AS A WHOLE

Table 7-29 Comparison of Verbatim Term with Preferred Term Amgen's WHOART Modified Dictionary and Body Class Term In Drop Out Subjects Head and Neck Cancer Safety Pool D

Table 7.29 Comparison of Verbatim Term with Preferred Term Amgen's WHOART Modified Dictionary and Body Class Term In Drop Out Subjects Head and Neck Cancer Safety Pool D		
Verbatim term	**Preferred term**	**Body Class Term**
SEPSIS	SEPSIS	RESISTANCE MECHANISM
1 HEPATIC FAILURE 2 INCREASED RENAL FAILURE	1 HEPATIC FAILURE 2 RENAL FAILURE	1 LIVER AND BILIARY 2 URINARY DISORDERS
1, 2 ABDOMINAL PAIN/PERITONITIS	1 PAIN ABDOMINAL 2 PERITONITIS	1 GASTROINTESTINAL 2 GASTROINTESTINAL
FEVER	FEVER	BODY AS A WHOLE
STRIDOR VOMITING	RESPIRATORY GASTROINTESTINAL	RESPIRATORY DISTRESS NAUSEA/VOMITING
1, 2 PANCREATITIS (ACUTE) & ACUTE EPIGASTRIC PAIN	1 PAIN ABDOMINAL 2 PANCREATITIS	1 GASTROINTESTINAL 2 GASTROINTESTINAL
JAUNDICE	JAUNDICE	LIVER AND BILIARY
1 INCREASED MUCOUS PRODUCTION (EXCESSIVE SALIVATION) 2 DEHYDRATION	1 SPUTUM INCREASED 2 DEHYDRATION	1 RESPIRATORY 2 METABOLIC/NUTRITION
1 PNEUMONIA 2 PULMONARY FAILURE 3 DIFFUSE INTRAVASCULAR COAGULOPATHY 4 RENAL FAILURE 5 LIVER FAILURE	1 PNEUMONIA 2 RESPIRATORY INSUFFICIENCY 3 DISSEM. INTRAVASC. COAGULATION 4 RENAL FAILURE 5 HEPATIC FAILURE	1 RESPIRATORY 2 RESPIRATORY 3 HEMATOLOGIC 4 URINARY DISORDERS 5 LIVER AND BILIARY
BILATERAL PULMONARY EMBOLI	EMBOLISM PULMONARY	RESPIRATORY
CVA	CEREBROVASCULAR DISORDER	CNS/PNS
1 ERYTHEMATOUS LESIONS OVER THE FACE AND NECK 2 NAUSEA 3 VOMITING 4 DIARRHEA 5, 6 SCLERA IRRITATION/CONJUCTIVITIS 7 FACIAL DROOP 8 SEPSIS 9 ASPIRATION PNEUMONIA	1 ERYTHEMA 2 NAUSEA 3 VOMITING 4 DIARRHEA 5 CONJUNCTIVITIS 6 SCLERITIS 7 PTOSIS 8 SEPSIS 9 ASPIRATION PNEUMONIA	1 SKIN AND APPENDAGES 2 GASTROINTESTINAL 3 GASTROINTESTINAL 4 GASTROINTESTINAL 5 VISION DISORDERS 6 VISION DISORDERS 7 CNS/PNS 8 RESISTANCE MECHANISM 9 RESPIRATORY
STROKE	CEREBROVASCULAR DISORDER	CNS/PNS
C/O CHEST PAIN (CARDIAC)	PAIN CHEST	MYO/ENDO/PERICARDIAL

Table 7-30 Comparison of Verbatim Term with Preferred Term Amgen's WHOART Modified Dictionary and Body Class Term In Drop Out Subjects Colorectal Cancer Safety Pool F

Table 7.30 Comparison of Verbatim Term with Preferred Term Amgen's WHOART Modified Dictionary and Body Class Term In Drop Out Subjects Colorectal Cancer Safety Pool F		
Verbatim term	**Preferred term**	**Body Class Term**
SEPTIC SHOCK	SEPTIC SHOCK	RESISTANCE MECHANISM
1, 2, 3 SM AREA (ERYTHEMA) DRYNESS AT BASE OF BACK-EXCORIATION+XERASIS	1 ABRASION 2 ERYTHEMA 3 SKIN DRY	SKIN AND APPENDAGES SKIN AND APPENDAGES SKIN AND APPENDAGES
1 RED MARK ON CHEST 2 REDDENED, IRRITABLE, SWOLLEN FACE 3 REDDENED BUTTOCKS	1 ERYTHEMA 2 EDEMA FACE 3 ERYTHEMA	1 SKIN AND APPENDAGES 2 BODY AS A WHOLE 3 SKIN AND APPENDAGES

COMMENT: *Based on review of the Verbatim term with Preferred term assigned by Amgen using WHOART dictionary, the categorization is generally appropriate.*

Of note, the preferred term for venoocclusive disease of the liver (VOD), a transplant related adverse event, was categorized in two ways: Preferred term - Venous occlusion; Body Class term - Vascular Disorder in 3 subjects and Preferred term - Venoocclusive liver disease; Body Class term – Liver and Biliary one subject. In the Hematologic Malignancy Safety Pool B no additional instances of venoocclusive disease of the liver were identified by reviewing all entries identified as Body Class term Liver and Biliary or Body Class Term Vascular disorder. Review of Liver and Biliary disorder identified one additional entry in this category Verbetim term - Jaundice / possible VOD; preferred term – Jaundice. This suboptimal categorization does not effect the overall assessment of the safety of palifermin. There were 3 placebo and 2 palifermin subjects identified with venoocclusive disease of the liver. There is no indication that palifermin increases the risk of venoocclusive disease of the liver.

No other categorization issues were identified.

7.1.5.3 Incidence of common adverse events

Hematologic Malignancy Studies:

A summary of adverse events is presented in the table below:

Table 7-31 Common Adverse Events in Hematologic Malignancy Safety Pool B

Table 7.31 Common Adverse Events in Hematologic Malignancy Safety Pool B			
Subjects n (%)	**Pre chemo Placebo 241 Palifermin 409**	**Post chemo Placebo 240 Palifermin 405**	**Total Placebo 241 Palifermin 409**
Placebo	194 (80%)	240 (100%)	241 (100%)
Palifermin	357 (88%)	404 (100%)	408 (100%)

Adverse events that were identified at a frequency ≥ 2% in the palifermin group compared to the placebo group in the pre- chemotherapy period were:

Table 7-32 Adverse Event Identified ≥ 2% in Palifermin vs. Placebo in Prechemo Period Hematologic Malignancy Safety Pool B

Table 7.32 Adverse Event Identified ≥ 2% in Palifermin vs. Placebo in Prechemo Period Hematologic Malignancy Safety Pool B		
	Placebo n = 241	Palifermin n = 409
Skin		
Pruritis	5%	8%
Rash	2%	12%
Flushing	4%	7%
Erythema	3%	14%
Edema	2%	6%
Edema face	0	6%
Edema peripheral	6%	12%
Oral		
Lesion oral	1%	7%
Tongue disorder	1%	5%
Taste loss	0	2%
Taste perversion	0	3%
Dry mouth	2%	5%
Dysesthesia		
Hyperesthesia, hypoesthesia, or paresthesia	2%	8%
Pain		
Pain	12%	15%
Arthralgia		
Arthralgia	1%	4%

The incidence of adverse events in the post chemotherapy period and overall was equivalent in the palifermin and the placebo groups. Overall the adverse events that occurred at a frequency greater than or equal to 5% in the palifermin group compared to the placebo group were:

Appears This Way
On Original

Table 7-33 Adverse Event Identified ≥ 5 % Palifermin vs. Placebo Overall Hematologic Malignancy Safety Pool B

Table 7.33 Adverse Event Identified ≥ 5 % Palifermin vs. Placebo Overall Hematologic Malignancy Safety Pool B		
	Placebo n = 241	Palifermin n = 409
Skin		
Pruritis	24%	35%
Rash	52%	62%
Erythema	22%	32%
Edema	21%	28%
Oral		
Lesion oral	5 %	11%
Mouth Tongue thickness discoloration	8%	17%
Taste altered	8%	16%
Taste loss	2%	6%
Taste perversion	6%	10%
Dysesthesia		
Hyperesthesia, hypoesthesia, or paresthesia	7%	12%
Arthralgia		
Arthralgia	5%	10%
Fever		
Fever	34%	39%
Pain		
Pain	11%	16%

COMMENT: *Fever did not appear to be an infusion-related toxicity. If it were an infusion-related toxicity, it would be easiest to detect in the pre-chemo therapy period. In the prechemotherapy period the incidence of fever was 2% in the placebo group and 3% in the palifermin group. The peak incidence of fevers was reported on days 3 to 7 post transplant during the period when subjects experience severe neutropenia.*

Dysesthesias, including hyperesthesia, hypoesthesia, and paresthesia, were more common in the palifermin subjects. In the majority of instances the dysethesias were localized to the perioral region in the palifermin subjects, whereas in the placebo subjects they were more likely to occur in extremities.

The following table summarizes the incidence of adverse events identified as treatment related:

Table 7-34 Common Adverse Events Identified as Treatment Related in Hematologic Malignancy Safety Pool B

Table 7.32 Common Adverse Events Identified as Treatment Related in Hematologic Malignancy Safety Pool B			
Subjects n (%)	Pre chemo 241 Placebo 409 Palifermin	Post chemo 240 Placebo 405 Palifermin	Total 241 Placebo 409 Palifermin
Placebo	25 (10%)	53 (22%)	71 (29%)
Palifermin	154 (38%)	156 (39%)	231 (57%)

The incidence of adverse events identified as treatment related was greater in the palifermin group compared to the placebo group in both the pre-chemotherapy time period (38% versus 10%) and the post chemotherapy therapy time period (38% versus 22%).

The following table summarizes the incidence of adverse events identified as treatment related in ≥ 2% of palifermin subjects compared to placebo subjects:

Table 7-35 Adverse Event Identified as Treatment Related ≥ 2% Hematologic Malignancy Safety Pool B

Table 7.35 Adverse Event Identified as Treatment Related ≥ 2% Hematologic Malignancy Safety Pool B		
	Placebo n = 241	Palifermin n = 409
Skin		
Pruritis	11 (5%)	29 (7%)
Rash	25 (10%)	99 (24%)
Skin discoloration	1 (<1%)	3 (1%)
Skin hyper pigmented	1 (<1%)	4 (1%)
Warm sensation	0	7 (2%)
Erythema / flushing	18 (7%)	106 (26%)
Edema	11 (5%)	75 (18%)
Oral		
Saliva / sputum altered	3 (1%)	13 (3%)
Lesion oral	4 (2%)	32 (8%)
Taste loss / perversion	2 (1%)	14 (3%)
Tongue discoloration / disorder	4 (2%)	33 (8%)
Dysesthesia		
Hyperesthesia, hypoesthesia, or paresthesia	2 (1%)	16 (4%)
Pain		
Abdomen/Oral/Limb	2 (1%)	33 (8%)

With the exception of arthralgias, these adverse events were the generally the same adverse events that were identified as occurring with an incidence greater than 2% in the palifermin group during the pre chemotherapy period or greater than 5% overall.

Notably, adverse events of arthralgias or arthritis were reported more frequently in both the pre chemotherapy period and overall, but were classified by investigators as not related to investigational agent in all 57 incidences reported (13 [5%] placebo, 44 [11%] palifermin).

Records of subjects with adverse events designated as arthralgias or arthritis that started after the first dose of investigational agent, but within a day of the first 3 doses of investigational agent were reviewed. All 15 subjects with arthralgia or arthritis that started within this time period received palifermin. The verbatim terms used to describe these events were: 8 incidences of shoulder pain, 3 incidences of joint pain, one each arthritis of the neck, hip pain, ankle and feet pain, knee pain.

The Adverse Reaction section of Amgen's proposed label (eCTD 1.14.1.3, Draft Labeling Text page 8) states, [ ]

[ ]

COMMENT: *This explanation is inadequate to account for the data presented above regarding arthralgias and arthritis. All these events during the administration of the initial doses of investigational agent occurred in the palifermin group. The concomitant therapy subjects received during this period is minimal and therefore these events are unlikely to be due to concomitant therapy. During this phase of transplant, that is prior to starting the preparative regimen, virtually no patients are receiving opioid analgesics. Therefore, more opioid exposure in the placebo subjects is not the explanation. Arthragia/ arthritis should be included as a potential adverse reaction and not explained as the result of less exposure to opioid analgesics.*

Amgen has included the following table (eCTD 1.14.1.3, Draft Labeling Text page 9) in the proposed label to summarize adverse reactions:

Figure 7-2 Amgen's Table of Adverse Events Occurring ≥ 5% in Palifermin Compared to Placebo

Table 3. Adverse Events Occurring With ≥ 5% Higher Incidence in [TRADE NAME™] vs Placebo

BODY SYSTEM Adverse Event	Placebo (n = 241)	[TRADE NAME™] (n = 409)
BODY AS A WHOLE		
Edema	21%	28%
Pain	11%	16%
GASTROINTESTINAL		
Mouth/Tongue Thickness or Discoloration	8%	17%
MUSCULOSKELETAL		
Arthralgia	5%	10%
SKIN AND APPENDAGES		
Rash	50%	62%
Pruritus	24%	35%
Erythema	22%	32%
SPECIAL SENSES		
Taste Altered	8%	16%

COMMENT: *This table does not include fever, which was reported in 40% of palifermin subjects and 34% of placebo subjects. The table does not include dysesthesia, which was reported in 14% of palifermin subjects and 7% of placebo subjects. Review of data suggests that perioral dysesthesias are a drug related event and should be described on label.*

With these exceptions the table adequately summarizes the adverse events with a 5% greater incidence in the palifermin subjects compared to the placebo subjects.

Solid Tumor Studies:

The following tables summarize adverse events in the solid tumor studies:

Table 7-36 Adverse Events in Solid Tumor Studies

Table 7.36 Adverse Events in Solid Tumor Studies		
Subjects	**Placebo - n (%)**	**Palifermin - n (%)**
Head and Neck Cancer 113 palifermin, 46 placebo	46 (100%)	111 (99%)
Colorectal Cancer 82 palifermin, 63 placebo	63 (100%)	82 (100%)

Table 7-37 Adverse Events in Solid Tumor Studies Identified as Treatment Related

Table 7.37 Adverse Events in Solid Tumor Studies Identified as Treatment Related		
Subjects	**Placebo - n (%)**	**Palifermin - n (%)**
Head and Neck Cancer 113 palifermin, 46 placebo	7 (15%)	35 (31%)
Colorectal Cancer 950225 82 palifermin, 63 placebo	31 (49%)	50 (60%)
Colorectal Cancer 950275 48 palifermin		37 (77%)

Table 7-38 Adverse Event Identified ≥ 5% Palifermin vs. Placebo in Head and Neck Cancer Safety Pool D

Table 7.38 Adverse Event Identified ≥ 5% Palifermin vs. Placebo in Head and Neck Cancer Safety Pool D		
	Placebo n = 46	**Palifermin n = 113**
Skin Oral		
Pruritis	2%	5%
Flushing	4%	9%
Erythema	4%	8%
Rash	6%	10%
Edema face / tongue	0	5%
Skin Oral any above	17%	29%
CNS/PNS		
Headache	7%	12%
Body as a whole		
Pain any site	19%	26%
Hematological		
Neutropenia	22%	34%

Table 7-39 Adverse Event identified ≥ 5% Treatment Related Head and Neck Cancer Safety Pool D

Table 7.37 Adverse Event identified ≥ 5% Treatment Related Head and Neck Cancer Safety Pool D		
	Placebo n = 46	Palifermin n = 113
Skin Oral		
Flushing	2%	7%
Erythema	0	5%
Rash	0	3%
Edema face / tongue	0	4%
Any Skin or Oral	2%	15%

COMMENT: *Skin and oral toxicity are recognized as side effects of palifermin. The role of palifermin in the excess neutropenia is unclear. Investigators did not assess neutropenia as related to investigational agent. In the context of the patients with hematologic malignancy undergoing transplant, neutropenia is not a significant issue. There was no evidence of delayed engraftment in the palifermin treated subjects.*

Table 7-40 Adverse Event Identified ≥ 5% Palifermin vs. Placebo in Colorectal Cancer Safety Pool F

Table 7.40 Adverse Event Identified ≥ 5% Palifermin vs. Placebo in Colorectal Cancer Safety Pool F		
	Placebo n = 63	Palifermin n = 82
Skin		
Pruritis	5%	21%
Flushing	5%	8%
Rash	28%	30%
Edema face / tongue	4%	19%
Skin any above	42%	78%
Hematological		
Anemia	5%	10%
Oral		
Dry mouth	6%	13%
Lesion oral	21%	29%
Tongue abnormality	9%	12%
Taste perversion	6%	20%
Body as whole		
Anorexia	14%	22%
Pain all	60%	90%
Pain abdominal	19%	30%

Table 7-41 Adverse Event Identified as Treatment Related ≥ 5% Palifermin in Colorectal Cancer Safety Pool F

Table 7.41 Adverse Event Identified as Treatment Related ≥ 5% Palifermin in Colorectal Cancer Safety Pool F		
	Placebo n = 63	Palifermin n = 82
Skin		
Pruritis	1%	13%
Flushing	2%	6%
Rash	4%	19%
Erythema	5%	14%
Oral		
Dry mouth	2%	6%
Lesion oral	5%	14%
Taste Perversion	2%	7%
Tongue Discoloration	4%	7%
Gastrointestinal		
Nausea	5%	7%

COMMENT: *The most common adverse events identified were skin and oral toxicity.*

Healthy Volunteer Studies:

The table below presents a summary of adverse events in the normal volunteer subjects (derived from Table 40 eCTD 2.7.4, Summary of Clinical Safety page 179):

Table 7-42 Adverse Event Identified in ≥ 5% in Palifermin Healthy Volunteer Studies

Table 7.42 Adverse Event Identified in ≥ 5% in Palifermin Healthy Volunteer Studies		
N (%)	Placebo N = 50	Palifermin N = 160
Number of Subjects Reporting Treatment-Emergent Adverse Events	26 (52%)	103 (64%)
Injection Site Erythema	0 (0%)	27 (17%)
Headache	7 (14%)	26 (16%)
Erythema	4 (8%)	21 (13%)
Access Pain	4 (8%)	18 (11%)
Injection Site Skin Hyperpigmentation	0 (0%)	13 (8%)
Pain Back	2 (4%)	13 (8%)
Warm Sensation	0 (0%)	12 (8%)
Anemia	3 (6%)	10 (6%)
Dermatitis Contact	3 (6%)	10 (6%)
Dizziness	3 (6%)	9 (6%)
Injection Site Inflammation	0 (0%)	10 (6%)
Pain Abdominal	1 (2%)	8 (5%)

Amgen summarizes the adverse events associated with palifermin as below (eCTD 2.7.4, Summary of Clinical Safety page 178):

- Dose-related erythema of the upper torso, head and arms, was reported in 13% of subjects receiving palifermin and 8% of subjects receiving placebo. A warm sensation, often associated with erythema, was noted in 8% of subjects exposed to palifermin versus none for placebo.
- Back pain was reported in 8% of all subjects exposed to palifermin versus 4% in those exposed to placebo.
- Injection site erythema was noted in 17% of subjects receiving palifermin and none receiving placebo. Injection site inflammation was noted in 6% of subjects receiving palifermin and none receiving placebo.

7.1.5.4 Common adverse event tables

The following 6 tables are an abridged version of Amgen's Adverse Event by Body System and Preferred Term Hematologic Malignancy Safety Pool B document (eCTD 5.3.5.2.1, Integrated Safety Analysis page 106). The Amgen Table consists of 37 pages. These abridged tables include any adverse event that was reported in ≥ 5% of palifermin subjects. They also include subsets of toxicities that did not meet the threshold incidence of 5%, such as pain, edema, skin, oral, dyesthesias, and infections.

These adverse events are reported by WHOART dictionary categorization of the preferred term. They are organized by Body Class term.

Table 7-43 Adverse Events in Hematologic Malignancy Safety Pool B with Incidence ≥ 5% in Palifermin Subjects or of Particular Interest Body as a Whole and Cardiovascular

Table 7.43 Adverse Events in Hematologic Malignancy Safety Pool B with Incidence ≥ 5% in Palifermin Subjects or of Particular Interest Body as a Whole and Cardiovascular						
BODY SYSTEM PREFRERED TERM	**Pre-chemotherapy**		**Post-chemotherpay**		**Total**	
N (%)	**Placebo n= 241**	**Palifermin n=409**	**Placebo n= 240**	**Palifermin n=405**	**Placebo n= 241**	**Palifermin n=409**
BODY AS A WHOLE	104 (43%)	186 (45%)	217 (90%)	366 (90%)	224 (93%)	387 (95%)
ACCESS ERYTHEMA	5 (2%)	14 (3%)	13 (5%)	13 (3%)	17 (7%)	27 (7%)
ACCESS INFECTION	0	7 (2%)	12 (5%)	21 (5%)	12 (5%)	29 (7%)
ACCESS PAIN	13 (5%)	28 (7%)	8 (3%)	26 (6%)	21 (9%)	52 (13%)
ASTHENIA	8 (3%)	9 (2%)	23 (10%)	40 (10%)	31 (13%)	47 (11%)
EDEMA	6 (2%)	23 (6%)	45 (19%)	93 (23%)	50 (21%)	114 (28%)
EDEMA CIRCUMORAL	0	12 (3%)	7 (3%)	5 (1%)	7 (3%)	17 (4%)
EDEMA DEPENDENT	0	0	1 (0%)	1 (0%)	1 (0%)	1 (0%)
EDEMA FACE	0	26 (6%)	17 (7%)	25 (6%)	17 (7%)	47 (11%)
EDEMA GENITAL	0	5 (1%)	8 (3%)	5 (1%)	8 (3%)	10 (2%)
EDEMA PERIORBITAL	2 (1%)	6 (1%)	5 (2%)	8 (2%)	7 (3%)	13 (3%)
EDEMA PERIPHERAL	15 (6%)	48 (12%)	66 (28%)	91 (22%)	76 (32%)	121 (30%)
FATIGUE	52 (22%)	46 (11%)	46 (19%)	70 (17%)	85 (35%)	107 (26%)
FEVER	5 (2%	11 (3%)	80 (33%)	157 (39%)	82 (34%)	159 (39%)
PAIN	15 (6%)	21 (5%)	14 (6%)	46 (11%)	27 (11%)	65 (16%)
PAIN CHEST	0	4 (1%)	7 (3%)	11 (3%)	7 (3%)	15 (4%)
PAIN CHEST, NON-CARDIAC	4 (2%)	2 (0%)	4 (2%)	12 (3%)	8 (3%)	14 (3%)
RIGORS	7 (3%)	9 (2%)	79 (33%)	107 (26%)	84 (35%)	114 (28%)
TRANSFUSION REACTION	1 (0%)	0	29 (12%)	38 (9%)	30 (12%)	38 (9%)
CARDIOVASCULAR	9 (4%)	20 (5%)	75 (31%)	97 (24%)	83 (34%)	112 (27%)
HYPERTENSION	1 (0%	6 (1%)	12 (5%)	24 (6%)	13 (5%)	30 (7%)
HYPOTENSION	8 (3%)	12 (3%)	59 (25%)	64 (16%)	67 (28%)	72 (18%)

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Table 7-44 Adverse Events Hematologic Malignancy Safety Pool B with Incidence of ≥ 5% in Palifermin Subjects or of Particular Interest Central and Peripheral Nervous System, Special Senses, Vision Disorders, Psychiatric, Heart Rhythm, and Myo/endopericardial

Table 7.44 Adverse Events Hematologic Malignancy Safety Pool B with Incidence of ≥ 5% in Palifermin Subjects or of Particular Interest Central and Peripheral Nervous System, Special Senses, Vision Disorders, Psychiatric, Heart Rhythm, and Myo/endopericardial						
N (%)	Pre-chemotherapy		Post-chemotherpay		Total	
BODY SYSTEM PREFRERED TERM	Placebo n= 241	Palifermin n=409	Placebo n= 240	Palifermin n=405	Placebo n= 241	Palifermin n=409
CNS/PNS	84 (35%)	122 (30%)	168 (70%)	247 (61%)	192 (80%)	291 (71%)
CONFUSION	1 (0%)	2 (0%)	29 (12%)	27 (7%)	30 (12%)	29 (7%)
HEADACHE	49 (20%)	48 (12%)	74 (31%)	130 (32%)	117 (49%)	174 (43%)
HYPERESTHESIA	0	5 (1%)	3 (1%)	0	3 (1%)	5 (1%)
HYPOESTHESIA	1 (0%)	14 (3%)	5 (2%)	9 (2%)	6 (2%)	22 (5%)
INSOMNIA	26 (11%)	44 (11%)	65 (27%)	90 (22%)	91 (38%)	132 (32%)
PARESTHESIA	4 (2%)	21 (5%)	7 (3%)	16 (4%)	11 (5%)	34 (8%)
SOMNOLENCE	7 (3%)	8 (2%)	22 (9%)	29 (7%)	29 (12%)	35 (9%)
SPECIAL SENSES	0	19 (5%)	20 (8%)	48 (12%)	20 (8%)	65 (16%)
TASTE LOSS	0	7 (2%)	6 (3%)	19 (5%)	6 (2%)	26 (6%)
TASTE PERVERSION	0	12 (3%)	14 (6%)	30 (7%)	14 (6%)	41 (10%)
VISION DISORDERS	7 (3%)	7 (2%)	30 (13%)	44 (11%)	37 (15%)	46 (11%)
PAIN EYE	0	0	1 (0%)	6 (1%)	1 (0%)	6 (1%)
VISION ABNORMAL	2 (1%)	2 (0%)	8 (3%)	19 (5%)	10 (4%)	21 (5%)
Psychiatric Disorder	21 (9%)	30 (7%)	79 (33%)	95 (23%)	92 (38%)	118 (29%)
ANXIETY	17 (7%)	22 (5%)	41 (17%)	61 (15%)	56 (23%)	82 (20%)
HEART RATE/RHYTHM						
TACHYCARDIA	10 (4%)	6 (1%)	50 (21%)	51 (13%)	60 (25%)	57 (14%)
CARDIOVASCULAR	9 (4%)	20 (5%)	75 (31%)	97 (24%)	83 (34%)	112 (27%)
HYPERTENSION	1 (0%)	6 (1%)	12 (5%)	24 (6%)	13 (5%)	30 (7%)
HYPOTENSION	8 (3%)	12 (3%)	59 (25%)	64 (16%)	67 (28%)	72 (18%)

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Table 7-45 Adverse Events Hematologic Malignancy Safety Pool B with Incidence of ≥ 5% in Palifermin Subjects or of Particular Interest Gastrointestinal, Liver and Biliary, Metabolic Nutrition

Table 7.45 Adverse Events Hematologic Malignancy Safety Pool B with Incidence of ≥ 5% in Palifermin Subjects or of Particular Interest Gastrointestinal, Liver and Biliary, Metabolic Nutrition						
BODY SYSTEM PREFRERED TERM	**Pre-chemotherapy**		**Post-chemotherapy**		**Total**	
N (%)	**Placebo n= 241**	**Palifermin n=409**	**Placebo n= 240**	**Palifermin n=405**	**Placebo n= 241**	**Palifermin n=409**
GASTROINTESTINAL	141 (59%)	232 (57%)	221 (92%)	378 (93%)	236 (98%)	399 (98%)
ANOREXIA	32 (13%)	39 (10%)	63 (26%)	93 (23%)	89 (37%)	124 (30%)
CONSTIPATION	28 (12%)	51 (12%)	39 (16%)	51 (13%)	63 (26%)	100 (24%)
DIARRHEA	0	0	5 (2%)	20 (5%)	5 (2%)	20 (5%)
DRY MOUTH	5 (2%)	19 (5%)	13 (5%)	17 (4%)	17 (7%)	34 (8%)
DYSPEPSIA	10 (4%)	9 (2%)	48 (20%)	57 (14%)	58 (24%)	65 (16%)
EDEMA TONGUE	0	6 (1%)	4 (2%)	1 (0%)	4 (2%)	7 (2%)
HICCUP	2 (1%)	8 (2%)	47 (20%)	32 (8%)	49 (20%)	40 (10%)
LESION ORAL	2 (1%)	28 (7%)	9 (4%)	18 (4%)	11 (5%)	45 (11%)
MONILIASIS ORAL	4 (2%)	1 (0%)	15 (6%)	31 (8%)	17 (7%)	32(8%)
NAUSEA	100(41%)	137(33%)	130(54%)	232(57%)	203(84%)	349(85%)
PAIN ABDOMINAL	11 (5%)	16 (4%)	86 (36%)	147 (36%)	92 (38%)	158 (39%)
PAIN ORAL	0	9 (2%)	5 (2%)	9 (2%)	5 (2%)	16 (4%)
PAIN RECTAL	0	2 (0%)	11 (5%)	14 (3%)	11 (5%)	16 (4%)
PAIN SALIVARY GLAND	7 (3%)	7 (2%)	0 (0%)	0 (0%)	7 (3%)	7 (2%)
SALIVA DECREASED	10 (4%)	18 (4%)	4 (2%)	11 (3%)	14 (6%)	29 (7%)
TONGUE DISCOLORATION	0	7 (2%)	5 (2%)	6 (1%)	5 (2%)	13 (3%)
TONGUE DISORDER	2 (1%)	20 (5%)	5 (2%)	7 (2%)	7 (3%)	25 (6%)
VOMITING	69 (29%)	94 (23%)	131 (55%)	228 (56%)	187 (78%)	306 (75%)
LIVER AND BILIARY	1 (0%)	2 (0%)	19 (8%)	21 (5%)	20 (8%)	23 (6%)
METABOLIC/NUTRITION	21 (9%)	26 (6%)	81 (34%)	121 (30%)	90 (37%)	128 (31%)

Table 7-46 Adverse Events Hematologic Malignancy Safety Pool B with Incidence of ≥ 5% in Palifermin Subjects or of Particular Interest Musculoskeletal, Reproductive Male and Female

Table 7.46 Adverse Events Hematologic Malignancy Safety Pool B with Incidence of ≥ 5% in Palifermin Subjects or of Particular Interest Musculoskeletal, Reproductive Male and Female						
BODY SYSTEM PREFRERED TERM	Pre-chemotherapy		Post-chemotherapy		Total	
N (%)	**Placebo n= 241**	**Palifermin n=409**	**Placebo n= 240**	**Palifermin n=405**	**Placebo n= 241**	**Palifermin n=409**
MUSCULO-SKELETAL	26 (11%)	50 (12%)	80 (33%)	131 (32%)	95 (39%)	160 (39%)
ARTHRALGIA	2 (1%)	15 (4%)	11 (5%)	27 (7%)	13 (5%)	40 (10%)
MYALGIA	10 (4%)	7 (2%)	12 (5%)	22 (5%)	22 (9%)	29 (7%)
PAIN BACK	7 (3%)	13 (3%)	21 (9%)	26 (6%)	27 (11%)	39 (10%)
PAIN GROIN	1 (0%)	2 (0%)	1 (0%)	1 (0%)	2 (1%)	3 (1%)
PAIN LIMB	4 (2%)	14 (3%)	31 (13%)	43 (11%)	34 (14%)	57 (14%)
PAIN MUSCULOSKELETAL	3 (1%)	0	2 (1%)	2 (0%)	4 (2%)	2 (0%)
PAIN NECK	2 (1%)	6 (1%)	6 (3%)	7 (2%)	8 (3%)	13 (3%)
PAIN SKELETAL	1 (0%)	2 (0%)	10 (4%)	28 (7%)	11 (5%)	30 (7%)
REPRODUCTIVE (FEMALE%) DENOMINATOR	n= 78	n=167	n= 78	n=163	n= 78	n=167
REPRODUCTIVE (FEMALE%)	0	5 (3%)	18 (23%)	36 (22%)	19 (24%)	39 (23%)
HEMORRHAGE VAGINAL	0	0 (0%)	7 (9%)	12 (7%)	8 (10%)	12 (7%)
URINARY DISCRDERS	8 (3%)%)	15 (4	64 (27%)	103 (25%)	70 (29%)	111 (27%)
DYSURIA	0	3 (1%)	15 (6%)	35 (9%)	15 (6%)	38 (9%)
HEMATURIA	1 (0%)	1 (0%)	24 (10%)	33 (8%)	25 (10%)	33 (8%)

Table 7-47 Adverse Events Hematologic Malignancy Safety Pool B with Incidence of ≥ 5% or Greater in Palifermin Subjects or of Particular Interest Resistance Mechanisms, Respiratory

Table 7.47 Adverse Events Hematologic Malignancy Safety Pool B with Incidence of ≥ 5% or Greater in Palifermin Subjects or of Particular Interest Resistance Mechanisms, Respiratory						
BODY SYSTEM PREFRERED TERM	**Pre-chemotherapy**		**Post-chemotherapy**		**Total**	
N (%)	**Placebo n= 241**	**Palifermin n=409**	**Placebo n= 240**	**Palifermin n=405**	**Placebo n= 241**	**Palifermin n=409**
RESISTANCE MECHANISM	3 (1%)	6 (1%)	44 (18%)	61 (15%)	45 (19%)	66 (16%)
HERPES SIMPLEX	1 (0%)	1 (0%)	8 (3%)	8 (2%)	9 (4%)	9 (2%)
HERPES ZOSTER	2 (1%)	0	1 (0%)	3 (1%)	2 (1%)	3 (1%)
INFECTION	0	1 (0%)	2 (1%)	6 (1%)	2 (1%)	7 (2%)
INFECTION BACTERIAL	0	0	6 (3%)	5 (1%)	6 (2%)	5 (1%)
INFECTION FUNGAL	0	0	2 (1%)	2 (0%)	2 (1%)	3 (1%)
SEPSIS	0	1 (0%)	9 (4%)	19 (5%)	9 (4%)	19 (5%)
SEPSIS BACTERIAL	0	0	4 (2%)	3 (1%)	4 (2%)	3 (1%)
SEPTIC SHOCK	0	0	2 (1%)	3 (1%)	2 (1%)	3 (1%)
RESPIRATORY	39 (16%)	62 (15%)	156 (65%)	247 (61%)	163 (68%)	258 (63%)
COUGH	9 (4%)	14 (3%)	36 (15%)	73 (18%)	43 (18%)	87 (21%)
COUGH DRY	5 (2%)	12 (3%)	19 (8%)	24 (6%)	24 (10%)	35 (9%)
COUGH PRODUCTIVE	2 (1%)	3 (1%)	9 (4%)	16 (4%)	11 (5%)	19 (5%)
DYSPNEA	6 (2%)	6 (1%)	27 (11%)	41 (10%)	32 (13%)	47 (11%)
EPISTAXIS	1 (0%)	0	58 (24%)	74 (18%)	58 (24%)	75 (18%)
INFECTION UPPER RESPIRATORY	3 (1%)	2 (0%)	9 (4%)	6 (1%)	11 (5%)	7 (2%)
PNEUMONIA	1 (0%)	1 (0%)	6 (3%)	7 (2%)	7 (3%)	8 (2%)
RALES	4 (2%)	1 (0%)	21 (9%)	20 (5%)	25 (10%)	21 (5%)
RHINITIS	4 (2%)	12 (3%)	15 (6%)	32 (8%)	17 (7%)	43 (11%)
UPPER RESPIRATORY TRK	2 (1%)	7 (2%)	20 (8%)	21 (5%)	22 (9%)	28 (7%)

Table 7-48 Adverse Events Hematologic Malignancy Safety Pool B With Incidence of ≥ 5% in Palifermin Subjects or of Particular Interest Skin And Appendages

Table 7.48 Adverse Events Hematologic Malignancy Safety Pool B With Incidence of ≥ 5% in Palifermin Subjects or of Particular Interest Skin And Appendages						
BODY SYSTEM PREFRERED TERM	**Pre-chemotherapy**		**Post-chemotherapy**		**Total**	
N (%)	**Placebo n= 241**	**Palifermin n=409**	**Placebo n= 240**	**Palifermin n=405**	**Placebo n= 241**	**Palifermin n=409**
SKIN AND APPENDAGES	46 (19%)	158 (39%)	182 (76%)	344 (85%)	188 (78%)	359 (88%)
ERYTHEMA	8 (3%)	56 (14%)	45 (19%)	96 (24%)	52 (22%)	131 (32%)
ERYTHEMA MULTIFORME	0	0	1 (0%)	4 (1%)	1 (0%)	4 (1%)
FLUSHING	10 (4%)	28 (7%)	38 (16%)	41 (10%)	43 (18%)	62 (15%)
FOLLICULITIS	2 (1%)	2 (0%)	9 (4%)	11 (3%)	11 (5%)	13 (3%)
LESION SKIN	0	2 (0%)	9 (4%)	7 (2%)	9 (4%)	9 (2%)
PAIN PERIANAL	0	0	6 (3%)	19 (5%)	6 (2%)	19 (5%)
PRURITIC ERYTHEMA	0	0	4 (2%)	4 (1%)	4 (2%)	4 (1%)
PRURITUS	12 (5%)	33 (8%)	47 (20%)	120 (30%)	57 (24%)	145 (35%)
PRURITUS ANI	0	1 (0%)	1 (0%)	1 (0%)	1 (0%)	2 (0%)
PRURITUS GENITAL	1 (0%)	5 (1%)	9 (4%)	8 (2%)	10 (4%)	13 (3%)
RASH	6 (2%)	48 (12%)	93 (39%)	173 (43%)	96 (40%)	198 (48%)
RASH ERYTHEMATOUS	5 (2%)	7 (2%)	16 (7%)	31 (8%)	20 (8%)	36 (9%)
RASH FOLLICULAR	0	0	9 (4%)	8 (2%)	9 (4%)	8 (2%)
RASH MACULO-PAPULAR	5 (2%)	7 (2%)	24 (10%)	45 (11%)	26 (11%)	51 (12%)
RASH PURPURIC	0	1 (0%)	3 (1%)	6 (1%)	3 (1%)	7 (2%)
RASH PUSTULAR	0	0	0	4 (1%)	0	4 (1%)
SKIN DISCOLORATION	0	3 (1%)	4 (2%)	4 (1%)	4 (2%)	7 (2%)
SKIN DISORDER	0	1 (0%)	0	4 (1%)	0	5 (1%)
SKIN DRY	4 (2%)	9 (2%)	21 (9%)	22 (5%)	25 (10%)	31 (8%)
SKIN EXFOLIATION	1 (0%)	1 (0%)	25 (10%)	45 (11%)	26 (11%)	46 (11%)
SKIN HYPERPIGMENTATI	2 (1%)	2 (0%)	8 (3%)	20 (5%)	10 (4%)	22 (5%)
SKIN NODULE	0	2 (0%)	0	5 (1%)	0	6 (1%)
SKIN ULCERATION	0	0	13 (5%)	8 (2%)	13 (5%)	8 (2%)
SWEATING INCREASED	1 (0%)	2 (0%)	7 (3%)	17 (4%)	8 (3%)	19 (5%)
URTICARIA	1 (0%)	0	2 (1%)	7 (2%)	3 (1%)	7 (2%)

The majority of adverse events in the transplant study are transplant related. The Amgen submission included a table listing all events that occurred in greater than 5% in either group. The table below is derived from that table; it includes those events that occurred in ≥5% of the placebo compared to palifermin. Those that occurred in ≥ 5% of palifermin compared to placebo are included in the 6 tables above. Review of events that are reported more frequently in the placebo subjects are of interest because the majority of adverse events reported are transplant related, not related to the investigational agent. Palifermin is an agent intended to contribute to supportive care. Transplant related adverse events that occur less frequently in palifermin treated patients may represent clinical benefit associated with palifermin treatment.

Table 7-49 Adverse Events Hematologic Malignancy Safety Pool B with incidence of ≥ 5% in Placebo Subjects Compared to Palifermin Subjects

Table 7.49 Adverse Events Hematologic Malignancy Safety Pool B with incidence of ≥ 5% in Placebo Subjects Compared to Palifermin Subjects						
PREFRERED TERM	Pre-chemotherapy		Post-chemotherapy		Total	
N (%)	Placebo n= 241	Palifermin n=409	Placebo n= 240	Palifermin n=405	Placebo n= 241	Palifermin n=409
OVERALL	159 (66%)	280 (68%)	237 (99%)	400 (99%)	240 (100%)	405 (99%)
NAUSEA	100 (41%)	137 (33%)	130 (54%)	232 (57%)	203 (84%)	349 (85%)
VOMITING	69 (29%)	94 (23%)	131 (55%)	228 (56%)	187 (78%)	306 (75%)
HEADACHE	49 (20%)	48 (12%)	74 (31%)	130 (32%)	117 (49%)	174 (43%)
INSOMNIA	26 (11%)	44 (11%)	65 (27%)	90 (22%)	91 (38%)	132 (32%)
ANOREXIA	32 (13%)	39 (10%)	63 (26%)	93 (23%)	89 (37%)	124 (30%)
RIGORS	7 (3%)	9 (2%)	79 (33%)	107 (26%)	84 (35%)	114 (28%)
FATIGUE	52 (22%)	46 (11%)	46 (19%)	70 (17%)	85 (35%)	107 (26%)
EPISTAXIS	1 (0%)	0	58 (24%)	74 (18%)	58 (24%)	75 (18%)
HYPOTENSION	8 (3%)	12 (3%)	59 (25%)	64 (16%)	67 (28%)	72 (18%)
DYSPEPSIA	10 (4%)	9 (2%)	48 (20%)	57 (14%)	58 (24%)	65 (16%)
TACHYCARDIA	10 (4%)	6 (1%)	50 (21%)	51 (13%)	60 (25%)	57 (14%)
HICCUP	2 (1%)	8 (2%)	47 (20%)	32 (8%)	49 (20%)	40 (10%)
CONFUSION	1 (0%)	2 (0%)	29 (12%)	27 (7%)	30 (12%)	29 (7%)
RALES	4 (2%)	1 (0%)	21 (9%)	20 (5%)	25 (10%)	21 (5%)
ABDOMEN ENLARGED	1 (0%)	2 (0%)	15 (6%)	5 (1%)	16 (7%)	7 (2%)

The following table is an abridged version of Amgen's Severe Adverse Event by Body System and Preferred Term Safety Pool B document (eCTD 5.3.5.2.1, Integrated Safety Analysis page 191). The Amgen Table consists of 13 pages. This abridged document includes any adverse event that was reported in ≥ 2 %.

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Table 7-50 Severe Adverse Events Hematologic Malignancy Safety Pool B with Incidence of ≥ 2% in Placebo or Palifermin Subjects

Table 7.50 Severe Adverse Events Hematologic Malignancy Safety Pool B with Incidence of ≥ 2% in Placebo or Palifermin Subjects						
BODY SYSTEM PREFRERED TERM	**Pre-chemotherapy**		**Post-chemotherapy**		**Total**	
N (%)	**Placebo n= 241**	**Palifermi n n=409**	**Placebo n= 240**	**Palifermin n=405**	**Placebo n= 241**	**Palifermin n=409**
OVERALL	21 (9%)	28 (7%)	78 (33%)	149 (37%)	85 (35%)	158 (39%)
BODY AS A WHOLE	4 (2%)	6 (1%)	22 (9%)	41 (10%)	25 (10%)	46 (11%)
FATIGUE	3 (1%)	1 (0%)	4 (2%)	4 (1%)	7 (3%)	5 (1%)
FEVER	0	1 (0%)	3 (1%)	18 (4%)	3 (1%)	18 (4%)
CARDIOVASCULAR	0	0	7 (3%)	11 (3%)	7 (3%)	11 (3%)
HYPOTENSION	0	0	7 (3%)	6 (1%)	7 (3%)	6 (1%)
CNS/PNS	3 (1%)	3 (1%)	10 (4%)	12 (3%)	13 (5%)	15 (4%)
HEADACHE	3 (1%)	2 (0%)	3 (1%)	5 (1%)	6 (2%)	7 (2%)
GASTROINTESTINAL	12 (5%)	13 (3%)	50 (21%)	71 (18%)	58 (24%)	77 (19%)
ANOREXIA	5 (2%)	1 (0%)	12 (5%)	15 (4%)	17 (7%)	16 (4%)
ESOPHAGITIS	0	1 (0%)	7 (3%)	6 (1%)	7 (3%)	6 (1%)
NAUSEA	5 (2%)	12 (3%)	19 (8%)	33 (8%)	24 (10%)	44 (11%)
PAIN ABDOMINAL	0	1 (0%)	3 (1%)	14 (3%)	3 (1%)	15 (4%)
VOMITING	4 (2%)	6 (1%)	12 (5%)	22 (5%)	16 (7%)	28 (7%)
HEART RATE/RHYTHM	0	0	6 (3%)	6 (1%)	6 (2%)	6 (1%)
FIBRILLATION ATRIAL	0	0	4 (2%)	2 (0%)	4 (2%)	2 (0%)
METABOLIC/NUTRITION	0	0	10 (4%)	10 (2%)	10 (4%)	10 (2%)
MUSCULO-SKELETAL	2 (1%)	3 (1%)	2 (1%)	7 (2%)	4 (2%)	10 (2%)
REPRODUCTIVE (FEMALE) DENOMINATOR	n= 78	n=167	n= 78	n=163	n= 78	n=167
REPRODUCTIVE (FEMALE)	0	0	2 (3%)	1 (1%)	2 (3%)	1 (1%)
RESISTANCE MECHANISM	0	0	9 (4%)	12 (3%)	9 (4%)	12 (3%)
SEPSIS	0	0	2 (1%)	7 (2%)	2 (1%)	7 (2%)
SEPSIS BACTERIAL	0	0	4 (2%)	0	4 (2%)	0 (0%)
RESPIRATORY	3 (1%)	2 (0%)	21 (9%)	28 (7%)	23 (10%)	28 (7%)
SORE THROAT	0	0	8 (3%)	7 (2%)	8 (3%)	7 (2%)
SKIN AND APPENDAGES	2 (1%)	3 (1%)	10 (4%)	19 (5%)	11 (5%)	22 (5%)
RASH	0	1 (0%)	5 (2%)	8 (2%)	5 (2%)	9 (2%)
URINARY DISORDERS	0	0	3 (1%)	8 (2%)	3 (1%)	8 (2%)

7.1.5.5 Identifying common and drug-related adverse events

The incidence of adverse events identified as treatment related was greater in the palifermin group compared to the placebo group both pre-chemotherapy time period (38% versus 10%) and in the post chemotherapy therapy time period (38% versus 22%).

The following table summarizes the incidence of adverse events identified as treatment related in ≥ 2% of palifermin subjects compared to placebo subjects.

Table 7-51 Adverse Event Identified as Treatment Related ≥ 2% Hematologic Malignancy Safety Pool B

Table 7.51 Adverse Event Identified as Treatment Related ≥ 2% Hematologic Malignancy Safety Pool B		
	Placebo n=241	Palifermin n=409
Skin		
Pruritis	11 (5%)	29 (7%)
Rash	25 (10%)	99 (24%)
Skin discoloration	1 (<1%)	3 (1%)
Skin hyper pigmented	1 (<1%)	4 (1%)
Warm sensation	0	7 (2%)
Erythema / flushing	18 (7%)	106 (26%)
Edema	11 (5%)	75 (18%)
Oral		
Saliva / sputum altered	3 (1%)	13 (3%)
Lesion oral	4 (2%)	32 (8%)
Taste loss / perversion	2 (1%)	14 (3%)
Tongue discoloration / disorder	4 (2%)	33 (8%)
Dysesthesia		
Hyperesthesia, hypoesthesia, or paresthesia	2 (1%)	16 (4%)
Pain		
Abdomen/Oral/Limb	2 (1%)	33 (8%)

COMMENT: *The majority of adverse events identified as treatment related are skin and oral toxicity.*

7.1.5.6 Additional analyses and explorations

The most significant palifermin drug related adverse events are oral and skin reactions. The following tables are derived from Amgen's additional analyses specifically comparing the adverse events associated with the initial 3 doses to the adverse events associated with the post transplant 3 doses (eCTD 5.3.5.2.1, Integrated Safety Analysis pages 574, 587, 589, 602, 622, 625). These tables compare severity, time to onset and duration.

Table 7-52 Subject Incidence of Oral-Related Adverse Events by Preferred Term and Severity Hematologic Malignancy Safety Pool B

Table 7.52 Subject Incidence of Oral-Related Adverse Events by Preferred Term and Severity Hematologic Malignancy Safety Pool B												
N (%)	Placebo (N=241)						Palifermin (N=409)					
Preferred Term	Mild	Mod.	Sev.	Life Threat.	Fatal	Total	Mild	Mod.	Sev.	Life Threat.	Fatal	Total
Number of Oral Related Adverse Events	97	12	1	0	0	110	207	58	1	0	0	266
Number of Subjects Reporting Oral Related Adverse Events	59(24)	11(5)	1(0)	0(0)	0(0)	64(27)	130 (32)	45 (11)	1 (0)	0(0)	0 (0)	157 (38)
CHEILITIS	5(2)	0(0)	0(0)	0(0)	0(0)	5(2)	6(1)	0(0)	0(0)	0(0)	0(0)	6(1)
DRY MOUTH	16(7)	0(0)	1 (0)	0(0)	0(0)	17(7)	27(7)	8(2)	0(0)	0(0)	0(0)	34(8)
EDEMA TONGUE	4(2)	0(0)	0(0)	0(0)	0(0)	4(2)	4(1)	3(1)	0(0)	0(0)	0(0)	7(2)
GINGIVAL	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(0)	0(0)	0(0)	0(0)	0(0)	1(0)
GINGIVITIS	1(0)	0(0)	0(0)	0(0)	0(0)	1 (0)	2(0)	1(0)	0(0)	0(0)	0(0)	3(1)
GLOSSITIS	1 (0)	0(0)	0(0)	0(0)	0(0)	1 (0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
LESION ORAL	11(5)	0(0)	0(0)	0(0)	0(0)	11(5)	38(9)	8(2)	0(0)	0(0)	0(0)	45(11)
SALIVA ALTERED	3(1)	0(0)	0(0)	0(0)	0(0)	3(1)	5(1)	1 (0)	0(0)	0(0)	0(0)	6(1)
SALIVA DECREASED	11 (5)	3 (1)	0(0)	0(0)	0(0)	14(6)	24(6)	5(1)	0(0)	0(0)	0(0)	29(7)
SALIVA INCREASED	6 (2)	3 (1)	0 (0)	0 (0)	0 (0)	9 (4)	7 (2)	3 (1)	0 (0)	0 (0)	0 (0)	9 (2)
TASTE LOSS	3 (1)	3 (1)	0 (0)	0 (0)	0 (0)	6 (2)	24 (6)	2 (0)	0 (0)	0 (0)	0 (0)	26 (6)
TASTE PERVERSION	12 (5)	2 (1)	0 (0)	0 (0)	0 (0)	14 (6)	28 (7)	13 (3)	0 (0)	0 (0)	0 (0)	41 (10)
THROAT TIGHTNESS	4 (2)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2)	4 (1)	2 (0)	1 (0)	0 (0)	0 (0)	7 (2)
TONGUE	5 (2)	1 (0)	0 (0)	0 (0)	0 (0)	5 (2)	10 (2)	4 (1)	0 (0)	0 (0)	0 (0)	13 (3)
TONGUE DISORDER	7 (3)	0 (0)	0 (0)	0 (0)	0 (0)	7 (3)	19 (5)	7 (2)	0 (0)	0 (0)	0 (0)	25 (6)

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Table 7-53 Summary of Incidence of Oral-Related Adverse Events Hematologic Malignancy Safety Pool B

Table 7.53 Summary of Incidence of Oral-Related Adverse Events Hematologic Malignancy Safety Pool B

N (%)	First Period of Dosing				Second Period of Dosing			
	Placebo	Palifermin			Placebo	Palifermin		
		Pre	Pre Post	Total		Pre	Pre Post	Total
	(N=241)	(N=180	(N=229)	(N=409)	(N=239)	(N=179)	(N=228)	(N=407)
Number of Subjects with Oral Related Adverse Events	34(14)	41(23)	76(33)	117(29)	42(18)	21(12)	58(25)	79(19)
CHEILITIS	0(0)	2(1)	0(0)	2(0)	5(2)	0(0)	4(2)	4(1)
DRY MOUTH	10(4)	6(3)	18(8)	24(6)	8(3)	3(2)	8(4)	11(3)
EDEMA TONGUE	0(0)	6(3)	1(0)	7(2)	4(2)	0(0)	0(0)	0(0)
GINGIVAL DISCOLORATION	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(0)	1(0)
GINGIVITIS	0(0)	1(1)	1(0)	2(0)	1(0)	1(1)	0(0)	1(0)
GLOSSITIS	1(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
LESION ORAL	5(2)	16(9)	22(10)	38(9)	8(3)	3(2)	4(2)	7(2)
SALIVA ALTERED	0(0)	0(0)	5(2)	5(1)	3(1)	0(0)	1(0)	1(0)
SALIVA DECREASED	13 (5)	5 (3)	15 (7)	20 (5)	1 (0)	4 (2)	5 (2)	9 (2)
SALIVA INCREASED	2 (1)	1 (1)	2 (1)	3 (1)	7 (3)	2 (1)	6 (3)	8 (2)
TASTE LOSS	1 (0)	5 (3)	5 (2)	10 (2)	5 (2)	4 (2)	12 (5)	16 (4)
TASTE PERVERSION	2 (1)	6 (3)	14 (6)	20 (5)	12 (5)	4 (2)	18 (8)	22 (5)
THROAT TIGHTNESS	4 (2)	0 (0)	4 (2)	4 (1)	0 (0)	0 (0)	3 (1)	3 (1)
TONGUE DISCOLORATION	2 (1)	4 (2)	6 (3)	10 (2)	3 (1)	2 (1)	2 (1)	4 (1)
TONGUE DISORDER	2 (1)	7 (4)	15 (7)	22 (5)	5 (2)	0 (0)	5 (2)	5 (1)

The First Period of Dosing is from the date of initiation of investigational product (IP) to the day before the first IP dose after PBSCT. If a subject did not receive IP on or after PBSCT, the First Period of Dosing is considered ended on the day before PBSCT (the date of PBSCT for 189). Second Period of Dosing is from the day after the First Period of Dosing to the end of study.

Table 7-54 Summary of Time to Onset and Duration of Oral-Related Adverse Events Hematologic Malignancy Safety Pool B

Table 7.54 Summary of Time to Onset and Duration of Oral-Related Adverse Events Hematologic Malignancy Safety Pool B

	First Period of Dosing				Second Period of Dosing			
	Placebo	Palifermin			Placebo	Palifermin		
		Pre	Pre Post	Total		Pre	Pre Post	Total
	(N=241)	(N=180)	(N=229)	(N=409)	(N=239)	(N=179)	(N=228)	(N=407)
Time to Onset (Days) Number subject with time to onset	42	59	114	173	68	24	69	93
Mean	7.0	4.3	5.5	5.1	9.4	11.6	9.3	9.9
SD	2.3	2.4	2.3	2.4	9.3	9.9	7.1	7.9
Median	7	4	5	5	5	8	9	8
Q1, Q3	5, 9	3, 5	4, 7	3, 7	3, 15	4, 17	3, 15	3, 15
Min, Max	2, 11	1, 11	1, 11	1, 11	1, 49	1, 31	1, 28	1, 31
Duration Days Number subject data available	42	56	114	170	67	24	68	92
Mean	11.2	7.9	11.6	10.4	6.1	6.8	7.7	8.1
SD	13.9	9.9	15.6	14.1	6.9	8.0	8.5	8.3
Median	2	4	5	5	3	3	5	4
Q1, Q3	1, 26	2, 8	2, 15	2, 13	1, 8	2, 11	1, 14	1, 14
Min, Max,	1,39	1,42	1,116	1,29	1,30	1,30	1,38	1,38

The First Period of Dosing is from the date of initiation of investigational product (IP) to the day before the first IP dose after PBSCT. If a subject did not receive IP on or after PBSCT, the First Period of Dosing is considered ended

on the day before PBSCT (the date of PBSCT for 189). Second Period of Dosing is from the day after the First Period of Dosing to the end of study.
Time to AE onset is relative to the date of the IP administration in the period the AE started.
Duration is the time from AE onset to AE resolution. If an AE is continuing and a resolution date is not present, the resolution date is imputed as the end of study date.

COMMENT: *The majority of oral-related adverse events are categorized as mild to moderate in severity; throat tightness was the only adverse event categorized as severe in the palifermin subjects. These reactions were more likely to occur after the initial 3 doses of palifermin. The median onset to an oral-related adverse event after the initial 3 doses of palifermin was 4 to 5 days. The median onset to an oral-related adverse event after the post transplant 3 doses of palifermin was 8 to 9 days. The median duration of an oral-related adverse event after the initial 3 doses of palifermin was 4 to 5 days. The median duration of an oral-related adverse event after the post transplant 3 doses of palifermin was 3 to 5 days.*

Table 7-55 Subject Incidence of Skin -Related Adverse Events by Preferred Term and Severity Hematologic Malignancy Safety Pool B

Table 7.55 Subject Incidence of Skin-Related Adverse Events by Preferred Term and Severity Hematologic Malignancy Safety Pool B

N (%)	Placebo (N=241)						Palifermin (N=409)					
Preferred Term	Mild	Mod.	Sev.	Life Threat	Fatal	Total	Mild	Mod.	Sev.	Life Threat.	Fatal	Total
Number of Oral Related Adverse Events	512	154	23	0	0	689	903	425	21	0	0	1349
Number of Subjects Reporting Skin Related Adverse Events	168 (70)	86 (36)	11 (5)	0 (0)	0 (0)	191 (79)	318 (78)	197(48)	19 (5)	0 (0)	0 (0)	360 (88)
EDEMA FACE	15 (6)	2 (1)	0(0)	0(0)	0(0)	17 (7)	34 (8)	14 (3)	1(0)	0(0)	0(0)	47 (11)
EDEMA PERIORBITAL	6 (2)	0(0)	1 (0)	0(0)	0(0)	7 (3)	11 (3)	2 (0)	0(0)	0(0)	0(0)	13 (3)
EDEMA PERIPHERAL	61 (25)	22 (9)	1(0)	0(0)	0(0)	76 (32)	95 (23)	41	2(0)	0(0)	0(0)	121 (30)
ERYTHEMA	45 (19)	10 (4)	2(1)	0(0)	0(0)	52 (22)	103 (25)	38 (9)	5(1)	0(0)	0(0)	131 (32)
FLUSHING	42 (17)	2 (1)	0(0)	0(0)	0(0)	43 (18)	52 (13)	12 (3)	1 (0)	0(0)	0(0)	62 (15)
HOT FLUSHES	3 (1)	0(0)	1(0)	0(0)	0(0)	4 (2)	3 (1)	2 (0)	0(0)	0(0)	0(0)	5 (1)
HYPERESTHESIA	3 (1)	0(0)	0(0)	0(0)	0(0)	3 (1)	3 (1)	3 (1)	0(0)	0(0)	0(0)	5 (1)
HYPERKERATOSIS	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1 (0)	1 (0)	0(0)	0(0)	0(0)	2 (0)
HYPERTRICHOSIS	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(0)	0(0)	0(0)	0(0)	0(0)	2(0)
HYPOESTHESIA	5 (2)	0 (0)	1 (0)	0 (0)	0 (0)	6 (2)	17 (4)	6 (1)	0 (0)	0 (0)	0 (0)	22 (5)
LESION SKIN	6 (2)	3 (1)	0 (0)	0 (0)	0 (0)	9 (4)	5 (1)	4 (1)	0 (0)	0 (0)	0 (0)	9 (2)
PARESTHESIA	9 (4)	0 (0)	2 (1)	0 (0)	0 (0)	11 (5)	30 (7)	7 (2)	0 (0)	0 (0)	0 (0)	34 (8)
PIGMENTATION ABNORMAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
PRURITIC ERYTHEMA	2 (1)	2 (1)	0 (0)	0 (0)	0 (0)	4 (2)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	4 (1)
PRURITUS	41 (17)	16 (7)	2 (1)	0 (0)	0 (0)	57 (24)	93 (23)	58	2 (0)	0 (0)	0 (0)	145 (35)
PUSTULE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0	0 (0)	0 (0)	1 (0)
RASH	68 (28)	37 (15)	5 (2)	0 (0)	0 (0)	96 (40)	134 (33)	86	9 (2)	0 (0)	0 (0)	198 (48)
RASH ERYTHEMATOUS	13 (5)	8 (3)	0 (0)	0 (0)	0 (0)	20 (8)	19 (5)	18 (4)	0 (0)	0 (0)	0 (0)	36 (9)
RASH FOLLICULAR	7 (3)	2 (1)	0 (0)	0 (0)	0 (0)	9 (4)	5 (1)	3 (1)	0 (0)	0 (0)	0 (0)	8 (2)
RASH MACULO-PAPULAR	18 (7)	9 (4)	0 (0)	0 (0)	0 (0)	26 (11)	35 (9)	21 (5)	0 (0)	0 (0)	0 (0)	51 (12)
RASH PURPURIC	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	4 (1)	3 (1)	0 (0)	0 (0)	0 (0)	7 (2)
RASH PUSTULAR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	2 (0)	0 (0)	0 (0)	0 (0)	4 (1)
RED-MAN SYNDROME	4 (2)	0 (0)	0 (0)	0(0)	0(0)	4 (2)	2 (0)	0 (0)	0(0)	0(0)	0(0)	2 (0)
SKIN DISCOLORATION	4 (2)	0 (0)	0 (0)	0(0)	0(0)	4 (2)	5 (1)	2 (0)	0(0)	0(0)	0(0)	7 (2)
SKIN DISORDER	0 (0)	0 (0)	0 (0)	0(0)	0(0)	0 (0)	1 (0)	0(0)	0(0)	0(0)	0(0)	5 (1)
SKIN DRY	24 (10)	1 (0)	0 (0)	0(0)	0(0)	25 (10)	26 (6)	5 (1)	0(0)	0(0)	0(0)	31 (8)
SKIN EXFOLIATION	13 (5)	12 (5)	3 (1)	0(0)	0(0)	26 (11)	30 (7)	19 (5)	0(0)	0(0)	0(0)	46 (11)
SKIN HYPERPIGMENTATION	8 (3)	2 (1)	1 (0)	0(0)	0(0)	10 (4)	17 (4)	5 (1)	0(0)	0(0)	0(0)	22 (5)
SKIN HYPERTROPHY	1 (0)	0(0)	0(0)	0(0)	0(0)	1 (0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
SKIN ULCERATION	9 (4)	4 (2)	0(0)	0(0)	0(0)	13 (5)	4 (1)	5 (1)	0(0)	0(0)	0(0)	8 (2)
SWEATING	6 (2)	2 (1)	0(0)	0(0)	0(0)	8 (3)	16 (4)	3 (1)	0(0)	0(0)	0(0)	19 (5)
URTICARIA	2 (1)	1 (0)	0(0)	0 (0)	0 (0)	3 (1)	5 (1)	2 (0)	0 (0)	0 (0)	0 (0)	7 (2)
WARM SENSATION	4 (2)	0 (0	0(0)	0 (0)	0 (0)	4 (2)	6 (1)	2 (0)	0 (0)	0 (0)	0 (0)	8 (2)

Table 7-56 Subject Incidence of Skin-Related Adverse Events by Preferred Term and Severity Hematologic Malignancy Safety Pool B

Table 7.56 Subject Incidence of Skin-Related Adverse Events by Preferred Term and Severity Hematologic Malignancy Safety Pool B

N (%)	Placebo (N=241)						Palifermin (N=409)					
Preferred Term	Mild	Mod.	Sev.	Life Threat	Fatal	Total	Mild	Mod.	Sev.	Life Threat.	Fatal	Total
Number of Oral Related Adverse Events	512	154	23	0	0	689	903	425	21	0	0	1349
Number of Subjects Reporting Skin Related Adverse Events	168 (70)	86 (36)	11 (5)	0 (0)	0 (0)	191 (79)	318 (78)	197(48)	19 (5)	0 (0)	0 (0)	360 (88)
EDEMA FACE	15 (6)	2 (1)	0(0)	0(0)	0(0)	17 (7)	34 (8)	14 (3)	1(0)	0(0)	0(0)	47 (11)
EDEMA PERIORBITAL	6 (2)	0(0)	1 (0)	0(0)	0(0)	7 (3)	11 (3)	2 (0)	0(0)	0(0)	0(0)	13 (3)
EDEMA PERIPHERAL	61 (25)	22 (9)	1(0)	0(0)	0(0)	76 (32)	95 (23)	41 (10)	2(0)	0(0)	0(0)	121 (30)
ERYTHEMA	45 (19)	10 (4)	2(1)	0(0)	0(0)	52 (22)	103 (25)	38 (9)	5(1)	0(0)	0(0)	131 (32)
FLUSHING	42 (17)	2 (1)	0(0)	0(0)	0(0)	43 (18)	52 (13)	12 (3)	1 (0)	0(0)	0(0)	62 (15)
HOT FLUSHES	3 (1)	0(0)	1(0)	0(0)	0(0)	4 (2)	3 (1)	2 (0)	0(0)	0(0)	0(0)	5 (1)
HYPERESTHESIA	3 (1)	0(0)	0(0)	0(0)	0(0)	3 (1)	3 (1)	3 (1)	0(0)	0(0)	0(0)	5 (1)
HYPERKERATOSIS	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1 (0)	1 (0)	0(0)	0(0)	0(0)	2 (0)
HYPERTRICHOSIS	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(0)	0(0)	0(0)	0(0)	0(0)	2(0)
HYPOESTHESIA	5 (2)	0 (0)	1 (0)	0 (0)	0 (0)	6 (2)	17 (4)	6 (1)	0 (0)	0 (0)	0 (0)	22 (5)
LESION SKIN	6 (2)	3 (1)	0 (0)	0 (0)	0 (0)	9 (4)	5 (1)	4 (1)	0 (0)	0 (0)	0 (0)	9 (2)
PARESTHESIA	9 (4)	0 (0)	2 (1)	0 (0)	0 (0)	11 (5)	30 (7)	7 (2)	0 (0)	0 (0)	0 (0)	34 (8)
PIGMENTATION ABNORMAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
PRURITIC ERYTHEMA	2 (1)	2 (1)	0 (0)	0 (0)	0 (0)	4 (2)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	4 (1)
PRURITUS	41 (17)	16 (7)	2 (1)	0 (0)	0 (0)	57 (24)	93 (23)	58 (14)	2 (0)	0 (0)	0 (0)	145 (35)
PUSTULE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0	0 (0)	0 (0)	1 (0)
RASH	68 (28)	37 (15)	5 (2)	0 (0)	0 (0)	96 (40)	134 (33)	86 (21)	9 (2)	0 (0)	0 (0)	198 (48)
RASH ERYTHEMATOUS	13 (5)	8 (3)	0 (0)	0 (0)	0 (0)	20 (8)	19 (5)	18 (4)	0 (0)	0 (0)	0 (0)	36 (9)
RASH FOLLICULAR	7 (3)	2 (1)	0 (0)	0 (0)	0 (0)	9 (4)	5 (1)	3 (1)	0 (0)	0 (0)	0 (0)	8 (2)
RASH MACULO-PAPULAR	18 (7)	9 (4)	0 (0)	0 (0)	0 (0)	26 (11)	35 (9)	21 (5)	0 (0)	0 (0)	0 (0)	51 (12)
RASH PURPURIC	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	4 (1)	3 (1)	0 (0)	0 (0)	0 (0)	7 (2)
RASH PUSTULAR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	2 (0)	0 (0)	0 (0)	0 (0)	4 (1)
RED-MAN SYNDROME	4 (2)	0 (0)	0 (0)	0(0)	0(0)	4 (2)	2 (0)	0 (0)	0(0)	0(0)	0(0)	2 (0)
SKIN DISCOLORATION	4 (2)	0 (0)	0 (0)	0(0)	0(0)	4 (2)	5 (1)	2 (0)	0(0)	0(0)	0(0)	7 (2)
SKIN DISORDER	0 (0)	0 (0)	0 (0)	0(0)	0(0)	0 (0)	1 (0)	0(0)	0(0)	0(0)	0(0)	5 (1)
SKIN DRY	24 (10)	1 (0)	0 (0)	0(0)	0(0)	25 (10)	26 (6)	5 (1)	0(0)	0(0)	0(0)	31 (8)
SKIN EXFOLIATION	13 (5)	12 (5)	3 (1)	0(0)	0(0)	26 (11)	30 (7)	19 (5)	0(0)	0(0)	0(0)	46 (11)
SKIN HYPERPIGMENTATION	8 (3)	2 (1)	1 (0)	0(0)	0(0)	10 (4)	17 (4)	5 (1)	0(0)	0(0)	0(0)	22 (5)
SKIN HYPERTROPHY	1 (0)	0(0)	0(0)	0(0)	0(0)	1 (0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
SKIN ULCERATION	9 (4)	4 (2)	0(0)	0(0)	0(0)	13 (5)	4 (1)	5 (1)	0(0)	0(0)	0(0)	8 (2)
SWEATING	6 (2)	2 (1)	0(0)	0(0)	0(0)	8 (3)	16 (4)	3 (1)	0(0)	0(0)	0(0)	19 (5)
URTICARIA	2 (1)	1 (0)	0(0)	0 (0)	0 (0)	3 (1)	5 (1)	2 (0)	0 (0)	0 (0)	0 (0)	7 (2)
WARM SENSATION	4 (2)	0 (0	0(0)	0 (0)	0 (0)	4 (2)	6 (1)	2 (0)	0 (0)	0 (0)	0 (0)	8 (2)

Table 7-57 Summary of Incidence Skin-Related Adverse Events Hematologic Malignancy Safety Pool B

Table 7.57 Summary of Incidence Skin-Related Adverse Events Hematologic Malignancy Safety Pool B

N (%)	First Period of Dosing				Second Period of Dosing			
	Placebo	Palifermin			Placebo	Palifermin		
		Pre	Pre Post	Total		Pre	Pre Post	Total
	(N=241)	(N=180)	(N=229)	(N=409)	(N=239)	(N=179)	(N=228)	(N=407)
Number of Subjects with Skin Related Adverse Events	122 (51)	121 (67)	146 (64)	267 (65)	159 (67)	83 (46)	189 (83)	272 (67)
EDEMA FACE	1 (0)	12 (7)	23 (10)	35 (9)	16 (7)	4 (2)	12 (5)	16 (4)
EDEMA PERIORBITAL	4 (2)	4 (2)	4 (2)	8 (2)	3 (1)	4 (2)	2 (1)	6 (1)
EDEMA PERIPHERAL	27 (11)	22 (12)	48 (21)	70 (17)	56 (23)	16 (9)	53 (23)	69 (17)
ERYTHEMA	20 (8)	31 (17)	51 (22)	82 (20)	36 (15)	14 (8)	57 (25)	71 (17)
FLUSHING	25 (10)	14 (8)	30 (13)	44 (11)	23 (10)	3 (2)	24 (11)	27 (7)
HOT FLUSHES	3 (1)	1 (1)	0 (0)	1 (0)	1 (0)	0 (0)	4 (2)	4 (1)
HYPERESTHESIA	1 (0)	1 (1)	4 (2)	5 (1)	2 (1)	0 (0)	0 (0)	0 (0)
HYPERKERATOSIS	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	1 (1)	0 (0)	1 (0)
HYPERTRICHOSIS	0 (0)	2 (1)	0 (0)	2 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HYPOESTHESIA	5 (2)	5 (3)	11 (5)	16 (4)	2 (1)	1 (1)	6 (3)	7 (2)
LESION SKIN	2 (1)	1 (1)	1 (0)	2 (0)	7 (3)	4 (2)	3 (1)	7 (2)
PARESTHESIA	6 (2)	11 (6)	15 (7)	26 (6)	5 (2)	2 (1)	9 (4)	11 (3)
PIGMENTATION ABNORMAL	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PRURITIC ERYTHEMA	1 (0)	1 (1)	0 (0)	1 (0)	3 (1)	1 (1)	2 (1)	3 (1)
PRURITUS	18 (7)	28 (16)	32 (14)	60 (15)	41 (17)	18 (10)	78 (34)	96 (24)
PUSTULE	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
RASH	34 (14)	50 (28)	42 (18)	92 (22)	71 (30)	35 (20)	95 (42)	130 (32)
RASH ERYTHEMATOUS	9 (4)	8 (4)	5 (2)	13 (3)	13 (5)	6 (3)	20 (9)	26 (6)
RASH FOLLICULAR	1 (0)	0 (0)	1 (0)	1 (0)	8 (3)	4 (2)	3 (1)	7 (2)
RASH MACULO-PAPULAR	6 (2)	6 (3)	8 (3)	14 (3)	23 (10)	13 (7)	25 (11)	38 (9)
RASH PURPURIC	0 (0)	2 (1)	0 (0)	2 (0)	3 (1)	2 (1)	3 (1)	5 (1)
RASH PUSTULAR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)	4 (1)
RED-MAN SYNDROME	2 (1)	0 (0)	1 (0)	1 (0)	2 (1)	1 (1)	0 (0)	1 (0)
SKIN DISCOLORATION	1 (0)	0 (0)	3 (1)	3 (1)	3 (1)	1 (1)	3 (1)	4 (1)
SKIN DISORDER	0 (0)	1 (1)	1 (0)	2 (0)	0 (0)	2 (1)	1 (0)	3 (1)
SKIN DRY	7 (3)	3 (2)	10 (4)	13 (3)	19 (8)	8 (4)	10 (4)	18 (4)
SKIN EXFOLIATION	1 (0)	2 (1)	2 (1)	4 (1)	25 (10)	10 (6)	33 (14)	43 (11)
SKIN HYPERPIGMENTATION	2 (1)	1 (1)	5 (2)	6 (1)	8 (3)	3 (2)	13 (6)	16 (4)
SKIN HYPERTROPHY	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SKIN ULCERATION	1 (0)	0 (0)	0 (0)	0 (0)	12 (5)	3 (2)	5 (2)	8 (2)
SWEATING INCREASED	2 (1)	2 (1)	1 (0)	3 (1)	6 (3)	3 (2)	13 (6)	16 (4)
URTICARIA	1 (0)	0 (0)	1 (0)	1 (0)	2 (1)	3 (2)	3 (1)	6 (1)
WARM SENSATION	3 (1)	2 (1)	4 (2)	6 (1)	1 (0)	0 (0)	2 (1)	2 (0)

The First Period of Dosing is from the date of initiation of investigational product (IP) to the day before the first IP dose after PBSCT. If a subject did not receive IP on or after PBSCT, the First Period of Dosing is considered ended on the day before PBSCT (the date of PBSCT for 189). Second Period of Dosing is from the day after the First Period of Dosing to the end of study.

Table 7-58 Summary of Time to Onset and Duration of Skin-Related Adverse Events Hematologic Malignancy Safety Pool B

Table 7.58 Summary of Time to Onset and Duration of Skin-Related Adverse Events Hematologic Malignancy Safety Pool B								
	First Period of Dosing				Second Period of Dosing			
	Placebo	Palifermin			Placebo	Palifermin		
		Pre	Pre Post	Total		Pre	Pre Post	Total
	(N=241)	(N=180)	(N=229)	(N=409)	(N=239)	(N=179)	(N=228)	(N=407)
Time to Onset (Days) Number subject with time to onset	201	223	357	580	488	182	583	765
Mean	6.9	5.1	5.5	5.4	8.8	8.8	8.0	8.2
SD	2.8	2.6	2.7	2.7	6.4	5.8	6.6	6.4
Median	7	4	5	4	8	8	6	7
Q1, Q3	5, 9	3, 7	3, 8	3, 8	5, 11	5, 12	3, 10	4, 11
Min, Max	1, 16	1, 11	1, 12	1, 12	1, 52	1, 32	1, 37	1, 37
Duration Days Number subject data available	198	218	357	575	486	178	580	758
Mean	7.3	8.1	9.4	8.9	6.6	9.3	7.2	7.7
SD	9.3	10.6	10.3	10.5	6.4	7.7	7.1	7.3
Median	3	4	4	4	5	7	5	6
Q1, Q3	1, 9	2, 9	2, 14	2, 13	2, 9	3, 14	2, 10	2, 10
Min, Max,	1, 61	1, 52	1, 52	1, 52	1, 36	1, 34	1, 41	1, 41

The First Period of Dosing is from the date of initiation of investigational product (IP) to the day before the first IP dose after PBSCT. If a subject did not receive IP on or after PBSCT, the First Period of Dosing is considered ended on the day before PBSCT (the date of PBSCT for 189). Second Period of Dosing is from the day after the First Period of Dosing to the end of study. Time to AE onset is relative to the date of the IP administration in the period the AE started. Duration is the time from AE onset to AE resolution. If an AE is continuing and a resolution date is not present, the resolution date is imputed as the end of study date.

COMMENT: *The majority of skin-related adverse events are categorized as mild to moderate in severity; only 5% of skin adverse events in both palifermin subjects and placebo subjects were categorized as severe.*

Skin related adverse events were as likely to occur after the initial 3 doses of palifermin as they were after the post transplant 3 doses of palifermin. The median onset of skin toxicity after the initial 3 doses of palifermin was 4 to 5 days. The median onset of skin toxicity after the post transplant 3 doses of palifermin was 6 to 8 days. The median duration of skin toxicity after the initial 3 doses of palifermin was 4 days. The median duration of skin toxicity after the post transplant 3 doses of palifermin was 5 to 7 days.

Amgen analyzed adverse events in subjects older than 64 years. There were 9 subjects included in the Transplant Safety Pool B in this age group (eCTD 5.3.5.2.1, Integrated Safety Analysis pages 226). The abridged tables below summarize oral and skin related adverse events for this age group.

Table 7-59 Summary of Incidence Oral Related Adverse Events Subjects ≥ 65 Hematologic Malignancy Safety Pool B

Table 7.59 Summary of Incidence Oral Related Adverse Events Subjects ≥ 65 Hematologic Malignancy Safety Pool B		
N (%)	Placebo n = 5	Palifermin n = 9
GINGIVITIS	0 (0)	1 (11)
HEMORRHAGE ORAL	1 (20)	0 (0)
LESION ORAL	0 (0)	1 (11)
SALIVA DECREASED	1 (20)	2 (22)
TASTE LOSS	0 (0)	2 (22)
TASTE PERVERSION	0 (0)	1 (11)
TONGUE DISORDER	0 (0)	1 (11)

Table 7-60 Summary of Incidence Skin Related Adverse Events Subjects ≥ 65 Hematologic Malignancy Safety Pool B

Table 7.60 Summary of Incidence Skin Related Adverse Events Subjects ≥ 65 Hematologic Malignancy Safety Pool B		
N (%)	Placebo n = 5	Palifermin n = 9
EDEMA FACE	1 (20)	0 (0)
EDEMA PERIPHERAL	3 (60)	3 (33)
ERYTHEMA	1 (20)	3 (33)
FLUSHING	2 (40)	2 (22)
HYPERESTHESIA	0 (0)	1 (11)
PARESTHESIA	0 (0)	1 (11)
PRURITUS	0 (0)	4 (44)
RASH	1 (20)	4 (44)
RASH MACULO-PAPULAR	1 (20)	1 (11)
SKIN DISORDER	0 (0)	1 (11)
SKIN EXFOLIATION	1 (20)	0 (0)
SKIN HYPERPIGMENTATION	0 (0)	1 (11)
SKIN ULCERATION	2 (40)	0 (0)
SWEATING INCREASED	2 (40)	0 (0)

COMMENT: *There does not appear to be excessive skin and oral adverse events in subjects ≥ 65 years enrolled in the studies included in the Transplant Safety Pool B. Definitive conclusions are limited by small number of subjects in this population.*

Amgen analyzed adverse events in the male and female population (eCTD 5.3.5.2.1, Integrated Safety Analysis pages 332, 387). The abridged table below compares male and female subjects from these tables presenting preferred terms for oral and skin related adverse events.

Table 7-61 Summary of Incidence Oral Related Adverse Events Comparing Male and Female Subjects Hematologic Malignancy Safety Pool B

Table 7.61 Summary of Incidence Oral Related Adverse Events Comparing Male and Female Subjects Hematologic Malignancy Safety Pool B				
	Males Total n = 405		Females n = 245	
N (%)	Placebo n = 163	Palifermin n = 242	Placebo n = 78	Palifermin n = 167
CHEILITIS	4 (2)	3 (1)	1 (1)	3 (2)
DRY MOUTH	11 (7)	21 (9)	6 (8)	13 (8)
EDEMA TONGUE	3 (2)	5 (2)	1 (1)	2 (1)
GINGIVAL DISCOLORATION	0 (0)	0 (0)	0 (0)	1 (1)
GINGIVITIS	1 (1)	1 (0)	0 (0)	2 (1)
GLOSSITIS	0 (0)	0 (0)	1 (1)	0 (0)
LESION ORAL	8 (5)	25 (10)	3 (4)	20 (12)
SALIVA ALTERED	3 (2)	5 (2)	0 (0)	1 (1)
SALIVA DECREASED	8 (5)	13 (5)	6 (8)	16 (10)
SALIVA INCREASED	5 (3)	5 (2)	4 (5)	4 (2)
TASTE LOSS	4 (2)	13 (5)	2 (3)	13 (8)
TASTE PERVERSION	190 (6)	21 (9)	4 (5)	20 (12)
THROAT TIGHTNESS	2 (1)	3 (1)	2 (2)	4 (2)
TONGUE DISCOLORATION	3 (2)	7 (3)	2 (3)	6 (4)
TONGUE DISORDER	3 (2)	9 (4)	4 (5)	16 (10)

Table 7-62 Summary of Incidence Skin Related Adverse Events Comparing Male and Female Subjects Safety Pool B

Table 7.62 Summary of Incidence Skin Related Adverse Events Comparing Male and Female Subjects Hematologic Malignancy Safety Pool B				
N (%)	Males Total n = 405		Females n = 245	
	Placebo n = 163	Palifermin n = 242	Placebo n = 78	Palifermin n = 167
EDEMA FACE	9 (6)	22 (9)	8 (10)	25 (15)
EDEMA PERIORBITAL	2 (1)	7 (3)	5 (6)	6 (4)
EDEMA PERIPHERAL	46 (28)	65 (27)	30 (38)	56 (34)
ERYTHEMA	33 (20)	76 (31)	19 (24)	55 (33)
FLUSHING	34 (21)	41 (17)	9 (12)	21 (13)
HOT FLUSHES	1 (1)	2 (1)	1 (1)	3 (2)
HYPERESTHESIA	2 (1)	1 (0)	1 (1)	4 (2)
HYPERKERATOSIS	0 (0)	2 (1)	0 (0)	0 (0)
HYPERTRICHOSIS	0 (0)	2 (1)	0 (0)	0 (0)
HYPOESTHESIA	5 (3)	10 (4)	1 (1)	12 (7)
LESION SKIN	6 (4)	6 (2)	3 (4)	3 (2)
PARESTHESIA	7 (4)	17 (7)	4 (5)	17 (10)
PIGMENTATION ABNORMAL	0 (0)	1 (0)	0 (0)	0 (0)
PRURITIC ERYTHEMA	4 (2)	3 (1)	0 (0)	1 (1)
PRURITUS	38 (23)	85 (35)	19 (24)	60 (36)
PUSTULE	0 (0)	1 (0)	0 (0)	0 (0)
RASH	69 (42)	113 (47)	27 (35)	85 (51)
RASH ERYTHEMATOUS	11 (7)	21 (9)	9 (120	16 (10)
RASH FOLLICULAR	8 (5)	7 (3)	1 (1)	1 (1)
RASH MACULO-PAPULAR	17 (10)	35 (14)	9 (12)	16 (10)
RASH PURPURIC	0 (0)	4 (2)	3 (4)	3 (2)
RASH PUSTULAR	0 (0)	4 (2)	0 (0)	0 (0)
RED-MAN SYNDROME	3 (2)	1 (0)	1 (1)	1 (1)
SKIN DISCOLORATION	3 (2)	3 (1)	1 (1)	4 (2)
SKIN DISORDER	0 (0)	4 (2)	0 (0)	1 (1)
SKIN DRY	18 (11)	19 (8)	7 (9)	12 (7)
SKIN EXFOLIATION	13 (8)	25 (10)	13 (17)	21 (13)
SKIN HYPERPIGMENTATION	5 (3)	8 (3)	5 (6)	14 (8)
SKIN HYPERTROPHY	1 (1)	0 (0)	0 (0)	0 (0)
SKIN ULCERATION	10 (5)	5 (2)	3 (4)	3 (2)
SWEATING INCREASED	6 (4)	12 (5)	2 (3)	7 (4)
URTICARIA	1 (1)	4 (2)	2 (3)	3 (2)
WARM SENSATION	2 (1)	4 (2)	2 (3)	4 (2)

COMMENT: *There were no meaningful differences in the overall incidence of skin and oral toxicity, or of specific types of oral or skin toxicity based on sex of the subject.*

7.1.6 Less Common Adverse Events

Given the high back ground incidence of adverse events and otherwise rare adverse events seen in the transplant setting, a significant but rare event with an incidence < 1 % will be difficult to detect. The following table lists all adverse events that occurred in less than 2% of subjects and occurred in ≥0.4% in the palifermin subjects compared to placebo subjects in Safety Pool B. This list excludes oral and skin adverse events, laboratory value abnormalities, infections known to occur during transplant, psychiatric complaints common during transplant, pain (discussed in Other Search Strategies Section [7.1.4]), dysesthesias (discussed in Common Adverse Events Section [7.1.5], arthralgias and arthritis (discussed in Common Adverse Events Section [7.1.5]).

Table 7-63 Less Common Adverse Events in Transplant Hematologic Malignancy Safety Pool B

Table 7.63 Less Common Adverse Events in Transplant Hematologic Malignancy Safety Pool B		
N (%)	**Placebo n = 241**	**Palifermin n = 409**
Body as a Whole		
Graft versus Host	0 (0)	5 (1)
Engraftment Syndrome	0 (0)	3 (1)
Ascites	1 (<1)	5 (1)
Cardiovascular		
Cardiomegally	0 (0)	1 (<1)
CNS/PNS		
Convulsions	0 (0)	2 (<1)
Trigeminal Neuralgia	0 (0)	1 (<1)
Extrapyramidal Disorder	0 (0)	1 (<1)
Endocrine		
Goiter	0 (0)	1 (<1)
Gastrointestinal		
Fecal Incontinence	0 (0)	2 (<1)
Duodenitiis	0 (0)	1 (<1)
Abdominal Hernia	0 (0)	3 (1)
Intestinal Perforation	0 (0)	1 (<1)
Proctitis Ulcerative	0 (0)	1 (<1)
Hearing/Vestibular		
Otitis Externa	0 (0)	1 (<1)
Ear Disorder	0 (0)	1 (<1)
Deafness	0 (0)	1 (<1)
Heart Rate/Rhythm		
ECG Abnormal	0 (0)	1 (<1)
Extrasystole	2 (1)	8 (2)
Liver and Bilary		
Cholecystitis	0 (0)	1 (<1)
Metabolism Nutrition		
Diabetes Mellitus	0 (0)	1 (<1)

Table 7.63 Less Common Adverse Events in Hematologic Malignancy Safety Pool B continued		
Myo/Epi/Endocardial		
Pericardial effusion	0 (0)	4 (1)
Reproductive		
Menstrual Disorder	0 (0)	3 (2) [167]
Vaginal Dryness	0 (0)	2 (1) [167]
Prostatic Disorder	0 (0)	1 (<1) [241]
Respiratory		
Cyanosis	0 (0)	2 (<1)
Special Senses		
Parosmia	0 (0)	1 (<1)
Urinary Disorders		
Hydronephrosis	0 (0)	1 (<1)
Renal Calculus	0 (0)	1 (<1)
Micturition Disorder	0 (0)	2 (<1)
Urinary Urgency	0 (0)	2 (<1)
Vascular Disorder		
Superior Vena Cave Syndrome	0 (0)	1 (<1)
Vision Disorder		
Uveitis	0 (0)	1 (<1)
Sty	0 (0)	1 (<1)

COMMENT: *The notable signals of concern from this analysis are Graft versus Host disease and Engraftment Syndrome, which were only identified in the palifermin subjects. These syndromes are distinct, but probably share underlying mechanisms of pathogenesis. Graft versus Host Disease is a multi-step process which is the result of tissue injury including injury by cytokines such as IL –1, IL-6, TNF-α. This leads recruitment of activated T lymphocytes and release of IL –2 and subsequent release of more secretory cytokines including IL-1, TNF-α, and IFN-γ. The result is target tissue damage. Engraftment syndrome is thought to be result of cellular interaction of T lymphocytes and monocytes that leads complement activation and cytokine production and release. Cytokines implicated include IL-1, TNF-α, and IFN-γ. In this setting, during neutrophil recovery, neutrophils may be sequestered in the lungs. As sequestered neutrophils degranulate, systemic tissue injury (capillary leak) may result. (Spitzer 2001)*

Amgen is seeking approval for palifermin in the transplant setting. The label states palifermin "is indicated . . . in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support." The studies to support licensure of palifermin have been conducted in the autologous transplant setting; however, the label indication could be interpreted to include allogeneic transplants. Based on this signal, additional analysis of the relationship of palifermin to Graft versus Host Disease was warranted.

Based on this analysis, this issue was discussed with Amgen. Amgen performed an analysis of the subjects identified with engraftment syndrome and autologous graft-versus-host disease. A summary of this analysis was sent by facsimile on 11/9/04. This analysis was discussed with Amgen during a telephone conference 11/12/04. The engraftment syndrome is a recently identified transplant complication and the 3 cases were all reported from a single institution on

subjects enrolled on an open label pharmacokinetic study. Amgen's analysis of the subjects reported to have autologous graft-versus-host indicated that timing of the graft-versus-host reaction was not consistent with hematologic recovery in these subjects.

The 120-Day Safety report contained the results of a randomized placebo controlled trial of palifermin in the allogeneic transplant setting (see Section 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety). The hypothesis of this study was that by decreasing mucositis palifermin would decrease the incidence of graft-versus-host disease. There was no indication that palifermin decreased the incidence of graft-versus-host disease nor was there an indication that palifermin-treated subjects experienced more graft-versus-host disease.

Based on this information, additional confirmation of the safety of palifermin in the allogeneic setting is not required.

7.1.7 Laboratory Findings

With the exception of amylase and lipase, which are discussed in detail in section 7.1.3.3 Other significant adverse events, no laboratory abnormalities appear to be associated with palifermin treatment. Serum chemistry assessments included albumin, ALT, AST, bilirubin, creatinine, LDH, and total protein. The mean and median baseline LDH values in most of the subjects were out of the normal range at baseline and remained relatively unchanged by the end of study evaluation, as would be expected in a transplant setting. In general, serum chemistry results were similar between placebo and palifermin subjects. There was no evidence that palifermin delays hematopoetic reconstitution after transplantation.

7.1.7.1 Overview of laboratory testing in the development program

The specific schedules of laboratory testing and the individual required tests included in the palifermin development program are specified in Section 7.1.5.1 Eliciting adverse events data in the development program. In general testing included:

1. Complete Blood Count performed at baseline, and after blood counts dropped due to transplant regimen, performed daily until recovery. Schedules varied in solid tumor settings appropriate to Chemotherapy and Radiation therapy schedules.
2. Standard Comprehensive Chemistry panel: the exact tests required varied among protocols. Tests were performed at baseline, then generally performed weekly.
3. Amylase and Lipase Schedules varied with trial and as kinetics of elevation of these enzymes became clearer. In later studies these were performed at outside laboratories in order to protect blinding of study.
4. Urinalysis was only included in Colorectal Cancer Studies early in drug development.
5. Anti- KGF antibody testing was collected at baseline then at later intervals.

The data set used to evaluate laboratory findings consisted of a line for each individual required test. There were six data sets for the transplant safety pool B, one for the Head and Neck Cancer

Safety Pool D, and two for the Colorectal Cancer Safety Pool F. The data for each subject consisted of 10 to 644 lines, a line for each individual test. Among the items a line of data included were date the test was obtained, normal values for the test, subject information, day of study, and a column indicating if test was high, low or normal.

Laboratory measurements taken prior to the end of study visit were used in the safety assessment. The following chemistry values were analyzed: Amylase, Lipase, Bilirubin, Total Protein, Albumen, Creatinine, LDH, AST, and AST. The following hematologic parameters were analyzed: Absolute Neutrophil Count (ANC), White Blood Count, Platelet Count, and Hemoglobin.

Evaluation of the completeness of laboratory data is presented below:

Hematologic Malignancy Studies

Table 7-64 Hematologic Malignancy Safety Pool B Subjects with Baseline Laboratory Values and Subsequent Post investigational Agent Administration Laboratory Values

Table 7.64 Hematologic Malignancy Safety Pool B Subjects with Baseline Laboratory Values and Subsequent Post investigational Agent Administration Laboratory Values				
Laboratory Value	**Placebo n = 241**		**Palifermin n = 409**	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
Amylase	231	239	391	409
Lipase	170	181	274	292
Bilirubin	238	241	399	408
Total Protein	232	241	399	408
Albumen	231	241	389	408
Creatinine	241	241	407	408
LDH	222	241	386	408
AST	237	241	395	408
ALT	226	241	401	408
ANC	235	241	402	408
WBC	238	241	410	409
Hgb	241	241	410	409
Platelet	238	241	410	409

Solid Tumor Studies:

Table 7-65 Head and Neck Cancer Safety Pool D Subjects with Baseline Laboratory Values and Subsequent Post Investigational Agent Administration Laboratory Values

Table 7.65 Head and Neck Cancer Safety Pool D Subjects with Baseline Laboratory Values and Subsequent Post Investigational Agent Administration Laboratory Values				
Laboratory Value	Placebo n = 46		Palifermin n = 114	
	Baseline	Follow-up	Baseline	Follow-up
Amylase	41	36	101	88
Lipase	37	44	104	104
Bilirubin	46	45	113	101
Total Protein	46	45	111	100
Albumen	46	45	110	100
Creatinine	46	45	113	102
LDH	44	41	111	97
AST	46	45	112	101
ALT	45	44	111	99
ANC	45	46	112	112
WBC	45	46	114	112
Hgb	45	46	114	112
Platelet	45	46	113	112

Table 7-66 Colorectal Cancer Safety Pool F Subjects with Baseline Laboratory Values and Subsequent Post Investigational Agent Administration Laboratory Values

Table 7.66 Colorectal Cancer Safety Pool F Subjects with Baseline Laboratory Values and Subsequent Post Investigational Agent Administration Laboratory Values				
Laboratory Value	Placebo n = 63		Palifermin n = 82	
	Baseline	Follow-up	Baseline	Follow-up
Amylase	62	60	79	80
Lipase	60	60	81	80
Bilirubin	63	63	82	82
Total Protein	63	63	82	82
Albumen	63	63	82	82
Creatinine	63	63	82	82
LDH	62	63	82	82
AST	63	63	82	82
ALT	62	63	80	82
ANC	62	63	82	82
WBC	62	63	82	82
Hgb	62	63	82	82
Platelet	62	63	82	82

COMMENT: *The vast majority of Transplant Safety Pool B subjects exposed to investigational agent had baseline and follow-up laboratory values. The exception was lipase, 32% of this data was missing. The explanation for this exception was that lipase was not a required study for cohort 1- 10 of Trial 960189, and only was collected in the final cohort. This accounts for most of the missing values. In the solid tumor setting, at least 94% of the baseline and follow up laboratory values were in the data set.*

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

As in the analysis of Adverse Events, virtually every subject is expected to have laboratory abnormalities as a consequence of chemotherapy and radiotherapy. Therefore all laboratory abnormalities in palifermin subjects were analyzed in comparison with the placebo subjects. Laboratory parameters were presented as tables of summary statistics, and the median and mean of each individual test was graphically displayed at the time points of testing. In addition amylase and lipase, and absolute netrophil count were displayed in shift tables.

Shift Tables displayed the maximum shift in toxicity grade. Laboratory toxicity was graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0. The grading criteria for LDH and Total Protein are not specified in CTCAE. These two labs were graded using Amgen modified WHO adverse events grading scale. If available, the laboratory normal ranges from the study center laboratory were used. If not available, the normal ranges of the central lab were applied.

Summary Statistics were presented for the each of the following items: baseline value, lab values at selected study time points and change in lab value from baseline to the selected time points. Graphic displays were used to present the data as a comparison of median, and values, comparing placebo to palifermin subjects on specific transplant days.

The Safety pools used for this analysis are the same as those in the adverse event analysis. The Transplant Safety Pool B contains all subjects that received investigational agent in the 4 transplant studies. The solid tumor subjects who received investigational agent are analyzed in Head and Neck Cancer Safety Pool D and Colorectal Cancer Safety Pool F.

7.1.7.3 Standard analyses and explorations of laboratory data

Amgen's tables for Transplant Safety Pool B summarizing the mean, median and interquartile values at time points tested, a graphic view of the median, mean and interquartile range are included in Appendix 10.3 Clinical Review Laboratory Values. For the Solid Tumor Head and Neck Cancer Safety Pool D and the Colorectal Cancer Safety Pool F the Graphic view of the median, mean and interquartile range results is included in Appendix 10.3 Clinical Review Laboratory Values.

Healthy Volunteer Studies:
The only laboratory values that were abnormal in the Healthy Volunteer population were amylase and lipase. Review of these is contained in Section 7.1.3 Laboratory abnormalities not meeting the definition of serious.

7.1.7.3.1 Analyses focused on measures of central tendency

See Appendix 10.3 Clinical Review Laboratory

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

See Appendix 10.3 Clinical Review Laboratory

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no subjects in the hematologic Hematologic Malignancy Safety Pool B who dropped out of a study due to laboratory abnormality. In the Head and Neck Cancer Safety Pool D one subject discontinued palifermin due to liver and renal failure and one discontinued palifermn due to jaundice. In the Colorectal Cancer Safety Pool F one subject was removed from study due to hyperbilirubinemia. These abnormalities were not categorized as due to investigational agent.

As a method to search for outliers the laboratory data sets of Safety Pool B, D and F were searched for grade 4 (CTCAE) toxicity for the following laboratory tests: bilirubin (>10X ULN), Creatinine (>6 X ULN), AST (>20X ULN), AST (20X ULN).

Hematologic Malignancy Studies:
There was one placebo subject with bilirubin 12.9 X ULN, and one palifermin subject with bilirubin 15.4 X ULN. The palifermin subject was diagnosed as having VOD. There is no signal that VOD is more frequent in the palifermn subjects. (See Section 7.1.5.2 Appropriateness of adverse event categorization and preferred terms.) There was one placebo subject with creatinine 6.1 X ULN. There was one palifermin subject with an AST 180 X ULN. This is the subject described above with VOD. There was one placebo subject with an ALT 29.8 X ULN.

The signal that would be clinically significant as a Hematologic laboratory outlier is failure to reconstitute an ANC > 500/UL by day 28. Review of Transplant Safety Pool B identified only one subject (on the placebo arm) who did not develop an ANC greater than 500/UL by day 28.

Solid Tumor Studies:
In Head and Neck Cancer Safety Pool D, there were no Grade 4 abnormalities in these laboratory tests. In Colorectal Cancer Safety Pool F, there was one palifermin subject with creatinine 9.5 X ULN. This subject underwent dialysis recovered and received a second cycle of palifermin.

7.1.7.4 Additional analyses and explorations

Amylase and Lipase:
Based on a review of data in the Pharmacokinetic and pharmacodynamic studies of palifermin in

normal volunteers, there was evidence of a dose relationship of palifermin on amylase of lipase at the highest cumulative levels. (See section 7.1.3.3 Other significant adverse events.) These are the only laboratory tests significantly affected by palifermin.

7.1.7.5 Special assessments

The only laboratory abnormalities that require special assessment are the elevations of amylase and lipase which are discussed in 7.1.2 Other significant adverse events.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were collected and analyzed in the dose escalation Transplant Study 960189. In the other trials, abnormal vital signs were reported as adverse events.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital signs were collected and analyzed prospectively, only in Study 960189.

7.1.8.3 Standard analyses and explorations of vital signs data

The vital signs analyzed in Study 960189 included systolic and diastolic blood pressure, resting pulse, and temperature. In this study, mean and median changes in vital signs from baseline and end of study were analyzed.

7.1.8.3.1 Analyses focused on measures of central tendencies

There were no consistent trends seen in the analysis of resting pulse and temperature at base line and end of study comparing placebo to palifermin, comparing dosing schedules or dose escalation of palifermin.

Amgen's analysis of blood pressure from Study 960189 is as follows (eCTD 5.3.5.1.2, Clinical Study Report 960189 page 158):
"Mean and median changes in systolic and diastolic blood pressure from baseline were similar between treatment groups and within palifermin dose groups In all groups, systolic and diastolic blood pressures increased during the study, primarily during the postchemotherapy period, but returned to baseline levels at the end of study. Median maximum changes from baseline to the end of study for systolic blood pressure were 20, 20, and 26 mmHg for subjects in the placebo, palifermin pre, and palifermin pre-post groups, respectively; and median maximum changes from baseline to the end of study for diastolic blood pressure were 10, 10, and 15 mmHg for subjects in the placebo, palifermin pre, and palifermin pre-post groups, respectively. A dose effect was observed; the highest median (range) maximum changes from baseline in systolic and

diastolic blood pressures were observed in the 80 µg/kg/day palifermin pre-post cohort: 38.0 (10, 70) mmHg and 20 (6, 30) mmHg, respectively."

During the prechemotherapy, hypertension was reported as an adverse event in 2% (3/177) of the palifermin-treated subjects compared with none in the placebo group. During the postchemotherapy period, hypertension was reported in 4% (5/123) of the subjects in the palifermin pre group, 10% (5/52) of the subjects in the palifermin pre-post group, and 7% (6/83) of the subjects in the placebo group. These events were primarily reported as mild to moderate in severity, were not considered by the investigator to be related to investigational product, and resolved with treatment.

Also during the postchemotherapy period, a possible dose-response relationship for hypertension was observed in the palifermin pre-post dosing schedule. The proportion of palifermin-treated subjects with an adverse event of hypertension increased with increasing dose: 0% (20 µg/kg/day), 9% (40 µg/kg/day), 13% (60 µg/kg/day), and 14% (80 µg/kg/day cohort) compared with 9% in the placebo group."

This result is also discussed in the clinical reviewer comment found in Section 7.1.4.2 Search based on preclinical toxiclogy findings and Section 3.2.2.3.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

In Study 960189 the subjects with extreme values for blood pressure were reviewed. There were 15 subject with systolic blood pressure ≥ to 170 mmHg, 2 (2%) placebo compared to 13 (7%) palifermin. There were 10 subjects with diastolic ≥ 110mmHg, 3 (3%) placebo and 7 (4%) palifermin.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no dropouts from any palifermin studies due to hypertension.

7.1.8.4 Additional analyses and explorations

Hematologic Malignancy Studies:

Hematologic Malignancy Safety Pool B, which includes subjects from Study 960189, was reviewed. The incidence of hypertension reported as an adverse event was 5% in the placebo subjects and 7% in the palifermin subjects.

Solid Tumor Studies:

Head and Neck Safety Pool D was reviewed. The incidence of hypertension reported as an adverse event was 2% in the placebo subjects and 2% in the palifermin subjects. In the Colorectal Safety Pool F only one incident of hypertension was reported in a placebo subject.

Healthy Volunteer Studies:

Palifermin has been administered to a total of 160 healthy subjects in 6 clinical pharmacology studies. A wide range of palifermin doses (0.2 to 250 µg/kg) was administered in these clinical pharmacology studies, with most subjects receiving a single dose. Vital signs were monitored in these trials. Amgen reports there were no clinically significant changes in vital signs (eCTD 2.7.4, Summary of Clinical Safety page 184).

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The only therapeutic trial of palifermin that monitored ECG was Study 950225 in Colorectal Cancer. ECG's were obtained at baseline and within 3 months. No comments on abnormalities were noted in the final study report (eCTD 5.3.5.4.1, Clinical Study Report 950225 page 257).

Healthy Volunteer Studies:

Palifermin has been administered to a total of 160 healthy subjects in 6 clinical pharmacology studies. A wide range of palifermin doses (0.2 to 250 µg/kg) was administered in these clinical pharmacology studies, with most subjects receiving a single dose. No clinically significant changes in ECGs were reported in the clinical pharmacology studies (eCTD 2.7.4, Summary of Clinical Safety page 184).

This assessment of ECG was adequate. Palifermn is not a drug that would be expected to cause conduction abnormalities, and a more detailed analysis of ECG studies is not required.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

These evaluations were not done and are not appropriate for this drug, as palifermn is not a drug that would be expected to cause conduction abnormalities.

7.1.9.3 Standard analyses and explorations of ECG data

The following evaluations were not done and are not appropriate for this drug, as palifermn is not a drug that would be expected to cause conduction abnormalities.

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.4 Additional analyses and explorations

These evaluations were not done and are not appropriate for this drug, as palifermn is not a drug that would be expected to cause conduction abnormalities.

7.1.10 Immunogenicity

As with all therapeutic proteins, palifermin has the potential for immunogenicity.

Immunoassays: Throughout Amgen's trials of palifermin, subjects have been monitored for the development of anti-palifermin antibodies. Amgen has sequentially developed four immunoassays to test for anti-palifermin antibodies in clinical serum samples of subjects who received palifermin.

The table below summarizes the chronology of development and characteristics of each of the assays developed and used in Amgen's Immunogenicity Assay Development Program (eCTD 5.3.5.3.3 Overview of Immunogenicity Testing page 26).

Table 7-67 Types and Comparison of Immunoassays Used in the Palifermin Clinical Program

Table 7.67 Types and Comparison of Immunoassays Used in the Palifermin Clinical Program				
Years of use	Assay Type	Limit of Detection/ Threshold	Positive Control	Characteristics
From 1996 to March 2000	RIA	ND	Rabbit anti-palifermin antisera (linear range between 1:800 to 1:12800 dilution of positive control)	1. low specificity 2. detects only IgG 3. low-affinity antibodies washed away
March 2000 to May 2002	ELISA	— ng/mL	Protein G-purified antipalifermin monoclonal Ab	1. high specificity 2. detects all Igs 3. low-affinity antibodies washed away
May 2002 to February 2004	ECL-based IGEN assay	— ng/mL	Affinity-purified rabbit antipalifermin polyclonal Ab	1. high specificity 2. detects all Igs 3. limited wash steps 4. high throughput
March 2004 to present	ECL-based — assay	~ ng/mL	Affinity-purified rabbit antipalifermin polyclonal Ab	

Note: RIA = radioimmunoassay, ELISA = enzyme-linked immunosorbent assay, ECL = electrochemical luminescence, IGEN = IGEN® International, Inc, Ab = antibody/antibodies, [ ] , ND = not determined

7.1.10.1 Evaluation of the Immunogenicity Testing Assays

The ECL-based[ ] assay was reviewed by CMC. See the CMC memorandum reproduced below:

MEMORANDUM
Date: final rev ver/ 17 Nov 04
From: Ralph M Bernstein
To: File, **STN 125103**
Through: Elizabeth Shores, Amy Rosenberg.
CC: Kurt Stromberg, Lead CMC reviewer STN **125103.**
Re: Review of STN 125103/Palifermin Immunogenicity Assay, Neutralization assay, labeling comments.

Immunogenicity Assay
Overview:
Amgen has submitted a package within the BLA submission for STN 125103 that addresses the validation of techniques developed to monitor the development of antibodies in patients treated with Palifermin/rHuKGF. The method, Amgen number [ ], entitled "Immunoassay to Detect Antibodies in rHuKGF in Human Serum using the [ ] is a bridging assay (herein referred to as the ECL assay) which utilizes two species of recombinant product (Palifermin/KGF) that is both labeled with a detection agent [cation) and [ ] antibody (patient sera) is preincubated with both species in a 96 well format plate, the wells of which are [ ] (see **Figure 1**, attached at end of document)[not included in this document]. If there is reactive antibody present in the wells, a bridge is formed between the [ ]Palifermin and the detection agent bound Palifermin. The addition of a substrate [ ] and an electrical current allows detection and quantification of the antibodies.

Assay components:
Negative control: pooled normal human serum (pNHS), diluted to 20% in assay diluent buffer, is used as the assay negative control. New lots of pNHS are tested against the current lot, and only lots with less than a 20% variance in raw ECL signal are used.

Positive control: affinity purified rabbit anti rHuKGF is diluted into neat pNHS to —ng/ml, then diluted to 20% in assay diluent. New lots of anti-KGF will be tested against the current lot to ensure a signal above the threshold (see threshold, below).

[ ] rHuKGF: rHuKGF is diluted into assay diluent to — g/ml, aliquots of which are stored at — or colder, and expire after one year post creation date. _ labeling is performed by Amgen's analytical sciences per SOP [ ] Binding of - HuKGF will be compared to that of the non labeled molecule using a [ ] instrument as described in validation report [ ], and the component will not be used if the two components vary more than 20% in binding rates.

[ ] rHuGKF: rHuGKF is diluted into assay diluent to — ng/ml, aliquots of which are stored at — or colder, and expire after one year post creation date. [—] labeling is performed by Amgen's analytical sciences per SOP [ ] Binding of — HuKGF will be compared to that of the non labeled molecule using a [ ] instrument as described in

validation report [ ] and the component will not be used if the two components vary more than 20% in binding rates.

Assay development:
Threshold: the threshold (or cutpoint) for the ECL assay was developed by analyzing the activity of 99 individual pre-treatment patient serum samples in the ECL assay: these samples generate a raw ECL value. This value was divided by the raw ECL value of pNHS also analyzed in the ECL; this value is called the signal to noise ratio, or S/N. All sample reactivity values are expressed in this manner: raw ECL of sample divided by raw ECL of a pNHS control. The mean S/N of these samples was analyzed and the upper bound of a one sided 95% prediction interval (the mean S/N plus 1.645 standard deviations (SD)) was determined to have a numerical value of 1.21. Amgen states that after statistical analysis of the distribution of the S/N values, that the distribution is normal, with no outliers (an outlier being defined as 3 SD from the mean). This is the assay cutpoint. This value allows for a 5% false positive rate, to minimize the occurrence of false negatives.

Assay sensitivity: the sensitivity of the assay was determined using affinity purified (AP) rabbit polyclonal anti rHuKGF. The sensitivity is the amount of antibody that can be detected in the assay above the threshold S/N value of 1.21. Antibody concentrations ranging from — ug/ml to — ng/ml spiked into 100% pNHS demonstrated that — ng/ml exhibited a S/N value of — demonstrating that the assay sensitivity is — ng/ml. See **Table 1**, attached at end of document [not included in this document].

Quantitiation limit: to determine the about of antibody in a given sample that could be reliably detected using the ECL assay, Amgen spiked individual serum samples from patients with hematological malignancies with 25, 50, and 100ng/ml of the rabbit AP anti-rHuKGF antibody. A statistical analysis of the S/N values generated demonstrated that assay variability allowed for the reliable detection of — g/ml of antibody. — ng/ml is the assay's limit of quantification (LOQ); this value has an S/N of —

Assay specificity:

1) Assay specificity was demonstrated using three approaches; the first demonstrated that while soluble rHuKGF preincubated with specific antisera inhibited detection of anti KGF antibodies, unlabled FGF-10 similarly preincubated showed little or no inhibition of signal. In contrast, unlabled FGF-7 (full length KGF) reduced the ECL signal when similarly preincubated, albeit at relatively high concentrations (e.g., 400 and 800 ng/ml, see **Figure 2** [not included in this document]. attached at the end of this document). In the BLA, (section 3-2-r) Amgen states that the dose dependant properties of rHuKGF, the FGF-10 non result, and the relatively uninhibitory result with FGF-7 demonstrates the specificity of the assay for KGF, and not other KGF family members. If anti KGF antibodies were to develop in a patient, this crossreactivity with FGF family members may be a concern for clinicians, but the clinical significance is not understood, and would be hard to predict, as FGF is a large family with some sequence similarities and some limited overlapping functions.

2) The second approach utilized unrelated antibodies, and demonstrated that they, in contract with anti rHuKGF, exhibited signals well below the threshold value of 1.21. This demonstrates that the detection of KGF is due to the specificity of anti KGF antibodies and not background or anomalous antibody binding.

3) Immunodepletion: this test is used to confirm the specificity of antisera that generate a signal above the threshold of 1.21. Amgen determined the concentration of rHuKGF that can reproducibly and significantly reduce the ECL values of specific antibody binding; this was accomplished by spiking pNHS with 100, 800, and 2400ng/ml of anti rHuKGF that was preincubated with increasing concentrations of rHuKGF. Amgen determined that 800ng/ml was effective in reducing wide antibody ranges by 50% or greater. (In all spiked antibody concentrations, Amgen determined that 800ng/ml of rHuKGF reduced the relative signal by greater than 97%).

Qualification and interference of labeling of rHuKGF assay components: a concern regarding the labeling of rHuKGF for use in the assay, is that the modification of the molecule might reduce antisera binding/recognition, or abrogate it completely. To address this issue, Amgen immobilized rHuKGF, — rHuKGF, and — rHuKGF onto a [redacted], and the binding of AP-rabbit polyclonal anti rHuKGF serum was evaluated and determined to have comparable affinities. This analysis suggests that rHuKGF conjugation may not significantly affect the monitoring of anti rHuKGF antibodies in patient samples.

Precision: Amgen demonstrated the intra assay precision (the reproducibility of the assay results regarding an individual sample) of the ECL assay to have a CV of — The inter assay precision (the measure of reproducibility over several days regarding an individual samples) to have a CV of —

Freeze thaw stability: Amgen addressed the issue of sample stability after multiple freeze thaws, by spiking 100 and 800ng/ml of anti rHuKGF antisera into pNHS samples and subjected these samples to — freeze thaw cycles; these experiments demonstrated that 100ng/ml spiked antibody yielded results ranging from [redacted] recovery with a CV of — 800ng/ml spiked antibody yielded results ranging from [redacted] with a — CV.

Assay analysis:
Sample positivity: samples are considered reactive if the S/N is greater than 1.21 (the threshold). Samples with S/N values greater than (the LOQ) are reanalyzed with the immunodepletion test; samples demonstrating a greater than 50% reduction in signal were then designated positive. Patients are considered positive for antibody development if :

Positive and negative reporting criteria: if a sample's S/N is lower than the threshold of 1.21, the sample is termed negative; if a sample's S/N is within the range of 1.21 to — the sample is positive below the quantifiable limit; if a sample's S/N is equal to or greater than — and demonstrates a 50% or greater loss of reactivity in the immunodepletion test, the sample is termed positive; if the sample demonstrates less than 50% reduction in reactivity in the immunodepletion, it is termed negative for anti- rHuGKF antibodies.

Post treatment reporting criteria: if a post treatment sample's S/N is greater than 1.21, and its post treatment to pre treatment ratio is greater than the quantitation threshold of [redacted]. if the sample demonstrates 50% or greater decrease in ECL signal in the immunodepletion test, then they are positive for post treatment development of anti KGF antibodies. Samples that have less than a 50% decrease in their ECL S/N signal in the immunodepletion test are termed negative.

Clinical trial immunogenicity results:
Amgen analyzed 964 patients using the ECL assay; 12 patients (~1%) tested positive above the assay threshold, i.e., 1.21, and were termed reactive. Two of these patients, in studies 980231 and 20000162, were above the LOQ of [redacted] and were tested in the immunodepletion assay; these samples did not have a reduced ECL value in the immunodepletion assay (personal communication 10 Nov 04, Dr. Gene Koren, see telecon notes, R Bernstein 10Nov04) and were suspected by Amgen to be "sticky" or non-specific binders. As per Amgens protocol, all 12 subjects above the threshold value of 1.21 were tested in the bioassay/neautralization assay; none of these subjects demonstrated neutralizing activity as assessed by the bioassay.

Conclusion:
Amgen has validated an anti rHuKGF detection assay that is able to reliably and reproducibly detect antibodies directed to rHuKGF to [redacted] ng/ml sensitivity. It is the opinion of this reviewer that this assay is a reasonably acceptable assay, and will allow the detection of anti rHuKGF antibodies in patient sera. Labeling should reflect the possibility of antisera generated to KGF/Palifermin being cross-reactive with FGF family members, and the potential clinical implications that may be associated with such a possibility.

Neutralization assay
Overview: Amgen has submitted a package within the BLA submission for STN 125103 that addresses the validation of techniques developed to monitor the ability of antibodies that are specific for rHuKGF /KGF to neutralize soluble KGF. The validation package, Amgen numbers [redacted], entitled "Validation of the Bioassay for the detection of Neutralizing antibodies against recombinant human keratinocyte growth factor (rHuKGF) in 1% human serum." and "Re-establishment of thresholds for the screening assay (Ratio 1), the pre-dose to post-dose ratio (ratio 2), and the specificity assay (ratio 3) for the bioassay detecting neutralizing antibodies against tHuKGF." are included in the BLA along with the Amgen analytical procedure [redacted] "A bioassay for the detection of neutralizing antibodies to rHuKGF in human serum." This assay, adapted from the KGF potency assay, uses a KGF/EPO receptor chimera that is stably transfected in a murine 32D cell line. These cells, when treated with KGF, respond in a dose dependant manner. When antibodies specific for KGF are present, it interferes with the ability of the KGF to bind the KGF receptors, thereby inhibiting proliferation ([redacted]. The sensitivity was validated to [redacted]ng/ml of anti KGF antisera in 100% human serum.

Assay validation:
Validation of the rHuKGF dose response using KECA cells: [redacted]

[redacted]

In conclusion: Amgen has developed a neutralization assay which, while not optimal, has acceptable specificity and reproducibility for a neutralization bioassay. Amgen has set the cutpoints for this assay at the [redacted] false positive rate. This should be acceptable in the case of a neutralizing bioassay, due to the similar ranges of [redacted] %. All patients that have been tested in the neutralization/ bioassay have been deemed negative.

7.1.10.2 Evaluation of the Clinical Immunogenicty Testing

The following table is a summary of the ECL testing done on subjects enrolled on Amgen palifermin trials. If ECL tested subjects were previously tested using RIA or ELISA the results of testing with these methods are also included.

Table 7-68 Types and Comparison of Immunoassays Used in the Palifermin Clinical Program

Table 7.68 Summary Subject Testing for Antibody					
Protocol Number (placebo/palifermin)	**Assay**	**Number Treated**	**Number Positive**	**Tested by Confirmatory Method**	**Number confirmed positive**
Hematologic Transplant					
20000162 212 (106/106) Ph3 Cy/VP/TBI	ECL -IGEN	Not provided	1(1/0)	Confirmatory step – 1 ECL- — - 1	0
	ECL —	210 (105/105)	9 (3/6) +1palifermin >1.59	Bioassay - 10 Immunodepletion – 1	0
980231 163 (51/112) Ph2 Cy/VP/TBI	RIA	Not provided			
	ELISA	Not provided	48 (11/37)	Confirmatory ELISA - 48	0
	ECL- —	135 (40/95)	1 (0/1)	Immunodepletion – 1 Bioassay - 1	0
960189 262 (85/177) Ph1 BEAM	RIA	237	11(5/6)	ECL-IGEN - 11	0
	ELISA	9	6 (1/5)	Confirmatory ELISA - 6	0
	RIA&ELISA	2	-	-	-
	ECL —	244 (78/166)	0	-	-
20010182 13 (0/13) Ph1 TBI/VP/Cy	ECL -IGEN	13	1(0/1)	Confirmatory step – 1 ECL- — - 1	0
	ECL- —	13 (0/13)	2 (0/2)	Bioassay - 2	0
Solid Tumor					
990119 99 (32/67) Ph2 Head & Neck	ELISA	76	18 (4/14)	Confirmatory ELISA - 18	0
	ECL —	76 (25/51)	0	-	-
970149 60 (14/46) Ph1 Head & Neck	RIA	40	5 (1/4)	ECL-IGEN - 5	0
	ELISA	3	2 (0/2)	Confirmatory ELISA - 2	0
	ECL- —	43 (8/35)	0	-	-
950225/950275 145 (63/82) Ph1 Colorectal	RIA	113	0		
	ELISA	51	37(20/17)	Confirmatory ELISA - 37	0
	RIA&ELISA	142	-	-	-
	ECL —	142 (43/99)	2 (1/1)	Bioassay - 2	0
Volunteer Pharmacokinetiics					
970136 24 (6/18) Dose range IV	RIA	24	0	-	-
	ECL —	24 (6/18)	0	-	-
20010192 79 (16/63) Dose range IV	ECL —	78 (16/63)	4 (1/3)	Bioassay - 4	0

The following table summarizes the results of immunogenicity testing that was done on Amgen palifermin trials with RIA Assay and not subsequently tested by ECL.

Table 7-69 RIA Testing for Antibody in Early Studies

Table 7.69 RIA Testing for Antibody in Early Studies				
Protocol Number (placebo/palifermin)	**Number Treated**	**Number Positive**	**Tested by Confirmatory Method**	**Number confirmed positive**
Volunteer Pharmacokinetiics				
950170 28 (7/21) Subcutaneous	28	0		
960136 61 (15/31) Dose range IV	60	0		
970276 18(6/12) Dose range IV	17	1	Bioassay - 1	0

COMMENT: *The data on duration of WHO grade 3 or 4 oral mucositis in subjects enrolled on Study 2000162 who received palifermin with samples tested above the threshold on the ECL-based[ ] assay for development of anti-palifermin antibody were reviewed. There were 7 palifermin subjects identified. The median duration of WHO grade 3 or 4 oral mucositiis was 4 days for these 7 subjects. Overall on Study 20000162 the median duration of WHO grade 3 or 4 oral mucositis for subjects who received palifermin was 3 days; for subjects who received placebo the median was 9 days. There is no suggestion that these 7 palifermin subjects experienced an erosion of the palifermin effect on the median duration of oral mucositis.*

A review of adverse events that occurred during the palifermin administered on transplant day 0-2 and a subsequent 24 hour did not suggest the occurrence of infusional or allergic reaction. All subjects did have skin, and oral symptoms associated with the palifermin, but the description of these events were typical of the palifermin related symptoms not an infusional or allergic reaction.

There were 1057 subjects, 373 placebo and 685 palifermin, enrolled on the Amgen palifermin trials with samples evaluated by the ECL-based — assay for development of anti-palifermin antibody. There were 964 (91%) subjects, 321 (86%) placebo and 645 (94%) palifermin, that had serum tested. Serum from 17 subjects, 12 palifermin and 5 placebo, tested above the threshold on the ECL-based — assay for development of anti-palifermin antibody. None of these samples demonstrated neutralizing antibody using the Bioassay.

7.1.11 Human Carcinogenicity

The potential carcinogenicity of palifermin is a concern because solid tumors of epithelial origin may express KGF receptors. Theoretically, exposure of cancer patients to pharmacologic doses of palifermin could be problematic in 3 ways:

1) direct growth stimulation of tumor cells (both of primary tumors and/or secondary tumors)
2) protection of tumor cells from apoptosis induced by cytotoxic treatments (chemotherapy or radiation)
3) promotion of the development of secondary malignancies.

The preclinical animal testing included evaluation of tumor promotion in a nude mouse tumor implantation studies. In one of 7 tumor cell lines studied there was evidence of tumor promotion. Amgen has agreed to perform a RAS H2 Mouse Model study to further evaluate tumor promotion.

Long-term follow-up of subjects enrolled on Amgen solid tumor studies, to determine the risk of tumor promotion, has been part of the development plan for palifermin. There are two solid tumor long-term follow-up studies, one for colorectal cancer, and one for head and neck cancer.

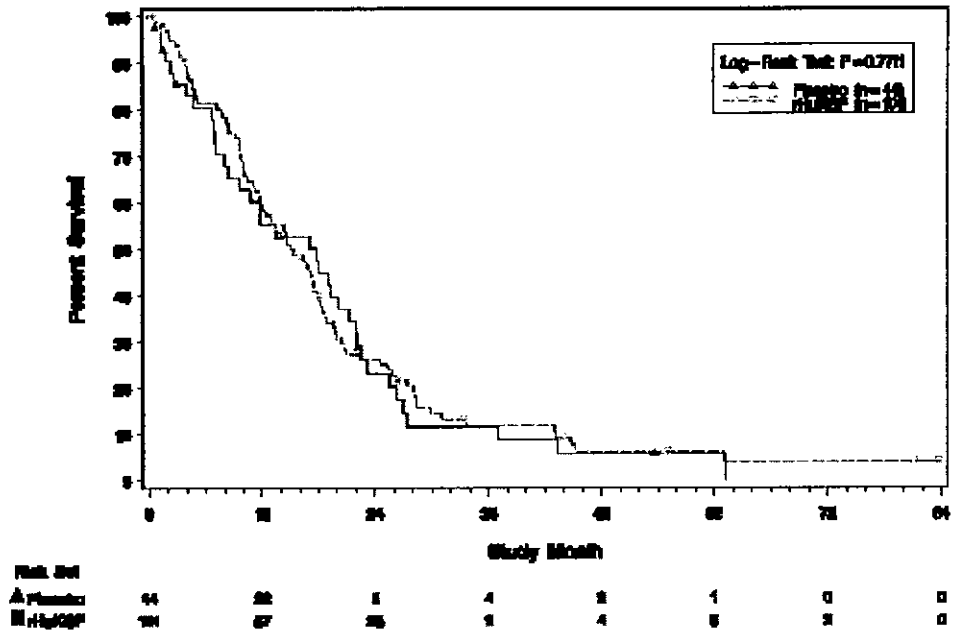
Study 950226 "A Long-term Follow-up Study of Colorectal Carcinoma Patients Who Were Previously Enrolled in Amgen sponsored Clinical Trials Using Recombinant Human Keratinocyte Growth Factor (rHuKGF)" has been completed and reported in a final study report dated 4/28/04. This study was initiated 1/14/97 and completed 1/29/04. One hundred forty-five subjects were enrolled on the therapeutic trial (44 placebo and 101 palifermin). One hundred thirty-two subjects (39 placebo, and 93 palifermin) were enrolled in the follow-up study.

The median duration of follow up was 13.4 months (12.6 months for the placebo group, 14.3 months for the palifermin group). Nine subjects (2 placebo, 7 palifermin) were lost to follow up during this follow-up study. At the end of the study (1/29/04), 4 subjects (1 placebo, 3 palifermin) were alive.

Ninety percent of all subjects (91% placebo, 90% palifermin) experienced disease progression. One hundred twenty-three subjects (84% in the placebo group, 85% palifermin group) died. Deaths primarily resulted from disease progression in both groups.

Kaplan-Meier estimated curves for overall survival time, time to disease progression, and progression-free survival of placebo and palifermin treated subjects were indistinguishable. See the Kaplan –Meier overall survival curve below (eCTD 5.3.5.4.5, Clinical Study Report 950226 page141):

Figure 7-3 Amgen's Kaplan-Meier Analysis of Overall Survival Colorectal Cancer Study



Based on this study, there is no evidence that palifermin affected the long-term survival of subjects with metastatic colorectal cancer receiving 5-FU and leucovorin chemotherapy. However, this study has a limited ability to evaluate the potential tumor promoting effects of palifermin on this population because of the overwhelming poor outcome due to tumor progression of the population.

Study 990123 A Long-term Follow-up Study of Head and Neck Cancer Study Subjects Previously Enrolled in Amgen sponsored Clinical Trials with Recombinant Human Keratinocyte Growth Factor (rHuKGF) is in ongoing follow-up. This study was initiated 7/29/99. Patients enrolled on this study were originally enrolled on 2 Amgen trials for head and neck cancer Study 970149 a phase 1 trail and Study 990119 a phase 2 trial. One hundred and fifty nine subjects who received investigational agent were enrolled on the parent studies, 46 received placebo and 113 received palifermin. One hundred of these subjects were enrolled on this follow-up study, 32 placebo and 68 palifermin.

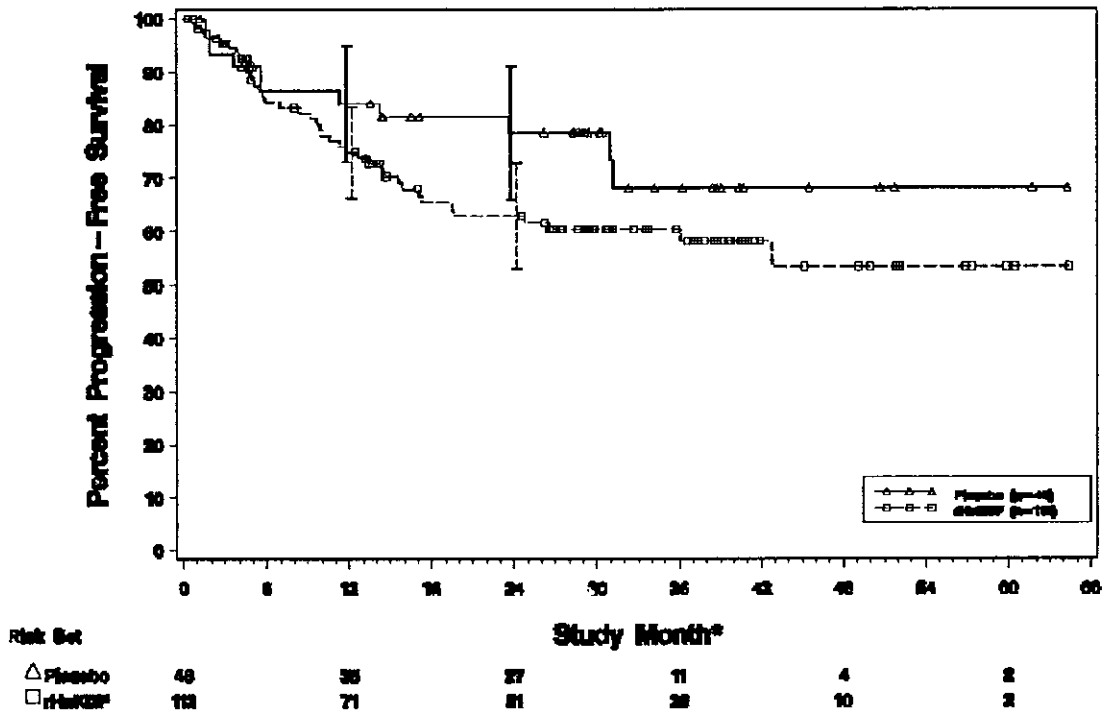
The outcomes reported are based on data as of 8/10/04 and was submitted with the 120-day safety update. The median follow-up is 38.6 months (range 1.2 to 64.3 months) for the placebo group and 19.5 months (range 0.4 to 71.3 months) for the palifermin group.

Amgen accounts for the difference in follow-up time between the placebo and palifermin groups as the result of a bimodal distribution of follow-up time, with the median follow-up in the placebo group falling into the left-hand portion of the curve and the median follow-up in the palifermin group falling into the right-hand portion.

Survival
The overall number of deaths is 11 subjects (24%) in the placebo group and 31 subjects (27%) in the palifermin group. Disease has progressed in 6 subjects (13%) in the placebo group and 29 subjects (26%) in the palifermin group.

The overall Kaplan-Meier progression free survival curve for this study is presented below (eCTD 5.3.5.4.6, Clinical Study Report 990123 page 336):

Figure 7-4 Amgen's Kaplan-Meier Analysis of Progression Free Survival in Head and Neck Cancer Study



The trend at this time is toward greater frequency of tumor progression in the palifermin subjects; the overall survival and the progression free survival are lower in the palifermin group compared to the placebo group

Amgen argues this observation should be interpreted with caution for the following reasons:
1. The rates of disease progression for both placebo and palifermin subjects are below the rates reported on the literature for a similar patient population, that is 40 to 60%.
2. There were major imbalances in disease characteristics at baseline favoring the placebo group. The study designs of the parent studies did not stratify the randomization for prognostic factors of tumor outcome and survival such as tumor resectability and stage.
3. The relatively limited overall duration of follow-up for both treatment groups

This follow up study is ongoing and will continue as a post marketing commitment.

Tumor promotion is less of a concern in the hematologic transplant setting because hematolgic tumors do not express KGF receptors. Therefore direct tumor stimulation is less of a concern. However, patients who undergo transplantation are known to be at risk to develop secondary cancers. Some of these tumors are epithelial in origin. Palifermin treated transplant patients should be monitored for increased development of these cancers.

Study 960226 "A Long-term Follow-up Study of Patients With Hematologic Malignancies Who Were Previously Enrolled in Amgen-sponsored Clinical Trials Using Recombinant Human Keratinocyte Growth Factor (rHuKGF) is in ongoing follow-up. This study was initiated on 5/26/97 and monitors disease status and the development of secondary malignancies in patients enrolled on Amgen's 4 clinical transplant studies (960189, 980231, 20000162, and 200010182). Six hundred and fifty subjects who received investigational agent were enrolled on the parent studies, 241 received placebo and 409 received palifermin. Five hundred and thirty seven of these subjects were enrolled on this follow-up study, 198 placebo and 339 palifermin.

The outcomes reported are based on data as of 8/4/04 and was submitted with the 120-day safety update. The median follow-up is 23.1 months for both the placebo and palifermin groups. The overall proportion of subjects with second malignancies remains the same in both treatment groups: 11/198 (6%) in the placebo group and 19/340 (6%) in the palifermin group. The most common second malignancies reported were secondary leukemias, and non-melanoma (squamous cell carcinoma and basal cell carcinoma) skin cancer. The proportion of subjects with hematologic second malignancies was the same (3.5%) for both treatment groups. The percentage of subjects with non-melanoma skin cancer is 1.0% (2/198) in the placebo group and 1.2% (4/340) in the palifermin group. The less frequent cancers included prostate cancer and pancreatic cancer in placebo subjects and adenocarcinoma of prostate, bladder cancer and prostate cancer in palifermin subjects.

Survival
The overall number of deaths is 62 subjects (26%) in the placebo group and 108 subjects (26%) in the palifermin group. The Kaplan-Meier progression free survival curve is presented below (eCTD 5.3.5.2.1, Clinical Study Report 960226 page 318):

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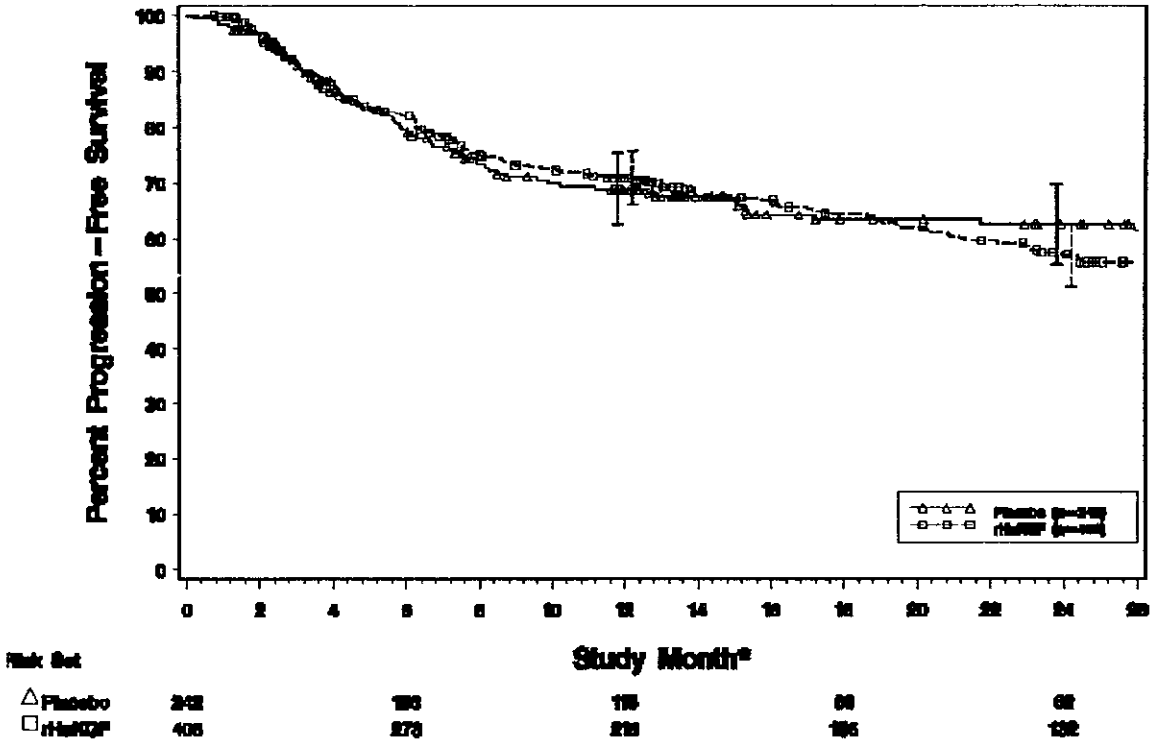
On Original

Figure 7-5 Amgen's Kaplan-Meier Analysis of Progression Free Survival Transplant Study



Conclusions
Based on this interim analysis, overall survival, disease progression, progression-free survival, and the incidences of second malignancies were similar between palifermin and placebo groups, and were in the range expected for this patient population. To date, no significant effect of palifermin on long-term disease outcomes in this patient population has been observed.

The proposed label for palifermin provides the following information regarding human carcinogenicity:

"Information for Patients" . . .

"Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity: The carcinogenic potential of palifermin has not been evaluated in long-term animal studies.
Mutagenicity: Palifermin was negative in in-vitro bacterial and mammalian mutagenicity assays, negative in the in vitro chromosome aberration assay, and negative in the in vivo mouse bone marrow micronucleus assay."

This information is adequate to support the use of this product in the hematopoetic transplant setting. Amgen [redacted]
[redacted] in the future.

7.1.12 Special Safety Studies

KGF receptors are present on the lens of the eye, and there is a potential risk for the development of cataracts in subjects who receive palifermin. Cataract formation is a common complication of transplantation. This risk is the result of total body irradiation and treatment with steroids. For this reason, visual evaluation with slit lamp was incorporated prospectively in Study 20000162 and Study 20010182. Left and right nuclear opalescence grades measured with the Lens Opacities Classification System III (LOCS III). Ophthalmologic Studies were scheduled at baseline, and follow-up between day 28 and 100.

In Study 20000162, baseline and post-baseline slit-lamp data are available for 171 subjects (85 placebo, 86 palifermin).

An Ophthalmologic consult to evaluate these results was obtained. (see separate consult). In this review the following flaws were identified in the conduct and results of this study:

Study Design
1. The majority of patients obtained follow-up examinations within 60 days of treatment. It is unlikely that cataract development, even if induced by the rHuKGF, would be detectable within 60 days.
2. LOCS III only permits evaluation of visible changes to the lens. The earliest changes to the lens are detected by changes in the refractive power of the lens. Baseline and final refractions, together with best corrected visual acuity, should have been evaluated in this study.

Study Execution
1. Twenty-one (20%) of the placebo subjects and 19 (18%) of the rHuKGF subjects did not have a follow-up eye examination. Without these examinations, a high potential rate of cataracts cannot be ruled out.

2. The investigator at site 38 never recorded a lens score above the minimal value of 0.1. Of the 25 patients examined at site 38, it is both highly unlikely and not physiologic for these patients to have only the minimal value at both baseline and follow-up visits given their cited ages.

3. Patient 3702 had a score of 0 for each part of the lens at baseline. The LOCS III score does not go below 0.1.

4. Several patients (3104, 4501, 4504, 4509, 4511 and 4512) had scores recorded in hundredths of a unit when the score is only defined to tenths of a unit.

Study Analysis
1. The analysis presented only evaluates nuclear opalescence. It suggests that only one placebo patient had a grade shift of ≥ 2. The analysis plan does not evaluate nuclear color, cortical cataracts, or posterior subcapsular cataracts.

a. Patient 3408, who received rHuKGF, had a change in posterior subcapsular cataract score in the right eye of 4 units and in the left eye of 2.8 units.

b. Patient 3605, who received rHuKGF, had a change in cortical cataract score of 1.8 in the right eye.

c. Patients 3116 and 3106, who received rHuKGF, had changes in the nuclear color of their lenses.

2. The analysis presents shift tables categorized in one unit increments instead of utilizing the actual score with its value in tens of a unit.

Conclusion of Ophthalmologic Consult
The study design, execution, analysis are insufficient to draw conclusions regarding any labeling statements or concerns of potential ocular toxicity.

COMMENT: *This evaluation was not informative regarding the risk of cataract formation. Further appropriately conducted studies will be required as a postmarketing committment.*

7.1.13 Withdrawal Phenomena and/or Abuse Potential

This section is not applicable. Palifermin poses no risk of abuse potential and does not pose risk of withdrawal phenomena.

7.1.14 Human Reproduction and Pregnancy Data

There are no studies of palifermin in pregnant or lactating women. The indication supported by this application is the use of palifermin in the hematopoetic transplant setting. Pregnancy is an absolute contraindication to undertaking hematopoetic transplantation.

7.1.15 Assessment of Effect on Growth

There is virtually no information of the use of this drug in children. The indication supported by this application is the use of palifermin in the hematopoetic transplant setting. Hematopoetic transplantation has a known and predictable negative effect on growth and development in children. Future studies of the possible contribution of palifermin to growth abnormalities in children after transplant will be difficult as the negative effect of transplant is so profound.

7.1.16 Overdose Experience

There is no experience with overdose in humans. . A dose of 250 µg/kg has been administered IV to 8 healthy volunteers without serious adverse effects.

7.1.17 Postmarketing Experience

This is the original application for this drug and therefore there is no postmaketing experience. There are no comparable agents.

7.2 Adequacy of Patient Exposure and Safety Assessments

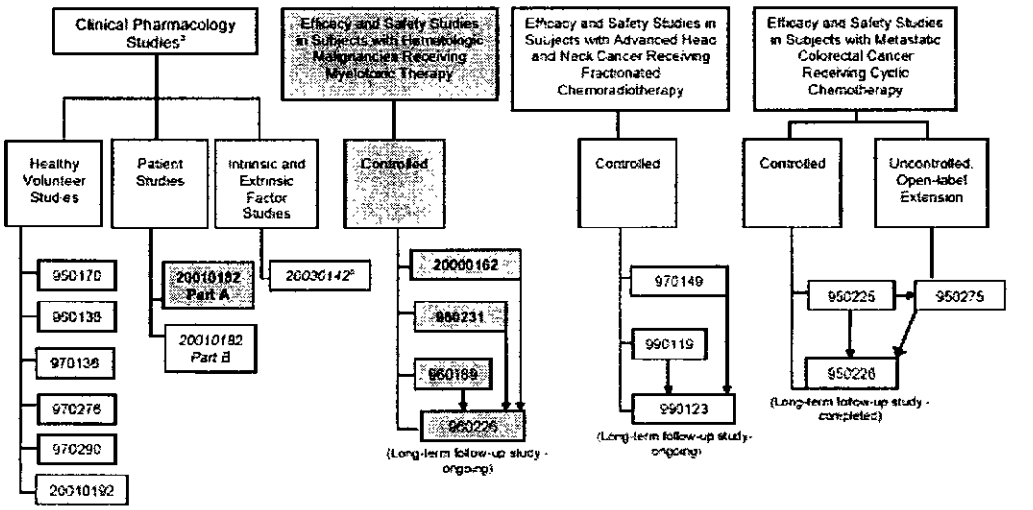
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The list of the studies and composition of Safety Pools used to support this application can be found in section 7.1 Methods and findings.

Amgen's Flow Chart Summarizing the Development Program follows (eCTD 2.7.4, Clinical Summary, Summary of Clinical Safety page 14):

Figure 7-6 Amgen's Chart of Studies Used to Support Safety



Note: Studies are organized by primary location in the license application (as safety, efficacy or clinical pharmacology studies). Italicized entries indicated studies not included in this application. Shaded studies are those in the indication for which approval is being sought in this application: myelotoxic therapy

a No biopharmaceutics studies were done (see Summary of Biopharmaceutics Studies and Associated Analytical Methodology, Section 2.7.1 of this application)

b Study 20030142 (a study in volunteers with renal impairment) was not yet complete at the time of this application. This study was the only study of intrinsic factors on the effect of palifermin; no extrinsic factor studies were done

The following type of safety data was supplied for these individual studies:

Table 7-70 Safety Data Supplied for Individual Studies

Table 7.70 Safety Data Supplied for Individual Studies				
Study	**Description of Study**	**Clinical study report**	**Case report forms[1]**	**SAS (XPT) Files**
Hematologic Malignancy Studies				
20000162	Ph3 Cy/VPTBI Randomized placebo	Final	All 214	X
980231	Ph2 Cy/VP/TBI Randomized placebo Schedules	Final	38/169	X
960189	Ph1 BEAM Randomized placebo Dose and Schedule	Final	58/264	X
20010182	Ph1 TBI/VP/Cy PK Schedule	Final	1/13	X
960226	Long term study	Interim	0	X
Solid Tumor Studies				
990119	Ph2 Head & Neck Randomized placebo	Final	60/101	X
970149	Ph1 Head & Neck Randomized placebo Dose escalation schedule	Final	44/60	X
990123	Long term study Head and Neck	Interim	0	X
950225	Ph1 Colorectal Dose escalation	Final	38/149	X
950275	Ph1 Colorectal Open label extension	Final	38/48	X
950226	Long term study Colorectal	Final	0	X
Healthy Volunteer Studies				
950170	Subcutaneous Dose escalation	Synopsis	0/28	X
960136	Dose range IV	Synopsis	2/61	X
970276	Dose range IV	Final	4/18	X
970136	Dose range IV	Synopsis	0/24	
970290	Repeat testing	Synopsis	0/4	
20010192	Dose range IV	Final	10/84	X

[1]Case report forms for all patients on pivotal study were submitted; in addition case report forms were submitted on all patients with serious adverse events and for subjects that discontinued treatment for any reason including death.

Amgen's Table with description of studies follows:

Hematologic Malignancy Studies:

(eCTD 2.7.4, Clinical Summary, Summary of Clinical Safety page 16):

Figure 7-7 Amgen's Table of Hematologic Malignancy Transplant Studies in Application

Table 1. Descriptions of the Studies Included in the License Application (Subjects with Hematologic Malignancies Receiving Myelotoxic Therapy)

Study Type/ Number	Entry Criteria	No. Subjects Treated[a]/ Treatment	Age Range (years)	Race/ Gender	Duration of Palifermin Exposure
CONTROLLED CLINICAL STUDIES					
Phase 3					
20000162	Subjects with NHL, Hodgkin's disease, AML, ALL, CML, CLL, or multiple myeloma scheduled to receive TBI plus high-dose etoposide and cyclophosphamide followed by autoPBSCT	N=212 106 palifermin/ 106 placebo	18-69	White, 167 Black, 18 Hispanic, 18 Other, 9 Men, 131 Women, 81	60 µg/kg palifermin 3 consecutive days before before TBI/CT, 3 consecutive days after PBSCT
Phase 2					
980231	Subjects with NHL, Hodgkin's disease, AML, ALL, CML, CLL, or multiple myeloma scheduled to receive TBI plus high-dose etoposide and cyclophosphamide followed by autoPBSCT	7-dose group. 34 subjects: 11 placebo, 12 palifermin pre, 11 palifermin pre-post	18-65	White, 21 Black, 5 Hispanic, 8 Men, 24 Women, 10	60 µg/kg palifermin 3 consecutive days before TBI/CT, day of last TBI fraction, 3 consecutive days after PBSCT
		6-dose group. 129 subjects. 40 placebo, 43 palifermin pre, 46 palifermin pre-post	18-65	White, 93 Black, 16 Hispanic, 14 Other, 6 Men, 76 Women, 53	As above; dose on day of last TBI fraction eliminated. Subjects in the palifermin pre group received 3 placebo doses after PBSCT

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Table 1. Descriptions of the Studies Included in the License Application (Subjects with Hematologic Malignancies Receiving Myelotoxic Therapy

Study Type/ Number	Entry Criteria	No. of Subjects Treated[a]/ Treatment	Age Range (years)	Race/ Gender	Duration of Palifermin Exposure
Phase 1					
960189	Subjects with Hodgkin's disease or NHL scheduled to receive BEAM or BuMel followed by autoPBSCT	N=262 178 palifermin/ 84 placebo	16-69	White, 250 Black, 7 Other, 5 Men, 167 Women, 95	5, 20, 40, 60, 80 µg/kg for 3 consecutive days before BEAM (pre); 20, 40, 80 µg/kg for 3 consecutive days before and after BEAM (pre-post), or 60 µg/kg/day for 3 consecutive days before and after BEAM or BuMel (pre-post)
20010182 Part A	Subjects with NHL, Hodgkin's disease AML ALL, CML CLL, or multiple myeloma scheduled to receive TBI plus high-dose etoposide and cyclophosphamide followed by autoPBSCT	N=13 (all palifermin)	18-63	White, 11 Black, 2 Men, 7 Women, 6	60 µg/kg for 3 consecutive days before TBI/CT, for 3 consecutive days after PBSCT (pre-post)
Long-term follow-up					
960226	Subjects previously enrolled in studies 20000162, 960231, 960189, and 20010182 Part A	N=650 242 placebo / 408 palifermin	16-69	White, 542 Black, 48 Hispanic 40 Other, 20 Men, 405 Women, 245	No investigational product administered

Solid Tumor Studies:

(eCTD 2.7.4, Clinical Summary, Summary of Clinical Safety page 95, 141):

Figure 7-8 Amgen's Table Oncology Studies Included in License Application in Head and Neck Cancer

Table 21. Descriptions of Other Oncology Studies Included in the License Application (Subjects Receiving Fractionated Chemoradiotherapy)

Study Type/ Number	Entry Criteria	No. of Subjects Treated[a]/ Treatment	Age Range (years)	Race/ Gender	Duration of Palifermin Exposure
CONTROLLED CLINICAL STUDIES					
Phase 1					
970149	Subjects with advanced carcinoma of the oral cavity, nasopharynx, oropharynx, hypopharynx or larynx scheduled to receive fractionated radiotherapy (HRT) with concomitant chemotherapy as definitive treatment.	N=60 46 palifermin/ 14 placebo	39-70	White, 39 Black, 14 Hispanic, 6 Other, 1 Men, 50 Women, 10	20,40,60 µg/kg: 3 consecutive daily doses before CT, 7 weekly doses post radiotherapy. 80 µg/kg: 1 dose before CT, 9 weekly doses post radiotherapy
Phase 2					
990119	Subjects with advanced carcinoma of the oral cavity, nasopharynx, oropharynx, hypopharynx or larynx, or of unknown origin scheduled to receive fractionated radiotherapy (HRT or SRT) with concomitant chemotherapy as definitive treatment	N=99 67 palifermin / 32 placebo	25-80	White, 79 Black, 14 Hispanic, 1 Other, 5 Men, 82 Women, 17	60 µg/kg day 1 before CT, 10 weekly post doses radiotherapy
Long-term follow-up					
990123	Long-term follow-up of subjects who participated in studies 970149 or 990119	N=159 113 palifermin/ 46 placebo	25-80	White, 118 Black, 28 Other, 13 Men, 132 Women 27	No active treatment

Figure 7-9 Amgen's Table Oncology Studies Included in License Application in Colorectal Cancer

Table 31. Descriptions of Other Oncology Studies Included in the License Application (Subjects Receiving Cyclic Chemotherapy)

Study Type/ Number	Entry Criteria	No of Subjects Treated[a]/ Treatment	Age Range (years)	Race/ Gender	Duration of Palifermin Exposure
CONTROLLED CLINICAL STUDIES					
Phase 1/2 (cyclic chemotherapy)					
950225 A		N=81 54 palifermin/ 27 placebo	41-86	White, 68 Black, 3 Other, 10 Men, 47 Women, 34	1, 10, 20, 40, 80, or 60 µg/kg for 3 consecutive days before 1 cycle of 5-FU/ leucovorin.
950225 B		N=64 28 palifermin/ 36 placebo	37-88	White, 54 Black, 5 Other, 5 Men, 42 Women, 22	40 µg/kg for 3 consecutive days before each of 2 cycles of 5-FU/leucovorin chemotherapy.
Long-term follow-up (cyclic chemotherapy)					
950226	Long-term follow-up of subjects who participated in Study 950225	N=145 101 palifermin/ 44 placebo	37-88	White, 122 Black, 8 Other, 15 Men, 89 Women, 56	No active treatment
UNCONTROLLED CLINICAL STUDIES					
Open-label extension study (cyclic chemotherapy)					
950275	Open-label extension study open to subjects who participated in Study 950225	N=48 19 prior placebo/ 29 prior palifermin	41-84	White, 40 Black, 3 Other, 5 Men, 32 Women, 16	Same dose as in 950225 part A, 3 consecutive days before each of up to 6 cycles of 5-FU/leucovorin

Healthy Volunteer Studies:

(eCTD 2.7.4, Clinical Summary, Summary of Clinical Safety page 174):

Figure 7-10 Amgen's Table of Studies in Healthy Volunteer Subjects

Table 37. Descriptions of the Studies Included in the License Application (Studies in Healthy Volunteers)

Study Number/ Type	Entry Criteria	No. of Subjects Treated/ Treatment	Age Range (years)	Race/ Gender	Duration of Palifermin Exposure
Healthy Volunteer Studies					
950170/ Phase 1	Healthy subjects between the ages of 18 and 45 years.	N=21 palifermin/ 7 placebo	19-42	White, 20 Black, 3 Hispanic, 5 men, 12 women, 16	3 single-dose cohorts received 1,10, and 30 μg/kg palifermin, and 3 multiple-dose cohorts received 1 and 10 μg/kg palifermin once daily for 3 consecutive days. No cohort was repeated
960136/ Phase 1	Healthy subjects between the ages of 18 and 45 years of age with a normal oral examination	N=46 palifermin/ 15 placebo	18-45	White, 43 Hispanic, 17 Asian, 1 Men, 35 Women, 26	5 cohorts received 0.2, 1, 5, 10, or 20 μg/kg palifermin administered IV one time, and 5 cohorts received 0.2, 1, 5, 10, or 20 μg/kg palifermin administered IV once daily for 3 consecutive days.
970276/ Phase 1	Healthy subjects with a normal oral examination	N=12 palifermin/ 6 placebo	18-63	White, 14 Hispanic, 4 men, 9 women, 9	20 or 40 μg/kg palifermin administered IV once daily for 3 consecutive days
970136/ Phase 1	Healthy Japanese men between the ages of 22 to 45 years of age, who were within ± 20% of ideal body weight	N=18 palifermin/ 6 placebo	20-35	Japanese, 24 Men, 24	5, 10 or 20 μg/kg palifermin administered IV one time

Table 37. Descriptions of the Studies Included in the License Application (Studies in Healthy Volunteers)

Study Number/ Type	Entry Criteria	No. of Subjects Treated/ Treatment	Age Range (years)	Race/ Gender	Duration of Palifermin Exposure
970290/ Phase 1	Subjects who received 10 µg/kg palifermin in Study 970136 (2 retest with low levels, 2 retest controls with expected levels)	N=4 palifermin	21-26	Japanese, 4 Men, 4	10 µg/kg palifermin administered IV one time
20010192/ Phase 1	Healthy adults between 18 and 55 years of age	N=63 palifermin/ 16 placebo	18-53	White, 60 Black, 14 Hispanic, 1 Asian, 2 Other, 2 Men, 76 Women, 3	60 to 250 µg/kg palifermin administered IV one time.

7.2.1.2 Demographics

Demographic of the Safety Pools used to support this application are listed in the following tables.

The demographics and patients characteristics of Hematologic Malignancy Safety Pool B were:

Table 7-71 Demographics Hematologic Malignancy Safety Pool B

Table 7.71 Demographics Hematologic Malignancy Safety Pool B		
	Placebo (N=241)	Palifermin (N=409)
Sex - n(%)		
Male	163 (68)	242 (59)
Female	78 (32)	167(41)
Race - n (%)		
Caucasian	208 (86)	334 (82)
Black	16(7)	32(8)
Hispanic	13(5)	27(7)
Asian	2(1)	10(2)
Other	2(1)	6(1)
Age (years) - n (%)		
<18	1(0)	2(0)
18-30	40(17)	59(14)
31-40	40(17)	84(21)
41-50	60 (25)	88 (22)
51-60	82 (34)	136(33)
61-64	13(5)	31(8)
65-70	5(2)	9(2)
Age (years)		
Mean	45	46
Median	48	48
Diagnosis –n (%)		
Hodgkin's disease	59 (24)	76(19)
Non-Hodgkin's lymphoma	159 (66)	300 (73)
Multiple Myeloma	15(6)	21(5)
Acute lymphoblastic leukemia	1(0)	3(1)
Acute myelogenous leukemia	6(2)	9(2)
Chronic lymphocytic leukemia	1(0)	0(0)
Original Protocol – n (%)		
960189	84(35)	178(44)
980231	51(21)	112(27)
20000162	106(44)	106(26)
20010182	0	13(3)

The safety evaluation of palifermin in the Head and Neck Carcinoma Solid Tumor cohort of subjects used the composite data sets of Pool D. This includes 159 patients who received at least 1 dose of investigational agent on study 970149 or 990119.

Table 7-72 Demographics of Patients in the Head and Neck Cancer Safety Pool D

Table 7.72 Demographics Head and Neck Cancer Safety Pool D		
	Placebo (N=46)	Palifermin (N=113)
Sex - n (%)		
Male	41(89)	91(81)
Female	5(11)	22(19)
Race - n (%)		
Caucasian	37(80)	81(72)
Black	6(13)	21(19)
Hispanic	2(4)	6(5)
Asian	1(2)	54)
Age (years)		
Mean	55.7	54.1
Median	54	54
Original Protocol – n (%)		
97	14(30)	46(41)
99	32(70)	67(59)

The safety evaluation of palifermin in the Colorectal Carcinoma Solid Tumor cohort of subjects includes all subjects who received at least one dose of investigational agent on study 950225. This includes 145 patients.

Table 7-73 Demographics Colorectal Study 950225

Demographics Colorectal Study 950225		
	Placebo (N=63)	Palifermin (N=82)
Sex - n (%)		
Male	42(67)	47(57)
Female	21(33)	35(43)
Race - n (%)		
Caucasian	55(87)	67(82)
Black	2(3)	6(7)
Hispanic	3(5)	5(6)
Asian	3(5)	2(2)
Other		2(2)
Age (years)		
Mean	65.1	63.1
Median	65	62

Subjects enrolled on Study 950225 were able to continue therapy on a Study 950275. Subjects originally randomized to receive placebo-received palifermin on the continuation trial. The demographics of subjects treated on Study 950275 are summarized in the table below:

Table 7-74 Demographics Colorectal Study 950275 All Subjects Received Palifermin

Table 7.74 Demographics Colorectal Study 950275 All Subjects Received Palifermin			
	Total (N= 48)	Palifermin prior placebo (N = 19)	Palifermin prior palifermin (N = 29)
Sex - n(%)			
Male	32 (67%)	13 (68%)	19 (66%)
Female	16 (33%)	6 (32%)	10 (34%)
Race - n (%)			
Caucasian	40 (83%)	16 (84%)	24 (83%)
Black	3 (6%)		3 (10%)
Hispanic	3 (6%)	2 (11%)	1 (3%)
Asian	2 (2%)	1 (5%)	1 (3%)
Age (years)			
Mean		64	63
Median		63	62

7.2.1.3 Extent of exposure (dose/duration)

The following table from Amgen summarizes the dose and duration exposure of the subjects in the Transplant Safety Pool B.

Figure 7-11 Dose Exposure Transplant Safety Pool

Table 5. Exposure to Investigational Product (Primary Safety Pool)

	Placebo (N=241)	Palifermin (N=409)
Total Number of Doses -n(%)		
7	11 (5)	21 (5)
6	165 (68)	245 (60)
5	1 (0)	4 (1)
4	1 (0)	4 (1)
3	62 (26)	129 (32)
2	0 (0)	5 (1)
1	1 (0)	0 (0)
Total Number of Doses		
n	241	409
Mean	5.2	5.0
SD	1.4	1.5
Median	6.0	5.0
Q1, Q3	3.0, 6.0	3.0, 6.0
Min, Max	1, 7	2, 7
Average Daily Dose by Weight (µg/kg/day)		
n	238	408
Mean	65.3	64.5
SD	63.3	44.8
Median	60.0	60.0
Q1, Q3	59.6, 60.1	59.7, 60.6
Min, Max	5, 814	5, 406

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The transplant safety Pool B included subjects receiving a total of 3, 6, or 7 per protocol doses. The median number of doses in both treatment groups was 6. The median average daily dose by weight was 60 µg/kg/day in each treatment group.

This pool included Study 960189, which was the only dose-escalation study in the myelotoxic therapy population.

In Amgen's Clinical Summary, Summary of Clinical Safety Module 2.7, the application contained similar tables of Subgroup Analyses that demonstrated that the exposure to investigational product analyzed by demographic subgroups (age [<65 years, ≥65 years], sex [men, women], and race [Caucasian, black, Hispanic, and other]) in the cumulative (µg/kg) or average daily (µg/kg) exposure was comparable when analyzed by these demographic subgroups.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

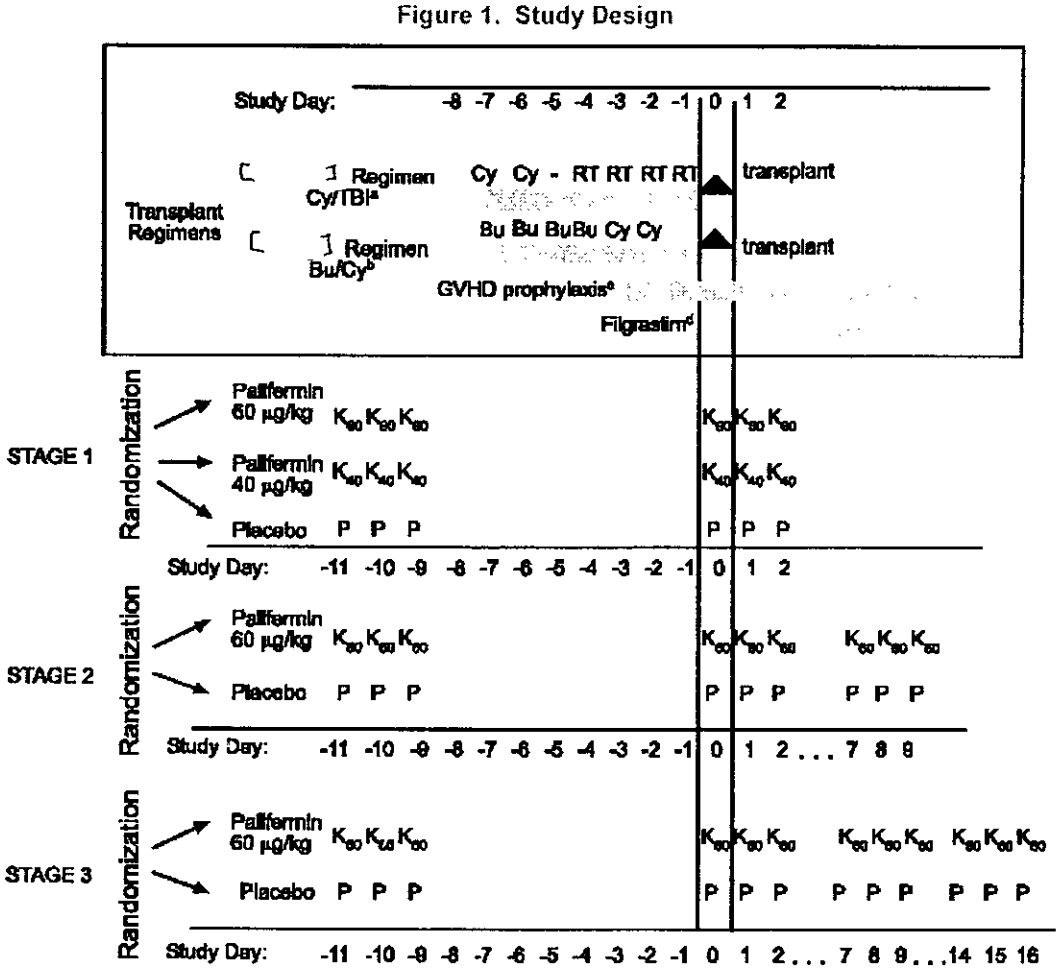
As part of Amgen's 120 Safety update a summary of an Investigator Sponsored IND 8783, "Keratinocyte Growth Factor Radiochemotherapy and G-CSF" was submitted. This study was conducted at the [ ] The principal investigator is [ ] There were two clinical trials done under this IND. This report only discusses the first trial completed under this IND.

Title: "A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation, Safety Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Patients Undergoing Allogeneic Bone Marrow (BM) or Peripheral Blood Progenitor Cell (PBPC) Transplantation"

Study Objectives:
1. To determine the safety and reliability of rHuKGF administration to patients with hematologic malignancies undergoing allogeneic BM or PBPC transplantation.
2. To determine the incidence and severity of acute GVHD, patient survival, the incidence of transplant-related toxicity, and the time to marrow engraftment. To evaluate the incidence, severity, and duration of oral and lower gastrointestinal tract (GI) mucositis during allogeneic transplantation.

Study Design:

Figure 7-12 Study Design IND 8783 Palifermin in Allogeneic Transplant Setting



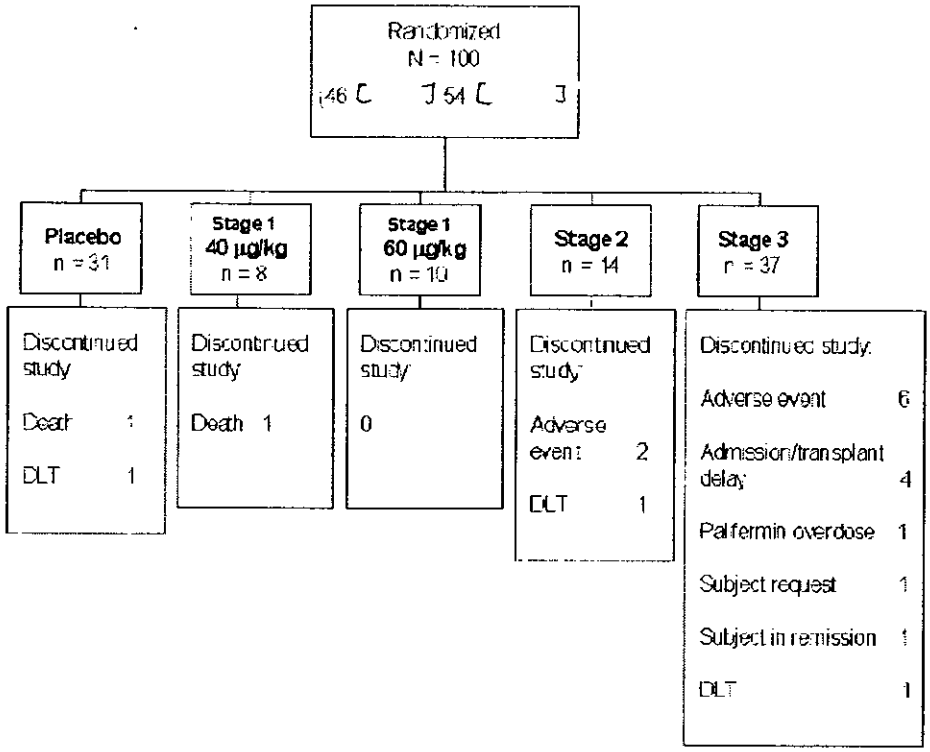
[ ] GVHD prophylaxis was to consist of cyclosporine A and methotrexate, with cyclosporine A starting at day -2; methotrexate 15 mg/m2, IV bolus on day + 1; and methotrexate 10 mg/m2, IV bolus on days 3, 6, and 11. In the absence of GVHD, cyclosporine was to be tapered by 10% per week beginning on day 60.

[ ] GVHD prophylaxis consisted of tacrolimus and methotrexate, with tacrolimus starting at day -2; methotrexate 15 mg/m2, IV bolus on day +1; and methotrexate 10 mg/m2, IV bolus on days 3, 6, and 11. In the absence of GVHD, tacrolimus was to be tapered by 10% per week beginning on day 60.

The following table summarizing patient enrollment was derived from the table in Amgen's submission.

Figure 7-13 Patient Disposition IND 8783 Palifermin in Allogeneic Transplant Setting

Figure 2. Patient Disposition



The exposure of investigational agent summarized by Amgen in the table below:

Figure 7-14 Investigational Agent Exposure IND 8783 Palifermin in Allogeneic Transplant Setting

	Placebo	KGF Stage I dose 40mg	KGF Stage I dose 60mg	KGF Stage II dose 60mg	KGF Stage III dose 60mg	All KGF	Total
N Randomized	31	8	10	14	37	69	100
Drug Exposure							
3 6	0	1 (13%)	0	0	0	1 (1%)	1
6 6	9 (29%)	7 (87%)	10 (100%)	0	0	17 (25%)	26
5 9	0	0	0	1 (7%)	0	1 (1%)	1
6 9	0	0	0	1 (7%)	0	1 (1%)	1
8 9	0	0	0	1 (7%)	0	1 (1%)	1
9 9	8 (26%)	0	0	11 (79%)	0	11 (16%)	19
1 12	0	0	0	0	2 (5%)	2 (3%)	2
3 12	0	0	0	0	5 (14%)	5 (7%)	5
6 12	0	0	0	0	2 (5%)	2 (3%)	2
7 12	0	0	0	0	1 (3%)	1 (1%)	1
9 12	0	0	0	0	2 (5%)	2 (3%)	2
10 12	1 (3%)	0	0	0	1 (3%)	1 (1%)	2
12 12	13 (42%)	0	0	0	23 (65%)	23 (35%)	37
Dose							
Median (range)	0 (0-0)	240 (120-240)	360 (360-360)	540 (300-540)	720 (60-720)	540 (60-720)	
Mean (StDev)	0 (0)	225 (42)	360 (0)	505 (77)	571 (232)	487 (210)	

Amgen's table of all adverse events to day 30 post transplant:

Figure 7-15 Adverse Events IND 8783 Palifermin in Allogeneic Transplant Setting

	Placebo	KGF Stage I dose 40mg	KGF Stage I dose 60mg	KGF Stage II dose 60mg	KGF Stage III dose 60mg	All KGF	Total
N Randomized	31	8	10	14	37	69	100
Patients w Events	31	8	10	14	37	69	100
Type							
Alk Phosphatase	3 (10%)	0	0	0	4 (11%)	4 (6%)	7
Amylase Lipase	10 (33%)	4 (50%)	1 (10%)	3 (21%)	13 (35%)	21 (30%)	31
Burning w Urinat	2 (6%)	0	0	1 (7%)	0	1 (1%)	3
Cardiac	5 (16%)	2 (25%)	0	1 (7%)	13 (35%)	16 (23%)	21
Death	1 (3%)	1 (13%)	0	0	1 (3%)	2 (3%)	3
Dizzy/Headache	0	0	0	1 (7%)	0	1 (1%)	1
Edema	20 (65%)	6 (75%)	6 (60%)	12 (86%)	30 (81%)	54 (78%)	71
GI Diarrhea	24 (77%)	5 (63%)	5 (50%)	13 (93%)	32 (69%)	55 (80%)	79
GI N-V	28 (90%)	8 (100%)	10 (100%)	14 (100%)	31 (92%)	66 (96%)	91
GU Bladder	8 (26%)	2 (25%)	0	5 (36%)	9 (24%)	16 (23%)	21
Hypotension	2 (2%)	0	0	0	5 (14%)	5 (7%)	7
Infection	0 (0%)	0	2 (20%)	0	2 (6%)	4 (11%)	4
Infection w Neut	0 (0%)	0	0	1 (7%)	0	1 (1%)	1
Liver	27 (87%)	8 (100%)	7 (70%)	13 (93%)	31 (92%)	62 (90%)	89
Neuro	12 (39%)	1 (13%)	2 (20%)	6 (43%)	13 (16%)	22 (32%)	31
Neuro(Cons/Beha)	7 (23%)	4 (50%)	2 (20%)	6 (43%)	6 (16%)	18 (26%)	25
Oral(Mucositis)	31 (100%)	6 (75%)	10 (100%)	13 (93%)	33 (89%)	62 (90%)	93
Oral - Other	7 (23%)	2 (25%)	1 (10%)	4 (29%)	18 (49%)	25 (36%)	32
Other	17 (55%)	0	3 (30%)	10 (71%)	18 (49%)	31 (45%)	48
Pain (Local)	23 (77%)	6 (75%)	6 (60%)	13 (93%)	36 (97%)	61 (88%)	84
Pain (Non-Local)	4 (13%)	0	0	1 (7%)	6 (16%)	7 (10%)	11
Renal Creatinine	14 (48%)	4 (50%)	2 (20%)	6 (43%)	21 (57%)	33 (48%)	47
Respiratory	20 (65%)	5 (63%)	3 (30%)	6 (43%)	26 (70%)	41 (59%)	61
Skin	21 (68%)	6 (75%)	9 (90%)	13 (93%)	36 (97%)	65 (94%)	86
Vision	0	1 (13%)	0	0	1 (3%)	2 (3%)	2

These adverse are similar to those reported in the Transplant Safety Pool B. Edema skin and oral events other than mucositis are more frequent in the palifermin subjects. There is less mucositis

in the palifermin subjects. Of note, unlike the data in the Transplant Safety Pool B there were more cardiac events and infectious events in the palifermin subjects.

Amgen's table of Grade 3 and 4 Adverse Events

Figure 7-16 Grade 3 and 4 Adverse Events IND 8783 Palifermin in Allogeneic Transplant Setting

	Placebo	KGF Stage I dose 40mg	KGF Stage I dose 60mg	KGF Stage II dose 60mg	KGF Stage III dose 60mg	All KGF	Total
N Randomized	31	8	10	14	37	69	100
Patients w/ Events	27	8	8	14	31	61	91
Type							
Amylase/Lipase	3 (10%)	0	1 (10%)	0	4 (11%)	5 (7%)	8 (8%)
Cardiac	2 (6%)	2 (25%)	0	0	6 (16%)	8 (12%)	10 (10%)
Creatinine/Renal	2 (6%)	0	0	1 (7%)	3 (8%)	4 (6%)	6 (6%)
Death	1 (3%)	1 (13%)	0	0	1 (3%)	2 (3%)	3 (2%)
Edema	3 (10%)	0	0	1 (7%)	4 (11%)	5 (7%)	8 (8%)
GI Diarrhea	2 (2%)	0	1 (10%)	1 (10%)	5 (14%)	7 (10%)	9 (9%)
GI N/V	3 (10%)	1 (13%)	2 (20%)	3 (21%)	3 (8%)	9 (13%)	12 (12%)
GU/Bladder	1 (3%)	0	0	0	1 (3%)	1 (1%)	2 (2%)
Hypotension	2 (2%)	0	0	0	5 (14%)	5 (7%)	7 (7%)
Infection	0 (0%)	0	2 (20%)	0	1 (3%)	3 (4%)	3 (3%)
Infection w/ Neut	0 (0%)	0	0	1 (7%)	0	1 (1%)	1 (1%)
Liver	9 (29%)	6 (75%)	0	6 (43%)	10 (27%)	22 (32%)	31 (31%)
Neuro	1 (3%)	0	0	0	2 (5%)	2 (3%)	3 (3%)
Neuro(Cons/Beha)	5 (16%)	3 (38%)	0	1 (7%)	3 (8%)	7 (10%)	12 (12%)
Oral(Mucositis)	24 (77%)	3 (38%)	6 (60%)	11 (79%)	24 (65%)	44 (64%)	68 (68%)
Other	3 (10%)	0	0	1 (7%)	0	1 (1%)	4 (4%)
Pain (Local)	2 (2%)	0	1 (10%)	4 (29%)	2 (5%)	7 (10%)	9 (9%)
Respiratory	7 (23%)	3 (38%)	2 (20%)	2 (20%)	8 (22%)	15 (22%)	22 (22%)
Skin	4 (13%)	1 (13%)	2 (20%)	6 (43%)	6 (16%)	15 (22%)	19 (19%)

Amgen's 3 tables summarizing the outcomes of study follows:

Appears This Way
On Original

Figure 7-17 Results IND 8783 Palifermin in Allogeneic Transplant Setting

	Placebo	KGF Stage I dose 40mg	KGF Stage I dose 60mg	KGT Stage II dose 60mg	KGF Stage III dose 60mg	All KGF	P
N of Patients	31	8	10	11	37	69	
Mucositis before D30							
# w Gr 3-4 (%)	24 (77%)	3 (38%)	6 (60%)	11 (79%)	23 (65%)	44 (64%)	.19 .26
none	0	2	0	1	4	7	
# w Grade 1	0	2	1	1	3	7	
# w Grade 2	7	1	3	1	6	11	
# w Grade 3	22	3	6	10	24	43	
# w Grade 4	2	0	0	1	0	1	
Mean grade (se)	2.8 (0.1)	1.6 (0.5)	2.5 (0.2)	2.6 (0.3)	2.1 (0.2)	2.3 (0.1)	.01 .02
Duration							
Median (range)	18 (3-41)	5.5 (0-28)	14 (7-24)	22.5 (0-47)	14 (0-42)	14 (0-47)	
Mean (std)	19.7 (13.3)	9.1 (9.8)	13.8 (4.8)	22.5 (15.0)	16.3 (11.9)	16.4 (12.1)	
Day 30 GI Diarrhea							
# w Gr 3-4 (%)	2 (6%)	0	1 (10%)	1 (7%)	5 (14%)	7 (10%)	.56 .36
none	7	3	5	1	5	14	
# w Grade 1	19	3	1	6	10	29	
# w Grade 2	3	2	0	6	11	19	
# w Grade 3	2	0	1	1	4	6	
# w Grade 4	0	0	0	0	1	1	
Mean grade (se)	1.6 (0.1)	0.9 (0.3)	0.7 (0.3)	1.5 (0.2)	1.5 (0.2)	1.3 (0.1)	.13 .01
Duration							
Median (range)	11 (0-49)	2 (0-45)	0.5 (0-17)	22 (0-43)	20 (0-49)	14 (0-49)	
Mean (std)	16.1 (15.7)	11 (18.2)	3.3 (5.9)	20.9 (16.8)	22.5 (17.3)	18.0 (17.3)	

P-value in black is comparison of Placebo to ALL KGF patients
P-value in red is comparison of Placebo to Higher dose KGF (Stage III)
All tests are stratified by center (frequencies of grades are tested by the **cochran-mantel-haenszel test**, mean grades are tested by linear regression)

	Placebo	KGF Stage I dose 40mg	KGF Stage I dose 60mg	KGF Stage II dose 60mg	KGF Stage III dose 60mg	All KGF	P
N of Patients	31	8	10	11	36	67	
Day 30 Survival							
# deaths	1	0	0	0	1	1	
Estimate (95% CI)	97% (91-100%)	100%	100%	100%	97% (92-100%)	99% (96-100%)	.37 .95
Day 100 Survival							
# deaths	5	2	1	3	6	12	
Estimate (95% CI)	84% (71-97%)	71% (37-105%)	90% (72-100%)	79% (57-100%)	83% (71-95%)	82% (73-91%)	.81 .91
ANC Engraftment							
# engrafted	30 (1 died early)	7	10	13 (1 failed)	36	66 (1 failed)	
Day 42 estimate	100%	100%	100%	93% (80-100%)	100%	99% (96-100%)	.98
Days to ANC Median (range)	15 (9-22)	13 (11-19)	15 (9-22)	16 (10-22)	14 (9-21)	14 (9-22)	.57
PLT Engraft (20K)							
# engrafted	26 (5 died)	5 (2 died)	10	13 (1 failed)	33 (3 died)	61 (5 died,1 failed)	
6 month estimate	83% (61-100%)	71% (39-100%)	100%	93% (66-100%)	92% (71-100%)	91% (77-100%)	.99
Days to Plat of 20k Median (range)	21 (9-221)	26 (14-41)	21 (12-31)	25 (10-38)	21.5 (10-111)	22 (10-111)	.89
Day 100 Relapse							
# relapsed progressed	4	1	1	2	2	6	.35
Estimate (95% CI)	13% (1-25%)	13% (0-37%)	10% (0-22)	18% (0-31%)	6% (0-13%)	9% (2-16%)	.28

	Placebo	KGF Stage I dose 40mg	KGF Stage I dose 60mg	KGF Stage II dose 60mg	KGF Stage III dose 60mg	All KGF	P
N of Patients	31	7	10	11	36	67	
Day 30 Grade II-IV Acute GvHD							
# w. gvhd	4	1	2	0	5	8	82
Estimate (95% CI)	13% (1-25%)	14% (0-38%)	20% (0-44%)	0%	11% (3-25%)	12% (4-20%)	93
Day 100 Grade II-IV Acute GvHD							
# w. gvhd	13	4	3	4	15	26	69
Estimate (95% CI)	42% (24-60%)	57% (20-94%)	30% (3-57%)	29% (6-52%)	42% (26-58%)	39% (27-51%)	81
Day 30 Grade III-IV Acute GvHD							
# w. gvhd	1	0	1	0	1	5	13
Estimate (95% CI)	3% (0-9%)	0%	10% (0-28%)	0%	11% (1-21%)	7% (1-13%)	21
D100 Gr III-IV Acute GvHD							
# w. gvhd	7	2	1	1	8	12	92
Estimate (95% CI)	19% (5-33%)	29% (0-60%)	10% (0-28)	7% (0-20%)	22% (9-35%)	18% (9-27%)	76

COMMENT: *These results suggest that additional doses of palifermin beyond day 2 post transplant abrogate the improvement in mucositis seen six doses (days –11, -10, -9, 0,1,2). This highlights how critical the timing of palifermin dosing is to its efficacy. There is no suggestion that treatment with palifermin reduces the incidence of aGVHD.*

7.2.2.1 Other studies

7.2.2.2 Postmarketing experience

There is no post marketing experience with palifermin.

7.2.2.3 Literature

There is no published experience of palifermin in the literature not included in this submission. There are no approved formulations of KGF, and all the data supporting the clinical experience with palifermin is contained in this application.

7.2.3 Adequacy of Overall Clinical Experience

For a drug for use as supportive care in the oncology setting, a safety database of 500 subjects exposed to the investigational agent is adequate. There are 650 subjects in the transplant safety pool with 409 palifermin subjects; there are 304 solid tumor subjects with 195 palifermin subjects; there are 210 normal volunteer pharmacology study subjects with 145 palifermin subjects. There are a total of 749 subjects with safety data from Amgen submitted to support this application. This is adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The development program of palifermin was appropriate to evaluate the toxicity of palifermin given in the transplant setting. In this setting, patients receive a single short course of palifermin. The potential risk of tumor promotion is less pressing in this population of patients; hematologic malignancies do not express KGF receptors. As Amgen expands the indication to solid tumors of epithelial origin, additional animal testing of tumor promotion will be required.

7.2.5 Adequacy of Routine Clinical Testing

The laboratory testing and required observations outlined in section 7.1.5.1 Eliciting adverse events data in the development program is appropriate to adequately identify adverse events related to palifermin in this setting. The vast majority of the observations and required studies were obtained and included in the data bases submitted with this application.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Amgen has conducted a study evaluating the pharmacokinetics of palifermin in subjects with renal insufficiency. This trial 20030142 has completed study enrollment.

The analysis and results will be submitted as a post marketing commitment to this application. Availability of this analysis after approval will not present a safety impediment to the indication covered in this submission. Transplantation is a partially elective procedure; adequate renal function is a prerequisite to proceeding with transplantation.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There are no recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

The adverse events specifically associated with recombinant human growth factors are allergic reactions and development of antibodies. The data submitted to support this application and the immunogenicity evaluation have thoroughly evaluated these issues in context of the indication supported by this application. Allergic reactions usually do not occur with the first exposure to a potential allergen, but with subsequent exposure. In the transplant setting with the dose and schedule supported by this application, allergic reactions with the second set of infusion of the drug on days 0, 1, 2 have not been identified. Amgen has developed and validated an ECL-based — assay; this validation has been reviewed by the FDA and is acceptable. Based on evaluation with this assay and with supplementary evaluation with a bioassay, antibodies reactive with KGF have not been detected in Amgen's clinical studies. Continued surveillance in

the solid tumor setting is important, as the risk of allergic reaction with infusion and development of antibodies is greater in subjects who receive multiple courses over time.

7.2.9 Additional Submissions, Including Safety Update

The safety update was electronically submitted to the BLA application 10/19/04. The following items were included in this submission.

• Additional data from two ongoing long-term safety follow-up studies; Study 960226 (long-term follow up for subjects enrolled in the setting of high-dose myelotoxic therapy studies 960189, 980231, 2000162 and 20010182) and Study 990123 (long-term follow up for subjects enrolled in the fractionated chemotherapy setting studies 970149 and 990119)
• Safety data from the ongoing study 20010182 Part B
• A comprehensive summary of slit lamp data which includes data provided in the original BLA submission now supplemented with data from the ongoing study 20010182 Part B
• A summary of safety from the completed, investigator-sponsored IND study 990750 examining the use of palifermin in the setting of allogeneic transplant

The long-term safety follow-up studies have been incorporated into section 7.1.11 Human Carcinogenicity. Results of slit lamp evaluation are included in section 7.1.12 Special Safety studies. The results of the investigator study of IND 8783 are presented in section 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety.

The information regarding 20010182 part B An Open-label Study of the Pharmacokinetics [PK] of Recombinant Human Keratinocyte Growth Factor [palifermin; rHuKGF] in Subjects With Hematologic Malignancies Undergoing Total Body Irradiation and High-dose Chemotherapy Followed by Peripheral Blood Progenitor Cell [PBPC] Transplantation is presented below:

This study is the second part of the pharmacokinetic study in transplant subjects undergoing transplant for the same indications and same transplant protocol used in the pivotal trial that supports the indication of palifermin in this application.

In part B of this trial palifermin is given as a dose of 180μg/kg on days –11, and day 0 after PBSC, in contrast to 60μg/kg on days –11, -10, -9, 0, 1, and 2 in Study 20000162 and in the subjects from Study 980231 used to support efficacy of this application.

Preliminary results from Part B are available for 8 of the 12 subjects planned to be enrolled in this part of the study.

Demographics:

Table 7-75 Demographics of Study 20010182 Part B

Table 7.75 Demographics of Study 20010182 Part B	
	Palifermin (N = 8)
Sex - n(%)	
Male	9 (63%)
Female	3 (38%)
Race - n(%)	
Caucasian	8 (100%)
Age (years) - n(%)	
31-40	2 (25%)
51-60	4 (50%)
61-64	1 (13%)
65-70	1 (13%)
Age (years)	
Mean	54.5
Median	58.0
Diagnosis –n (%)	
Non-Hodgkin's lymphoma	8 (100%)

Deaths:
No subjects died.

Dropouts due to adverse events:
No subjects dropped out due to adverse events. One subject (124) received only 1 dose and then withdrew consent; the reason was not provided.

Overall Summary of Adverse Events:

Table 7-76 Overall Summary of Adverse Events Study 20010182 Part B All Subjects Treated with Palifermin

Table 7.76 Overall Summary of Adverse Events Study 20010182 Part B All Subjects Treated with Palifermin (N=8)	
EVALUABLE FOR SAFETY	8 (100)
ALL ADVERSE EVENTS	8 (100)
Serious adverse events	2 (25)
TREATMENT-RELATED ADVERSE EVENTS	4 (50)
Serious adverse events	0 (0)
DISCONTINUATIONS DUE TO ADVERSE EVENTS	0 (0)
DEATHS ON STUDY	0 (0)

As in previous studies all subjects experienced adverse events. The majority of these events were related to chemotherapy and radiotherapy.

The table below summarizes the adverse events that were designated as treatment related.

Table 7-77 Adverse Events Categorized as Treatment Related Study 20010182 Part B

Table 7.77 Adverse Events Categorized as Treatment Related Study 20010182 Part B				
Day Onset	Verbatim term	Preferred term	Severity	Serious
-8	SKIN REDNESS ABD, CHEST, FACE, HANDS	ERYTHEMA	Mild	No
0	FLUSHING	FLUSHING	Mild	No
-9	RASH	RASH	Moderate	No
0	TASTE DISTURBANCE	TASTE PERVERSION	Moderate	No
-11	THICK / TINGLING FEELING ON TONGUE / LIPS	PARESTHESIA	Mild	No
-11	SWELLING UNDER MANDIBLE	EDEMA	Moderate	No
-11	MANDIBLE TENDERNESS	PAIN	Moderate	No
-8	COATING ON TONGUE	TONGUE DISORDER	Moderate	No

The summary of adverse events designated as severe are summarized in the table below.

Table 7-78 Subject Incidence of Severe Adverse Events in Descending Order of Frequency Study 20010182

Table 7.78 Subject Incidence of Severe Adverse Events in Descending Order of Frequency Study 20010182			
	Pre-Chemo (N = 8)	**Post-Chemo (N = 8)**	**All Adverse Events (N = 8)**
Number of Subjects Reporting Severe Adverse Events	**2 (25)**	**6 (75)**	**6 (75)**
Febrile Neutropenia	0 (0)	3 (38)	3 (38)
Fever	1 (13)	2 (25)	3 (38)
Diarrhea	0 (0)	2 (25)	2 (25)
Anorexia	0 (0)	1 (13)	1 (13)
Arthralgia	1 (13)	1 (13)	1 (13)
Earache	1 (13)	0 (0)	1 (13)
Epistaxis	0 (0)	1 (13)	1 (13)
Pain	1 (13)	0 (0)	1 (13)
Pain Neck	1 (13)	0 (0)	1 (13)
Pain Pleural	0 (0)	1 (13)	1 (13)
Pneumonia	0 (0)	1 (13)	1 (13)
Taste Perversion	0 (0)	1 (13)	1 (13)
Thrombocytopenia	0 (0)	1 (13)	1 (13)

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Skin and oral adverse events – The characteristic adverse events associated with treatment with palifermin are skin and oral toxicity. These adverse events are likely related to palifermin's pharmacologic action on KGFR-expressing tissues.

The skin toxicity is reported as rashes, pruritus, erythema, and edema. The oral toxicity is reported as mouth/tongue discoloration or thickness, and taste disorders.

These events are reversible, usually mild to moderate in severity. Usually these events do not require discontinuation of dosing. In the transplant setting the median time to onset for skin and oral related events was 6 days after the first of 3 consecutive daily doses, with a median duration of 5 days.

The skin and oral toxicity are discussed in more detail in the following sections:
Section 7.1.2 Other serious adverse events
Section 7.1.3 Dropout and other significant adverse events
Section 7.1.4 Other search strategies
Section 7.1.5 Common adverse events
Section 7.2.9 Additional submissions, including safety update

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Overall the study data was pooled into three groups, transplant, head and neck cancer, and colorectal cancer. It is important to look at this data separately. Most adverse events on these trials were due to the chemotherapy and radiotherapy, adverse event related to palifermin can only be analyzed in groups who received similar therapy.

7.4.1.2 Combining data

Overall the study data was pooled into three groups, transplant, head and neck cancer, and colorectal cancer. It is important to look at this data separately. Most adverse events on these trials were due to the chemotherapy and radiotherapy, adverse event related to palifermin can only be analyzed in groups who received similar therapy.

7.4.2 Explorations for Predictive Factors

No predictive factors for treatment adverse events due to age sex or race were identified in this analysis.

7.4.2.1 Explorations for dose dependency for adverse findings

In the normal volunteer population transient increases in amylase and lipase were documented. The incidence of elevated amylase and lipase was slightly higher in healthy subjects receiving cumulative palifermin doses of ≥120 μg/kg, compared to placebo. The elevated amylase and lipase is not clinically significant. A dose related increase of systolic blood pressure related to palifermin was also observed.

7.4.2.2 Explorations for time dependency for adverse findings

In the transplant setting skin and oral adverse events the median time to onset for skin and oral related events was 6 days after the first of 3 consecutive daily doses, with a median duration of 5 days.

7.4.2.3 Explorations for drug-demographic interactions

Adverse event were analyzed by age, ≥ 65 years; sex; race, Caucasian, Black, Hispanic and other. There were no obvious drug – demographic interactions.

7.4.2.4 Explorations for drug-disease interactions

There was no evaluation of the relationship of drug – disease interactions and incidence of adverse events.

7.4.2.5 Explorations for drug-drug interactions

There was no evaluation of the relationship of drug – drug interactions and incidence of adverse events.

7.4.3 Causality Determination

The causality determinations for the adverse events were reviewed by reviewing the CRF's for Study 20000162. Overall these were appropriate. There was a tendency to categorize adverse events most likely to be related to another drug the subject received as related or possibly related.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing schedule chosen for palifermin in the transplant setting, 3 days prior to staring the preparative regimen and 3 days after completion of therapy and after infusion of stem cells was chosen based on the following observations. The protective function of palifermin is attributed to its mitogenic effect on the mucosal epithelium. When palifermin is administered prior to the cytotoxic insult, it stimulates increased epithelial thickness. When dosed after the cytotoxic insult it promotes epithelial recovery.

In the phase 2 transplant trial 980231 Amgen evaluated a schedule of palifermin administration of 60μg/kg days -11, -10, -9, prior to preparative regimen; day-5 at the end of total body irradiation and prior to chemotherapy; day 0, 1, 2. after infusion of stem cells. Subjects who received the day – 5 dose had worse mucositis than the subjects who received placebo. The schedule of the dosing of palifermin is critical, as poorly timed administration can be detrimental. The recommended schedule was demonstrated to be very effective in subjects who receive the preparative regimen used in Studies 20000162 and 980231.

The dose of 60μg/kg for 3 doses (180μg/kg) is justified based on pharmacodynamic studies in normal volunteers. In these studies, the endpoint to assess epithelial cell proliferation was Ki67 staining in buccal biopsies. The pharmacologic effect, that is Ki67 staining indicating proliferation, persisted beyond the time the drug levels were detectable. The epithelial proliferative response increased with increasing doses from 60 to 250 μg/kg , reaching a plateau at 160μg/kg.

Amgen is currently evaluating a schedule of 180μg/kg days –11 and 0. This schedule delivers the same total dose, but simplifies the administration. The results of this trial are not available at this time.

The recommended route of administration is intravenous. In the first study of palifermin in healthy volunteers, Study 950170, palifermin was administered subcutaneously. There was a high incidence of injection site reactions. These were mild in severity and did not require treatment. The study was terminated due to these, and the decision was made to use the intravenous route in the future development of the drug.

8.2 Drug-Drug Interactions

There were no drug-drug interaction studies performed.

8.3 Special Populations

There were no studies performed to evaluate dosing based on race, gender, age, or pediatric age group. Amgen has submitted a protocol and plans to study pharmacokinetics of palifermin in a

pediatric population receiving high dose methotrexate for treatment of non-Hodgkin's lymphoma. Amgen has completed a pharmacokinetic study in subjects with renal impairment; the final study report of this trial will be submitted in the near future.

8.4 Pediatrics

See section 8.3 regarding pediatric study. A consult with the Division of Pediatric Drug Development was not considered necessary. The study in pediatric non-Hodgkin's disease will be one of Amgen's postmarketing commitments.

8.5 Advisory Committee Meeting

An Advisory Committee meeting was not considered necessary for this product.

8.6 Literature Review

The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology created a Mucositis Study Section in 1998. In 2000, the Mucositis Study Section established a panel of experts charged to develop evidence-based guidelines for the prevention and treatment of oral and GI mucositis. In July of 2004 the results of this effort was published in a Supplement to Cancer entitled Mucositis: Perspectives and Clinical Practice Guidelines. It consisted of two review articles entitled Perspectives on Cancer Therapy-Induced Mucosal Injury (Sonis and Elting et al. 2004), and Clinical Practice Guidelines for the Prevention and Treatment of Cancer Therapy-Induced Oral and Gastrointestinal Mucositis (Rubenstein and Peterson et al. 2004). The content of this review is based on these articles.

Oral mucositis is a common complication of cancer therapy, both radiotherapy and chemotherapy. Oral mucositis is associated with pain and impairs the quality of life of cancer patients and in neutropenic patients increases the risk of sepsis (Elting and Cooksley et al. 2003). In some patients it becomes a dose limiting toxicity preventing delivery of cancer therapy.

Chemotherapy/Radiotherapy induced oral mucositis has been demonstrated to be a complex process involving tissue and cellular elements of the mucosa (Sonis and Elting et al. 2004). Mucosal barrier injury can be divided into 5 phases. 1. Initiation, this is the initial tissue injury mediate by oxidative stress and reactive oxygen species. 2. Up-regulation and generation of messenger signals, nuclear factor-κB is a leading contender as a transcription factor identified as important in initiating events in response to radiation or chemotherapy. This factor up-regulates genes that result in the production of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6. This leads to tissue injury and apoptosis. Up-regulation of other genes leads to expression of adhesion molecules, cyclooxygenase-2 and angiogenesis. 3 Signaling and amplification, proinflammatory cytokines can activate other pathways such as ceramide and caspase pathways that lead to further tissue damage. 4. Ulceration, this phase is characterized by an inflammatory infiltrate of polymorphonuclear cells and mononuclear inflammatory cells. During this phase bacterial colonization occurs. This leads to activation of macrophages and stimulates more proinflammatory cytokine production. These result in pain and risk for bacteremia and sepsis. 5.

Healing, in this phase there is renewal of epithelial proliferation and differentiation and subsequent reestablishment of the local microbial flora.

In this review article the Mucositis Study Section of the Multinational Association for Supportive Care in Cancer; International Society for Oral Oncology reviewed 14 measurement tools used to assess mucositis. Below is an abridged table. This includes WHO (1), RTOG (2), and WCCNR (3) scales, the scales used to evaluate palifermin. The NCI-CTC(4, Trotti and Byhardt et al. 2000) scale is also included.

Table 8-1 Abridged Table Derived from Mucositis Study Section Report Comparing Mucositis Grading Scales

Table 8.1 Abridged Table Derived from Mucositis Study Section Report Comparing Mucositis Grading Scales

Scale (use)	Elements measured	Advantages	Disadvantages
WHO (clinical and research)	Combined elements, symptom (pain) signs (erythema, ulceration); function: type of dietary intake	Used widely in research and clinical care settings; specific scales for mucositis in patients undergoing head/neck radiation, chemotherapy or transplant	Research assessment potentially confounded by combination of symptoms, signs, and functional changes
RTOG (clinical and research)	Combined elements, symptom (pain) signs (unspecified); function: unspecified	Used widely in research and clinical care settings	Research assessment potentially confounded by combination of symptoms, signs, and functional changes
WCCNR (clinical)	Lesions, color, bleeding, subjective variables	Global scale that can reflect clinical status/outcomes, refined in 1998 based on elimination of five measures other than lesions, color, or bleeding	Mixed objective, subjective and functional variables; difficult to score precisely
NCI-CTC (clinical and research)	Combined elements, symptom (pain) signs (erythema, ulceration); function: type of dietary intake	Used widely in research and clinical care settings; specific scales for mucositis in patients undergoing head/neck radiation, chemotherapy or transplant	Research assessment potentially confounded by combination of symptoms, signs, and functional changes

A table comparing the WHO, RTOG, and WCCNR scale is presented in Section 1.3.2 Efficacy. The conclusion from this review, confirms the scales used in this application are currently the best assessment tools available to study oral mucositis due to chemotherapy and radiotherapy. Proper training of evaluators is an important factor in the reliability and reproducibility of data derived form these scales.

Outcome and cost of oral mucositis is significant. Among adult hematopoetic transplant recipients 85% require feeding tubes, 80% require opioid analgesics. An evaluation of the economic impact of severe mucositis determined that patients with ulcerative mucositis received 5.8 additional days of narcotics and 1.9 additional days of total parenteral nutrition compared to patients who did not have ulceration (Sonis and Oster et al.2001). A second study documented a 3 times greater risk of streptococcal bacteremia in patients with ulcerative mucositis compared to transplant patients without ulceration (Ruescher and Sodeifi et al.1998).

The state of the art of clinical approach to the prevention and treatment of oral mucositis was evaluated by the Mucositis Study Section of the Multinational Association of Supportive Care in an Cancer and the International Society for Oral Oncology A panel of 36 mucositis experts reviewed the literature between January 1966 and May 2002 (Rubenstein and Peterson et al. 2004). This review was done using the evidence-based guidelines according to Hadourn et al. (Hadorn and Baker et al.1996). The following guidelines were recommended:

Table 8-2 Recommendations for Treatment and Prevention Oral Mucositis by Mucositis Study Section Based on Evidence Based Review of Literature

Table 8.2 Recommendations for Treatment and Prevention Oral Mucositis by Mucositis Study Section Based on Evidence Based Review of Literature		
Guideline	**Level of evidence**	**Strength of Recommendation**
Oral care protocols that include patient education in an attempt to reduce the severity of mucositis from chemotherapy or radiotherapy	Well designed, quasi-experimental studies, such as nonrandomized, controlled, single-group, pretest-posttest comparison, cohort, time, or matched case-control series (Level III)	Evidence and findings are generally consistent from trials reviewed (Grade B)
Patient-controlled analgesia (PCA) with morphine as the treatment of choice for oral mucositis pain in patients undergoing hematopoietic transplant	Meta-analysis of multiple well designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power) (Level I)	Evidence of Level I or consistent findings from multiple studies of Level II, III, or IV (Grade A)
Topical preparations including: viscous lidocaine, benzocaine, milk of magnesia, kaolin, pectin, chlorhexadine, dyphenhydramine, benzydamine	No evidence of effectiveness or tolerability	Because of potential toxicity of adsorption of amide anesthetics through damaged mucosal surface requires study to determine toxicity and efficacy
AGAINST Chlorhexidine to prevent oral mucositis in patients with solid tumors of the head and neck who are undergoing radiotherapy	At least one well designed experimental study, randomized trials with high false-positive or high false-negative errors or both (low power)(Level II)	Evidence and findings are generally consistent from trials reviewed (Grade B)
Patients receiving bolus 5-FU chemotherapy undergo 30 minutes of oral Cryotherapy to prevent oral mucositis	At least one well designed experimental study, randomized trials with high false-positive or high false-negative errors or both (low power)(Level II)	Evidence of Level I or consistent findings from multiple studies of Level II, III, or IV (Grade A)
Patients who are treated with bolus doses of edatrexate 20-30 minutes of oral Cryotherapy to decrease mucositis	Well designed, nonexperimental studies, such as comparative and correlational descriptive and case studies (Level IV)	Evidence and findings are generally consistent from trials reviewed (Grade B)
AGAINST Acyclovir used routinely to prevent mucositis	At least one well designed experimental study, randomized trials with high false-positive or high false-negative errors or both (low power)(Level II)	Evidence and findings are generally consistent from trials reviewed (Grade B)
AGAINST Chlorhexidine to treat established oral mucositis	At least one well designed experimental study, randomized trials with high false-positive or high false-negative errors or both (low power)(Level II)	Evidence and findings are generally consistent from trials reviewed (Grade B)
AGAINST Pentoxifylline to prevent mucositis in patients undergoing hematopoietic transplant	At least one well designed experimental study, randomized trials with high false-positive or high false-negative errors or both (low power)(Level II)	Evidence and findings are generally consistent from trials reviewed (Grade B)
Centers with capability Low-level laser therapy to reduce the incidence of oral mucositis patients undergoing hematopoietic transplant (Expensive/complicated/time-consuming)	At least one well designed experimental study, randomized trials with high false-positive or high false-negative errors or both (low power)(Level II)	Evidence and findings are generally consistent from trials reviewed (Grade B)

The review of the literature supports the approval of this application. Palifermin promotes epithelial proliferation. Epithelial proliferation is an integral step in the resolution of mucositis based on the current understanding of the pathophysiology of mucositis. The trials used to

support this application were conducted using the best available assessment tools available to grade mucositis. There are no approved drugs of treatments that reduce incidence duration or severity of mucositis associated with chemotherapy and radiotherapy.

8.7 Postmarketing Risk Management Plan

The post-marketing risk management plan includes:

- Amgen will perform a RAS H2 Mouse Model study in order to understand the potential risk of secondary tumor development when KGF is used to treat mucositis.
- Amgen will develop a comprehensive long-term follow up program for solid tumors.

8.8 Other Relevant Materials

There is no additional relevant material.

9 OVERALL ASSESSMENT

9.1 Conclusions

The information submitted in this BLA demonstrates that palifermin decreases the incidence and duration of severe mucositis associated with Total Body Irradiation and myeloablative chemotherapy administered to subjects undergoing autologous stem cell transplant. The clinical benefit to transplant subjects justifies the side effects associated with palifermin. The major side effects are associated with the pharmacological effect of palifermin on normal epithelial cells, primarily skin and oral mucosa.

9.2 Recommendation on Regulatory Action

Recommend palifermin be approved for the indication "to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support."

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The major potential risk identified at this time is the risk of tumor promotion. Amgen proposes to address the potential risk through routine labeling and pharmacovigilance. The pharmacovigilance plan includes the following:

- Post-marketing surveillance with special attention to malignancies
- Long-term follow-up of patients enrolled in clinical studies conducted in the hematologic malignancy setting
- A prospective cohort study using available US International Bone Marrow Transplant Registry and the Autologous Blood and Marrow Transplant Registry databases to establish an adequate control group for the long-term follow-up studies

9.3.2 Required and /or Agreed Upon Phase 4 Commitments

Product Post Marketing Commitments

1. 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 multi-agent 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.

2. To complete and submit data from study protocol 960226, a long-term observational follow-up study of subjects previously enrolled in any palifermin study conducted in the myelotoxic therapy setting. Interim results will be provided to the FDA annually with amendments to the label if applicable, beginning 15 December 2005, for 10 years. The final study report will be submitted to the FDA by 30 June 2015.

3. To complete and submit data from study protocol 990123, a long-term observational follow-up study of subjects with head and neck cancer previously enrolled in palifermin studies in the fractionated chemoradiotherapy setting. Interim results will be provided to the FDA annually with amendments to the label if applicable, beginning 15 December 2005, for 10 years. The final study report will be submitted to the FDA by 30 June 2015.

4. To submit the final study report for protocol 20030142, a phase 1 study to evaluate the pharmacokinetics of palifermin in subjects with renal impairment. The study was completed by May 2004 and a final study report will be submitted to the FDA by January 2005.

5. To conduct an *in vivo* study inhealthy volunteers to evaluate the drug-drug interaction of palifermin with heparin. The study protocol will be submitted to the FDA by 1 September 2005, will be initiated by 1 November 2005 and will be completed by 30 September 2006 and final study report submitted to the FDA by 30 March 2007.

6. To conduct an *in vitro* study to evaluate the drug-drug interaction of palifermin with low molecular weigh heparins. The study protocol will be submitted to the FDA by 1 July 2005, will be initiated by 1 October 2005; the study will be completed by 30 April 2006 and final study report submitted to the FDA by 30 October 2006.

7. To conduct an *in vivo* study in healthy volunteers, contingent on the results of the *in vitro* study, to evaluate the drug-drug interaction of palifermin with low molecular weight heparin. If required, the study protocol will be submitted to the FDA by 30 September 2006, will be initiated by 30 November 2006; the study will be completed by 30 September 2007 and final study report submitted to the FDA by 30 March 2008.

8. To conduct a study to determine the incidence of cataracts, and decreased visual acuity in patients who have received palifermin. This study will be a component of the clinical study 20040253 in patients with metastatic breast cancer receiving multicycle chemotherapy. The final protocol will be submitted to the FDA by 30 September 2005, will be initiated by 30 January 2006; the study will be completed by 30 July 2008 and the final study report submitted to the FDA by 31 December 2008.

9. To evaluate the incidence and characteristics (severity, duration, reversibility and clinical sequelae) of proteinuria in patients receiving palifermin. Appropriate testing will be conducted in a clinical study of adequate size. The study protocol will be submitted to the FDA by 30 September 2005, will be initiated by [redacted]ebruary 2006, will be completed by

30 June 2008 and the final study report will be submitted to the FDA by 31 December 2008.

10. To complete study 103599 to evaluate the potential of palifermin to enhance the incidence of spontaneous tumors in the Tg.rasH2 transgenic mouse model. This study was initiated in July 2004. An audited draft report will be available by June 2005. The final report will be submitted to the FDA by December 2005.

11. To conduct a prospective cohort study using the available International Bone Marrow Transplant Registry (IBMTR) and Autologous Blood and Bone Marrow Registry (ABMTR) databases, to evaluate the incidence of secondary malignancies, cancer relapse rates and survival in patients who received palifermin compared to a matched patient control group who have not received palifermin. The study protocol will be submitted to the FDA by 30 July 2005, will be initiated by 31 January 2006. Interim data will be provided to the FDA at 2-year intervals for a period of 10 years, beginning 31 July 2008. The final study report will be submitted to the FDA by 31 July 2016.

12. To re-evaluate the following:

a) Action and acceptance limits for Palifermin Drug Substance yields after manufacture of —lots;
b) In-process controls, release, and stability specifications on all Drug Product lots manufactured through the end of 2007; and
c) In-process controls, release, and stability specifications on all Drug Substance lots manufactured through the end of 2008.
Results of these re-evaluations will be submitted to the agency by March 31, 2008 for d rug product and March 31, 2009 for drug substance.

13. To evaluate the photo stability of Palifermin Drug Product under conditions that are representative of the conditions for use of the lyophilized and reconstituted Palifermin Drug Product, and to submit the results of the study with revised labeling, if necessary, by September 30, 2005.

14. To evaluate the specificity of the ELISA — Method as an identity test for the Palifermin Drug Product, by a quantitative comparison of cross-reactivity to a series of FGF-related growth factors that are highly homologous in amino acid sequence to Palifermin, and report the results of this study by December 31, 2005.

15. To establish an in-process control test [ ] in the manufacture of Palifermin Drug Substance by September 30, 2005.

16. To submit ED50 control limits for the reference standard used in the bioassay [ ] to the FDA by September 30, 2005.

17. To evaluate [ ] test in Palifermin Drug Product vials exposed to accelerated storage conditions including heat and light, and to report results of the study by September 30, 2005.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

9.4.1 Review of Package Insert

The format of the review of the proposed Package Insert is as follows:
The section heading from Amgen's draft labeling listed all in bold

- followed by reviewer's comments as bullets

DESCRIPTION

- Weight per volume percentage of polysorbate 20 should be added.
- Otherwise no revision necessary

CLINICAL PHARMACOLOGY
Mechanism of Action

- Revise for scientific accuracy, to remove non-relevant information, and to limit overbroad, speculative or promotional language.
- Recommend deletion of most literature references. Published literature is generally not referenced in labeling because the information has not been reviewed, can become quickly outdated.

CLINICAL PHARMACOLOGY
Preclinical Experience

- Revise this section to clarify meaning, to maintain scientific accuracy and clinical relevance, and to only present findings for which the primary data are available for review.
- Merge into **CLINICAL PHARMACOLOGY, Mechanism of Action**

CLINICAL PHARMACOLOGY
Pharmacologic Effects of [TRADE NAME™]

- Revise this section as **CLINICAL PHARMACOLOGY, Pharmacodynamics**, omitting less relevant material.

CLINICAL PHARMACOLOGY
Pharmacokinetics

- Revise this section for accuracy and clarity

CLINICAL PHARMACOLOGY

Special Populations

- No revision necessary

CLINICAL STUDIES

- Revise **CLINICAL STUDIES** section to accurately and concisely discuss the two studies in which the safety and efficacy of palifermin were established. (Study 20000162 denoted as "study 1" and Study 980231 as "study 2").
- Replace "primary endpoint" with "main efficacy endpoint".
- Present Study 1 efficacy results in Table 1 only.
- Replace discussion of patient reported outcomes with a short statement supported by data. After review only Mouth and Throat Soreness data were acceptable for inclusion in label. Delete Table 2.

Comments on Table 1

- [ ] P value for primary endpoint should be presented as footnote only.
- Placebo and Tradename columns should be transposed.
- Inclusion of decimal points implies accuracy to numbers of significant digits not supported by data.

Comments on Figure 1

- Substitute bar graph for draft Figure 1 to provide more valid representation of the data.

Comments on Table 2

- Use of p values and exact percentages of symptomatic improvement implies level of accuracy not supported by the data. Table 2 should be deleted.

INDICATIONS AND USAGE

- Revise to include results of primary endpoint only.
- Add statement regarding lack of information on safety and efficacy in patients with non-hematologic malignancies.

CONTRAINDICATIONS

- No revision necessary

PRECAUTIONS

[ ]

- Delete this section and integrate information into new PRECAUTIONS, Drug Interactions section to be developed. The new PRECAUTIONS, Drug Interactions section will discuss absence of formal drug-drug interaction studies, binding to heparin in vitro, and timing of administration of palifermin.
- Develop section entitled PRECAUTIONS, Potential for Stimulation of Tumor Growth discussing concerns and evidence regarding palifermin's potential for stimulation of growth of non-hematopoietic tumors.

PRECAUTIONS
Information for Patients

- Description of possible adverse effects needs to be expanded. Will recommend patients be notified regarding palifermin's potential for stimulation of growth of non-hematopoietic tumors.

PRECAUTIONS
Carcinogenesis, Mutagenesis, Impairment of Fertility

- No revision necessary

PRECAUTIONS
Pregnancy Category C

- Provide short introductory summary statement.
- Delete discussion of [ ]. Despite these findings, embryotoxic events have occurred.
- Delete references to [ ]

PRECAUTIONS
Lactating Women

- No revision necessary

PRECAUTIONS
Pediatric use

- No revision necessary

PRECAUTIONS
Geriatric Use

- Delete reference to [ ] Too few subjects > age 65 were studied to draw conclusions.

ADVERSE REACTIONS

- Add reference to section on Potential for Stimulation of Tumor Growth.
- Clarify nature of AES.
- Delete reference to [ ]
- Insert new sections on Hypertension and Proteinuria based on review findings.
- Delete discussion of [ ]
- Add discussion of Skin Rash as most common SAE.

Comments on Table 3

- Revise table to transpose [Trade Name] and placebo columns
- Revise table to reflect incidence of AEs from FDA review
- Add AEs from FDA review of data, including fever, CNS, and metabolic.
- Add data regarding elevations of amylase and lipase

ADVERSE REACTIONS

Immunogenicity

- Revise for clarity and to conform to FDA review data.

OVERDOSAGE

- Revise to include data from patients receiving multiple doses of 80 mcg/kg/day. Five of 14 experienced serious or severe AEs.

DOSAGE AND ADMINISTRATION

- Revise for consistency with remainder of label.

PREPARATION OF [TRADE NAME™]

- Revise for clarity and consistency.
- Omit lengthy recommendation [ ]
- Add "Do not freeze the reconstituted solution".

ADMINISTRATION OF [TRADE NAME™]

- No revision necessary

[ ]

- Delete section and incorporate elements into Preparation section.
- Omit lengthy discussion of [ ]

HOW SUPPLIED

- Revise for clarity

REFERENCES

- Delete unnecessary references

9.4.2 Review of Other Labeling Elements

PACKAGE AND CARTON LABELING

No comments

TRADE NAME REVIEW

Amgen originally proposed a Tradename; however this Tradename was not approved by European Regulatory Agencies, and was withdrawn from consideration.
Subsequently, Amgen proposed the tradename Kepivance™. A consultative review was requested from the Division of Medication Errors and Technical Support (DMETS). They found Kepivance™ to be acceptable as a tradename for Amgen's palifermin.

MEDICATION GUIDE OR PATIENT PACKAGE INSERT

9.5 Comments to Applicant

No additional comments to Amgen.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Final Clinical Study Report Summary Study 20000162

IND#: [ ] **Amendment #:** 179
Date of Submission: 11/25/03
Sponsor: Amgen
Product: Palifermin(rHuKGF)

Protocol:
Clinical Trial Title/Number: 20000162 A Phase 3, Randomized, Double-blind, Placebo-controlled Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) for Reduction of Mucositis in Patients with Hematologic Malignancies Undergoing Total Body Irradiation (TBI) and High-dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell (PBPC) Transplantation

Dose: 60ug/kg/day daily starting 3 days before preparative regimen, then 3 days starting day 0. (Total 6 doses)
Route: IV bolus
Indication: [ ]
Planned enrollment: 210
Actual enrollment: 214 enrolled and randomized 212 received investigational agent
Terminated early (YES/NO): No

Amendments:
8/14/04

Addition of RTOG as the secondary oral mucositis assessment tool.
Time window for screening subjects extended from 21 to 42 days for some evaluations.
Addition of Safety Monitoring Board
Steroid rinses added to proscribed therapies
Slit lamp test formally integrated into the study

Post Hoc Changes:
None

Results:

Disposition: (copied from sponsors report)
Of 245 subjects screened, 214 subjects were randomized and equally distributed between treatment groups. One hundred six subjects in each treatment group received investigational product (placebo or palifermin). Of subjects who received placebo, 2

discontinued treatment, and of subjects who received palifermin, 3 discontinued treatment. Thus, 104 subjects in the placebo group and 103 in the palifermin group completed treatment with investigational product.

Demographics: (copied from sponsors report)
Placebo Group:
Sex: 34 women, 72 men treated
Mean Age: 46 years
Ethnicity (Race):
White: 84%;
Black: 7%,
Hispanic: 7%,
Asian: 1%,
Other: 2%
Palifermin Group:
Sex: 47 women, 59 men treated
Mean Age: 46 years
Ethnicity (Race):
White: 74%
Black: 10%,
Hispanic: 10%;
Asian: 4%,
Other: 2%

Baseline Characteristics: (copied from sponsors report)
Subjects 18 years of age or older with a Karnofsky performance score (KPS) > or = 70% who were scheduled to undergo autologous PBPC transplantation after a conditioning treatment of TBI plus high-dose etoposide and cyclophosphamide for one of the following hematologic malignancies:

- non-Hodgkin's lymphoma (NHL)
- Hodgkin's disease
- acute myelogenous leukemia
- acute lymphoblastic leukemia
- chronic myelogenous leukemia
- chronic lymphocytic leukemia
- multiple myeloma

Efficacy: (copied from sponsors report)

Primary:

Palifermin 60 ug/kg/day administered on 3 consecutive days before and after TBI, chemotherapy, and PBPC infusion resulted in statistically significant and clinically meaningful improvement in duration and incidence of severe oral mucositis. The mean (SD) duration of WHO grade 3 or 4 oral mucositis, the primary endpoint for this study, was 10.4 (6.2) days for the placebo group compared with 3.7 (4.1) days for the palifermin group (a 64% reduction for the palifermin group compared with the placebo group; $p < 0.001$). Similar results were also observed in sensitivity analysis applying worst-case imputation rules.

Ninety-eight percent of subjects in the placebo group experienced > 1 day of WHO grade 3 or 4 oral mucositis compared with 63% of subjects in the palifermin group ($p < 0.001$).

Secondary:

The robustness of palifermin's effect on the primary endpoint was supported by statistically significant decreases in oral mucositis duration as assessed by other criteria, including duration of WHO grade 2 to 4 oral mucositis, RTOG grade 3 or 4 oral mucositis, and WCCNR grade 2 or 3 oral mucositis. Palifermin also statistically significantly reduced the incidence of WHO grade 4 oral mucositis (placebo, 62%; palifermin, 20%).

The effects of palifermin on PRO measurements, including mouth and throat soreness and related functional impairment, were consistent with the clinical findings. The area under the curve (AUC) for mouth and throat soreness on the verbal descriptive scale (VDS), with smaller AUC indicating improvement, showed a statistically significant benefit for the palifermin group: mean (SD) = 52.5 (22.4) for placebo and 32.6 (20.8) for palifermin; $p < 0.001$.

Consistent with the decrease in mouth and throat soreness, statistically significant decreases in median cumulative dose of parenteral opioid analgesics (mg morphine equivalents) also were observed in the palifermin group compared with the placebo group: 534.9 mg for placebo and 211.6 mg for palifermin; $p< 0.001$.

Safety: (copied from sponsors report)

For the 212 subjects in the safety analysis subset, the frequency of all adverse events and of serious adverse events was similar between treatment groups. Most adverse events were related to complications associated with the conditioning regimen or complications of the underlying disease.

All subjects reported at least 1 adverse event. Forty-five percent (48/106) of subjects who received placebo and 42% (45/106) of subjects who received palifermin had severe, life-threatening, or fatal adverse events. Serious adverse events were reported in 27% (29/106) of subjects who received placebo and 22% (23/106) of subjects who received palifermin. One subject in each treatment group had a treatment-related serious adverse event: hypotension in a subject who received placebo and rash in a subject who received palifermin. Two deaths occurred on study: 1 subject who received placebo died of sepsis and 1 subject who received palifermin died of veno-occlusive liver disease. These deaths were reported by the investigator as not related to investigational product. Forty-two percent (45/106) of subjects in the placebo group and 72% (76/106) of subjects in the palifermin group had at least 1 treatment-related adverse event. Adverse events consistent with KGF stimulation of epithelial cells in the skin and oral mucosa were reported more frequently in the palifermin group than the placebo group. Skin events (placebo, palifermin) included rash (46%, 55%), pruritus (32%, 50%), erythema (30%, 44%), hypoesthesia (4%, 10%), and paresthesia (1%, 9%). Oral events (placebo, palifermin)

included taste perversion (9%, 22%), lesion oral (excluding oral mucositis) (10%, 18%), tongue disorder (6%, 12%), and taste loss (4%, 10%). In general, these events were reported as mild to moderate in severity, were transient (median time to onset approximately 3 days after the third dose of palifermin, with approximately 3 days duration), and were not cause for discontinuation of investigational product administration. One subject in the placebo group discontinued from study due to pruritus.

Transient, asymptomatic increases in serum amylase levels (primarily salivary in origin) were observed in both treatment groups. Asymptomatic increases in serum lipase levels were observed in both treatment groups; peak levels were observed on the last day of TBI and returned to near baseline levels by the day of PBPC transplant. No clinically significant or unexpected findings were observed for other chemistries or hematologic laboratory parameters. No subjects' antibody assay results indicated antibody formation to palifermin.

Conclusions:
The results from this study demonstrate that palifermin at the dose/schedule tested is well-tolerated and is an efficacious agent in reducing the incidence and duration of severe oral mucositis in subjects with hematologic malignancies who are undergoing myeloablative high-dose therapy with PBSC support.

Summary: This trial is the pivotal trial supporting approval of a BLA for the use of palifermin in the hematopoeitic transplant to decrease the incidence, duration and severity of severe mucositis. This trial demonstrates the safety and efficacy of palifermin in this setting.

_____ 12/11/04

Patricia Dinndorf, MD — Date
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10.1.2 Final Clinical Study Report Summary Study 980231

IND#: Submitted with BLA
Date of Submission: 6/15/04
Sponsor: Amgen
Product: Palifermin(rHuKGF)

Protocol:
Clinical Trial Title/Number: 980231 A Randomized, Double-blind, Placebo controlled Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation (TBI) and High-dose Chemotherapy with Autologous Peripheral Bloor Progenitor Cell (PBPC) Transplantation.

Dose:60ug/kg/day daily starting 3 days before preparative regimen, on day –5 after TBI before etoposide, then 3 days starting day 0. (Total 7 doses)
Study was amended
Dose: 60ug/kg/day daily starting 3 days before preparative regimen, then 3 days starting day 0. (Total 6 doses)
Route: IV bolus
Indication: [redacted]
Planned enrollment: 111 subjects total 37 in each of palifermin group and 37 placebo
Actual enrollment: 169 subjects enrolled and randomized; 163 subjects received investigational agent; 34 randomized 7 day schedule; 129 randomized 6 day schedule
Terminated early (YES/NO): No

Amendments:
5/27/99

- Include children 12 years of age and above
- Include Multiple Myeloma
- Allow platelet count > 50 x 109/L
- Allow planned tandem transplant subjects
- Allow CD34+ selection of stem cell product
- TBI fractions allowable changed from 6 or 8 to 6,8, or 10 fractions
- Intrathecal methotrexate allowed 8/17/99
- Elimination 4th dose investigational agent

Post Hoc Changes:
Final Statistical Analysis Plan written 4/23/04

Results:
Disposition: (copied from sponsors report)

One hundred sixty-nine subjects were randomized. One subject in the placebo group and 5 subjects in the palifermin groups never received investigational product. Of the 163 subjects in the study who received investigational product, 34 were randomized under the original protocol to receive 7 doses of investigational product (7-dose schedule) (11

placebo, 12 palifermin pre, 11 palifermin pre-post) and 129 subjects were randomized under the amended protocol (Amendment 2) to receive 6 doses of investigational product (6-dose schedule) (40 placebo, 43 palifermin pre, 46 palifermin pre-post).

Demographics:

7-dose Schedule:

Placebo Group:
Sex: 4 women, 7 men treated
Mean Age: 48 years
Ethnicity (Race):
White: 55%;
Black: 27%,
Hispanic: 18%,
Palifermin pre Group:
Sex: 3 women, 9 men treated
Mean Age: 53years
Ethnicity (Race):
White: 67%
Hispanic: 33%
Palifermin pre post Group:
Sex: 3 women, 8 men treated
Mean Age: 45years
Ethnicity (Race):
White: 64%
Black: 18%
Hispanic: 18%

6-dose Schedule:

Placebo Group:
Sex: 20 women, 20 men treated
Mean Age: 42 years
Ethnicity (Race):
White: 75%;
Black: 13%,
Hispanic:10%,
Asian 3%
Palifermin pre Group:
Sex: 30 women, 30 men treated
Mean Age: 46 years
Ethnicity (Race):
White: 70%
Black 16%
Hispanic: 7%
Asian 5%
Other 2%

Palifermin pre post Group:
Sex: 20 women, 26 men treated
Mean Age: 44 years
Ethnicity (Race):
White: 72%
Black: 9%
Hispanic: 15%
Asian 2%
Other 2%

Baseline Characteristics: (copied from sponsors report)

Subjects 16 to 65 years of age or older with a Karnofsky performance score (KPS) > or = 70% who were scheduled to undergo autologous PBPC transplantation after a conditioning treatment of TBI plus high-dose etoposide and cyclophosphamide for one of the following hematologic malignancies:

- non-Hodgkin's lymphoma (NHL)
- Hodgkin's disease
- acute myelogenous leukemia
- acute lymphoblastic leukemia
- chronic myelogenous leukemia
- chronic lymphocytic leukemia
- multiple myeloma

Efficacy: (copied from sponsors report)

7-dose Schedule:

For subjects treated under the 7-dose schedule, no significant statistical or clinical improvements in oral mucositis indices were observed. Furthermore, in the analyses for subjects who actually received 7 doses, a negative, although not statistically significant, trend in oral mucositis parameters was consistently observed for the palifermin pre-post group.

6-dose Schedule:

For subjects treated according to the 6-dose schedule, both the palifermin pre and pre-post groups demonstrated statistically significant and clinically meaningful improvements in duration of severe oral mucositis (WHO grade 3 or 4; the primary endpoint for this study). The mean (SD) duration of WHO grade 3 or 4 oral mucositis for the mITT population was 5.2 (6.1) days for the palifermin pre group and 4.7 (5.7) days for the palifermin pre-post group, compared with 8.6 (8.2) days for the placebo group (p-values for both comparisons < 0.01).

Safety: (copied from sponsors report)

7-dose Schedule:

For subjects treated under the 7-dose schedule, the incidence and types of adverse events generally were similar between treatment groups. Most adverse events were related to complications associated with the conditioning regimen or complications of the

underlying hematologic malignant disease. All subjects experienced at least 1 adverse event. Thirty-six percent (4/11) of subjects in the placebo group, 50% (6/12) of subjects in the palifermin pre group, and 55% (6/11) of subjects in the palifermin pre-post group experienced severe adverse events. A smaller proportion of subjects in the placebo group (18% [2/11]) experienced serious adverse events compared with subjects in the palifermin pre (33% [4/12]) and pre-post groups (27% [3/11]). Serious adverse events reported in the palifermin groups were consistent with those expected in this patient population and primarily included events associated with gastrointestinal and fever/infection-related toxicities associated with the conditioning regimen. A smaller proportion of subjects in the placebo group (18% [2/11]) experienced treatment-related adverse events than in the palifermin pre group (58% [7/12]) and palifermin pre-post group (45% [5/11]). Most treatment-related events were reported as mild to moderate in severity, and none were cause for premature discontinuation from the study. Skin- and oral-related events (eg, rash, erythema, tongue edema) were the most commonly reported treatment-related adverse events. One subject in the palifermin pre-post group experienced a serious treatment-related event (rash). No subjects discontinued the study prematurely because of an adverse event. One subject in the placebo group died of adult respiratory distress syndrome (ARDS) on study day 16. Transient, asymptomatic increases in serum amylase and lipase levels were observed in all treatment groups. In general, peak levels were observed on the day of the last TBI fraction and returned to near or below baseline by the day of PBPC infusion. These increases were not associated with the clinical symptoms of pancreatitis. Notably, the increases in both amylase and lipase were noted only after the administration of the first 3 doses of investigational product and were not observed when assessed after subsequent investigational product administrations (ie, assessments performed on day 14 and/or 28 [end of study]). No clinically significant or unexpected findings were observed for other chemistry or hematologic laboratory parameters. None of the subjects tested in this study were positive for anti-palifermin antibodies.

6-dose Schedule: (copied from sponsors report)

For subjects treated according to the 6-dose schedule, the incidence and types of adverse events were generally similar between treatment groups. Most adverse events were related to complications associated with the conditioning regimen or complications of the underlying hematologic malignant disease. All subjects experienced at least 1 adverse event. Thirty-three percent (13/40) of subjects in the placebo group, 16% (7/43) of subjects in the palifermin pre group, and 30% (14/46) of subjects in the palifermin pre-post group experienced severe, life-threatening, or fatal adverse events. The incidence of serious adverse events was similar between the placebo and palifermin groups. Eighteen percent (7/40) of subjects in the placebo group, 14%(6/43) of subjects in the palifermin pre group, and 17% (8/46) of subjects in the palifermin pre-post group experienced at least 1 serious adverse event. A smaller proportion of subjects in the placebo group (23% [9/40]) experienced treatment-related adverse events compared with subjects in the palifermin pre (42% [18/43]) and palifermin pre-post (52% [24/46]) groups. Most treatment-related events were reported as mild to moderate in severity, and none were cause for premature discontinuation from the study. Two subjects in the palifermin pre-

post group discontinued test article prematurely because of treatment-related adverse events: maculo-papular rash (head) and oral edema in 1 subject and maculo-papular rash (trunk) in the other subject. Skin-related events (rash, erythema, flushing, and pruritus) were the most commonly reported treatment-related adverse events. Three subjects (1 placebo, 2 palifermin pre-post) experienced serious treatment-related events. These events included pain
and abrasion (verbatim term reported as skin toxicity, pain/excoriation) in 1 subject in the palifermin pre-post group, and acute renal failure in 1 subject each in the palifermin pre-post and placebo groups. One subject discontinued the study prematurely because of an adverse event (myocardial infarction reported not related to palifermin) and no subjects died on-study. Transient, asymptomatic increases in serum amylase and lipase levels were observed in all treatment groups. In general, peak levels were observed on the day of the last TBI fraction and returned to near or below baseline by the day of PBPC infusion. These increases were not associated with the clinical symptoms of pancreatitis. Notably, the increases in both amylase and lipase were noted only after the administration of the first 3 doses of investigational product and were not observed when assessed after subsequent investigational product administrations (ie, assessments performed on day 14 and/or 28 [end of study]). No clinically significant or unexpected findings were observed for other chemistry or hematologic laboratory parameters. None of the subjects tested in this study were positive for anti-palifermin antibodies.

Conclusions: (copied from sponsors report)
The observations made in this study led to the following conclusions:

- The timing of administration of palifermin (in relation to cytotoxic insult) seems to be important for efficacy; ie, dosing too close in time to cytotoxic insult (the 7-dose schedule) resulted in loss of protective activity or worsening of mucositis in this study.
- The palifermin pre and palifermin pre-post treatment regimens (with the 6-dose schedule) were both clinically and statistically efficacious in reducing oral mucositis and related sequelae, with a trend towards numerically better results for pre-post treatment.
- The incidence and types of adverse events were generally similar between the placebo and palifermin groups. Most adverse events were related to complications associated with the conditioning regimen or the underlying hematologic malignant disease. Treatment-related adverse events, reported by greater proportions of subjects in the palifermin groups than in the placebo group, were consistent with the pharmacologic action of palifermin and included primarily skin-related events (rash, erythema, flushing and pruritus).
- The safety profile of palifermin was generally similar between subjects in the palifermin pre and palifermin pre-post groups, with a trend of greater incidence of adverse events related to the pharmacologic action of palifermin in the palifermin pre-post group.

Summary: (copied from sponsors report)
On the basis of these data, the treatment schedule used in the pivotal phase 3 study is 3 consecutive daily doses of palifermin 60 µg/kg before conditioning and 3 consecutive doses after PBPC infusion.

12/11/04

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Date

10.2 Line-by-Line Labeling Review

This section is a separate electronic document titled Appendix 10.2 Line-by-Line Labeling Review

10.3 Laboratory Values

This section is a separate electronic document titled Appendix 10.3 Laboratory Values

10.4 Protocol Schemas

This section is a separate electronic document titled Appendix 10.4 Protocol Schemas

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Appendix 10.3 Laboratory Values

Amgen's tables for Transplant Safety Pool B summarizing the mean, median and interquartile values at time points tested, a graphic view of the median, mean and interquartile range are included. For the Solid Tumor Head and Neck Cancer Safety Pool D and the Colorectal Cancer Safety Pool F the Graphic view of the median, mean and interquartile range results are included in this appendix.

7.1.7.3.1 Analyses focused on measures of central tendency

Hematologic Malignancy Patient Population:

Chemistry – Amylase (range of normal in standard units used 1 – 88 IU/L):

Table 16.1.b. Summary of Amylase at Selected Time Points (Hematology Transplant: Safety Pool B)

Amylase (IU/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	190	303
Mean	50.72	53.12
SD	28.61	32.53
Median	46.00	47.00
Q1, Q3	32.00, 63.00	35.00, 63.00
Min, Max	[	]
Day -8		
n	132	188
Mean	61.03	101.96
SD	56.86	83.96
Median	47.50	89.00
Q1, Q3	33.00, 68.50	64.00, 116.00
Min, Max	[	]
Change from Baseline to Day -8		
n	129	182
Mean	13.95	51.35
SD	50.41	78.08
Median	1.00	36.00
Q1, Q3	-3.00, 11.00	17.00, 59.00
Min, Max	[	]
Day -7		
n	29	60
Mean	86.41	154.59
SD	129.80	278.96
Median	55.00	79.50
Q1, Q3	36.00, 74.00	54.50, 116.50
Min, Max	[	]

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N=Number of subjects n=non-missing values SD=sample standard deviation

Table 16.1.b. Summary of Amylase at Selected Time Points (Hematology Transplant: Safety Pool B)

Amylase (IU/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -7		
n	28	53
Mean	40.89	99.55
SD	135.09	278.95
Median	2.50	26.00
Q1, Q3	-5.00, 31.50	11.00, 53.00
Min, Max	[	]
Day -6		
n	27	71
Mean	71.48	159.03
SD	46.28	323.21
Median	54.00	80.00
Q1, Q3	43.00, 88.00	52.00, 120.00
Min, Max	[	]
Change from Baseline to Day -6		
n	24	66
Mean	6.92	108.67
SD	29.21	333.04
Median	-0.50	22.00
Q1, Q3	-7.00, 9.50	11.00, 45.00
Min, Max	[	]
Day -5		
n	135	196
Mean	291.77	434.95
SD	476.45	672.42
Median	153.00	232.00
Q1, Q3	70.00, 330.00	95.50, 495.00
Min, Max	[	]

Table 16.1.b. Summary of Amylase at Selected Time Points (Hematology Transplant: Safety Pool B)

Amylase (IU/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	131	189
Mean	244.58	384.32
SD	477.52	679.42
Median	93.00	167.00
Q1, Q3	25.00, 269.00	49.00, 428.00
Min, Max	[	]
Day -4		
n	39	76
Mean	66.49	143.06
SD	39.00	234.84
Median	49.00	74.50
Q1, Q3	36.00, 91.00	50.50, 138.50
Min, Max	[	]
Change from Baseline to Day -4		
n	36	71
Mean	10.75	92.41
SD	36.60	237.76
Median	3.00	23.00
Q1, Q3	-9.00, 35.00	1.00, 87.00
Min, Max	[	]
Day 0		
n	171	274
Mean	46.16	46.12
SD	45.64	32.12
Median	35.00	37.00
Q1, Q3	22.00, 56.00	29.00, 55.00
Min, Max	[	]

N=Number of subjects,n=non-missing values,SD=sample standard deviation

Table 16.1.b. Summary of Amylase at Selected Time Points (Hematology Transplant: Safety Pool B)

Amylase (IU/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 0		
n	165	259
Mean	-6.98	-7.42
SD	33.39	33.19
Median	-10.00	-8.00
Q1, Q3	-23.00, 0.00	-19.00, 5.00
Min, Max	[	]
Day 4		
n	116	157
Mean	37.79	44.24
SD	38.29	51.73
Median	25.00	31.00
Q1, Q3	17.00, 40.50	21.00, 52.00
Min, Max	[	]
Change from Baseline to Day 4		
n	114	151
Mean	-12.25	-9.57
SD	29.84	38.14
Median	-15.00	-13.00
Q1, Q3	-27.00, -4.00	-24.00, -1.00
Min, Max	[	]
Day 14		
n	125	181
Mean	32.87	30.98
SD	24.60	21.67
Median	28.00	27.00
Q1, Q3	17.00, 40.00	18.00, 36.00
Min, Max	[	]

Table 16.1.b. Summary of Amylase at Selected Time Points (Hematology Transplant: Safety Pool B)

Amylase (IU/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 14		
n	121	176
Mean	-15.93	-19.21
SD	25.05	29.39
Median	-17.00	-18.00
Q1, Q3	-30.00, -5.00	-29.00, -6.00
Min, Max	[	]
Day 28		
n	122	153
Mean	52.57	52.29
SD	30.44	32.23
Median	45.50	45.00
Q1, Q3	29.00, 70.00	31.00, 62.00
Min, Max	[	]
Change from Baseline to Day 28		
n	121	151
Mean	6.82	1.51
SD	25.72	37.59
Median	3.00	3.00
Q1, Q3	-8.00, 20.00	-12.00, 15.00
Min, Max	[	]

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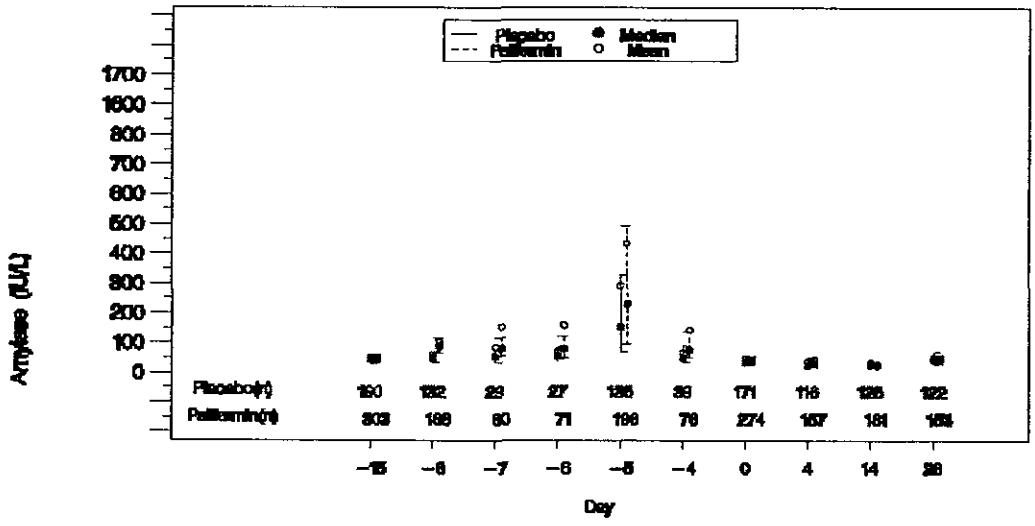
Figure 1.5.b. Median of Amylase by Study Day (Hematology Transplant: Safety Pool B)



Chemistry - Lipase(range of normal in standard units used 0 - 63 IU/L):

Table 16.3.b. Summary of Lipase at Selected Time Points (Hematology Transplant: Safety Pool B)

Lipase (IU/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	173	277
Mean	43.08	59.87
SD	45.11	129.54
Median	30.00	32.00
Q1, Q3	22.00, 46.00	21.00, 61.00
Min, Max	[	]
Day -8		
n	128	188
Mean	39.45	102.12
SD	33.64	168.67
Median	30.00	52.00
Q1, Q3	21.50, 42.00	28.00, 106.50
Min, Max	[	]
Change from Baseline to Day -8		
n	125	184
Mean	1.64	41.41
SD	17.57	109.88
Median	2.00	9.50
Q1, Q3	-3.00, 7.00	-2.00, 48.50
Min, Max	[	]
Day -7		
n	24	50
Mean	58.25	167.29
SD	43.77	361.70
Median	40.50	63.50
Q1, Q3	23.50, 90.50	27.00, 121.00
Min, Max	[	]

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N=Number of subjects,n=non-missing values,SD=sample standard deviation

Table 16.3.b. Summary of Lipase at Selected Time Points (Hematology Transplant: Safety Pool B)

Lipase (IU/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -7		
n	21	47
Mean	2.86	73.35
SD	31.57	230.15
Median	2.00	12.00
Q1, Q3	-5.00, 17.00	-1.00, 60.00
Min, Max	[	]
Day -6		
n	18	51
Mean	108.11	226.34
SD	91.37	584.12
Median	94.50	67.00
Q1, Q3	27.00, 129.00	30.00, 167.00
Min, Max	[	]
Change from Baseline to Day -6		
n	17	49
Mean	27.00	113.87
SD	56.26	360.98
Median	8.00	6.00
Q1, Q3	-2.00, 36.00	-5.00, 53.00
Min, Max	[	]
Day -5		
n	136	195
Mean	50.43	87.35
SD	60.60	346.03
Median	34.00	35.00
Q1, Q3	24.00, 52.50	22.00, 68.00
Min, Max	[	]

Table 16.3.b. Summary of Lipase at Selected Time Points (Hematology Transplant: Safety Pool B)

Lipase (IU/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	132	191
Mean	10.40	25.75
SD	49.22	211.09
Median	4.00	1.00
Q1, Q3	-4.00, 14.50	-8.00, 20.00
Min, Max	[	]
Day -4		
n	39	73
Mean	64.67	230.62
SD	102.77	1023.04
Median	36.00	51.00
Q1, Q3	16.00, 78.00	25.00, 87.00
Min, Max	[	]
Change from Baseline to Day -4		
n	33	70
Mean	12.21	142.01
SD	97.23	832.36
Median	-6.00	0.50
Q1, Q3	-14.00, 4.00	-22.00, 22.00
Min, Max	[	]
Day 0		
n	159	249
Mean	43.46	41.62
SD	64.38	58.36
Median	22.00	22.00
Q1, Q3	15.00 45.00	16.00, 45.00
Min, Max	[	]

Table 16.3.b. Summary of Lipase at Selected Time Points (Hematology Transplant: Safety Pool B)

Lipase (IU/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 0		
n	153	238
Mean	-3.82	-7.36
SD	53.80	58.99
Median	-6.00	-6.00
Q1, Q3	-17.00, 0.00	-16.00, 2.00
Min, Max	[	]
Day 4		
n	107	142
Mean	21.21	35.21
SD	22.88	55.22
Median	14.00	15.00
Q1, Q3	11.00, 19.00	11.00, 25.00
Min, Max	[	]
Change from Baseline to Day 4		
n	107	138
Mean	-14.38	-31.93
SD	35.40	155.58
Median	-12.00	-12.00
Q1, Q3	-21.00, -5.00	-22.00, -7.00
Min, Max	[	]
Day 14		
n	125	181
Mean	37.18	33.73
SD	76.92	52.56
Median	20.00	18.00
Q1, Q3	14.00, 29.00	12.00, 31.00
Min, Max	[	]

Table 16.3.b. Summary of Lipase at Selected Time Points (Hematology Transplant: Safety Pool B)

Lipase (IU/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 14		
n	121	177
Mean	-2.72	-13.80
SD	72 84	56.40
Median	-8.00	-9.00
Q1, Q3	-17.00, -1.00	-21.00, -3.00
Min, Max	[	]
Day 28		
n	120	152
Mean	50.57	49.01
SD	58.86	61.37
Median	31.00	29.00
Q1, Q3	22.00, 53.50	20.00, 47.50
Min, Max	[	]
Change from Baseline to Day 28		
n	117	150
Mean	14.23	9.69
SD	49.40	41.30
Median	4.00	2.00
Q1, Q3	-4.00, 18.00	-5.00, 11.00
Min, Max	[	]

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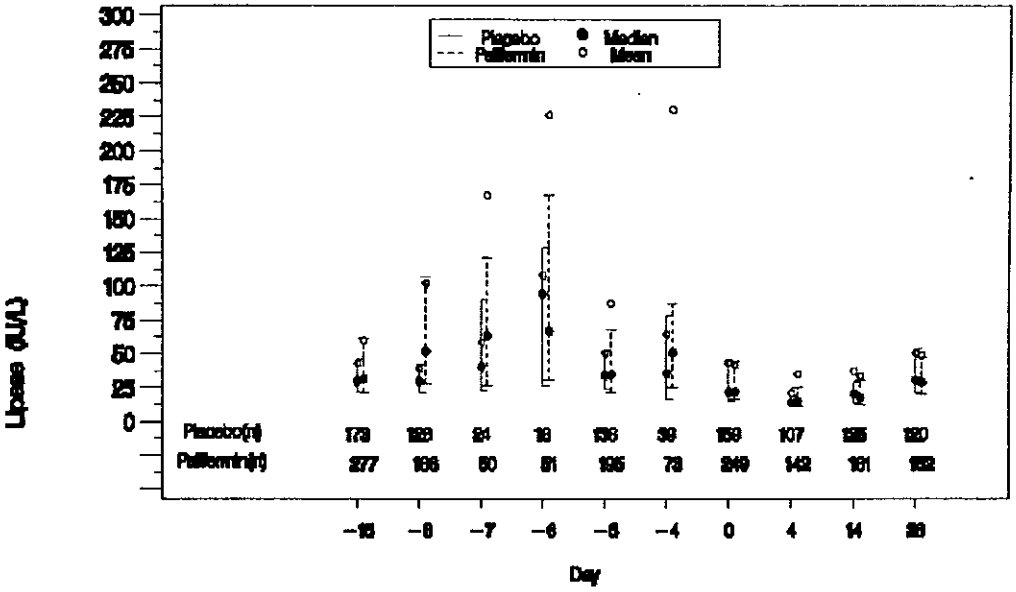
Figure 1.6.b. Median of Lipase by Study Day (Hematology Transplant: Safety Pool B)



Chemistry - Bilirubin(range of normal in standard units used 0 – 25.6 µmol/L):

Table 16.5.b. Summary of Total Bilirubin at Selected Time Points (Hematology Transplant: Safety Pool B)

Total Bilirubin (umol/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	238	397
Mean	8.53	8.99
SD	4.47	5.48
Median	8.00	8.00
Q1, Q3	5.13, 10.26	6.00, 10.26
Min, Max	[	]
Day -8		
n	98	135
Mean	8.22	8.70
SD	5.12	5.00
Median	6.84	8.55
Q1, Q3	5.13, 10.26	5.13, 10.26
Min, Max	[	]
Change from Baseline to Day -8		
n	96	133
Mean	-0.13	0.54
SD	4.02	4.09
Median	0.00	0.00
Q1, Q3	-1.71, 1.71	-1.71, 1.71
Min, Max	[	]
Day -5		
n	165	244
Mean	11.00	11.69
SD	5.87	6.29
Median	10.26	10.26
Q1, Q3	6.84, 13.68	6.84, 13.68
Min, Max	[	]

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Table 16.5.b. Summary of Total Bilirubin at Selected Time Points (Hematology Transplant: Safety Pool B)

Total Bilirubin (umol/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	162	240
Mean	2.49	2.85
SD	5.29	5.51
Median	1.71	1.71
Q1, Q3	0.00, 5.13	0.00, 5.13
Min, Max	[	]
Day 0		
n	147	215
Mean	9.65	9.38
SD	4.84	5.33
Median	8.55	8.55
Q1, Q3	5.47, 13.00	6.84, 11.97
Min, Max	[	]
Change from Baseline to Day 0		
n	145	209
Mean	1.39	0.98
SD	5.14	5.23
Median	1.71	0.00
Q1, Q3	-1.71, 3.42	-1.71, 3.42
Min, Max	[	]
Day 7		
n	177	284
Mean	16.24	14.49
SD	16.94	14.13
Median	11.97	10.86
Q1, Q3	6.84, 17.10	7.09, 15.39
Min, Max	[	]

Table 16.5.b. Summary of Total Bilirubin at Selected Time Points (Hematology Transplant: Safety Pool B)

Total Bilirubin (umol/L)

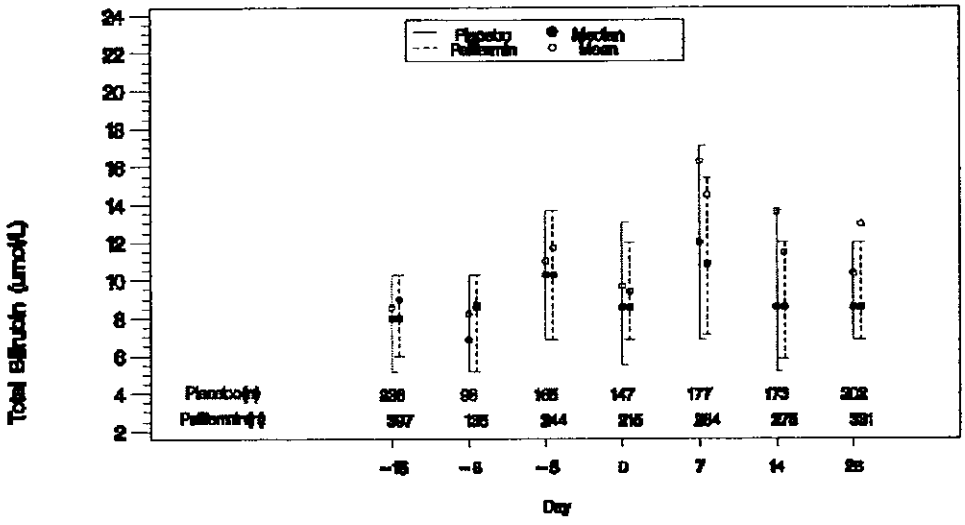
	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 7		
n	174	276
Mean	7.58	5.94
SD	15.87	13.88
Median	3.42	2.39
Q1, Q3	0.00, 8.00	0.00, 6.84
Min, Max	[	]
Day 14		
n	173	275
Mean	13.58	11.44
SD	24.13	20.05
Median	8.55	8.55
Q1, Q3	5.13, 13.68	5.81, 11.97
Min, Max	[	]
Change from Baseline to Day 14		
n	171	268
Mean	5.05	2.52
SD	23.47	20.64
Median	0.00	0.00
Q1, Q3	-1.71, 5.00	-2.00, 3.42
Min, Max	[	]
Day 28		
n	202	331
Mean	10.33	12.92
SD	7.35	41.18
Median	8.55	8.55
Q1, Q3	6.84, 11.97	6.84, 11.97
Min, Max	[	]

Table 16.5.b. Summary of Total Bilirubin at Selected Time Points (Hematology Transplant: Safety Pool B)

Total Bilirubin (umol/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 28		
n	201	325
Mean	1.90	4.07
SD	7.19	41.60
Median	1.03	0.00
Q1, Q3	-1.71, 3.42	-1.71, 3.42
Min, Max	[	]

Figure 1.9.b. Median of Total Bilirubin by Study Day (Hematology Transplant: Safety Pool B)



Chemistry - Total Protein(range of normal in standard units used 58 - 84 g/L):

Table 16.6.b. Summary of Total Protein at Selected Time Points (Hematology Transplant: Safety Pool B)

Total Protein (g/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	233	396
Mean	65.49	66.43
SD	6.39	7.01
Median	65.00	66.00
Q1, Q3	62.00, 69.80	62.00, 71.00
Min, Max	[	]
Day -8		
n	96	127
Mean	62.97	61.47
SD	5.89	6.53
Median	63.00	61.00
Q1, Q3	58.00, 67.00	57.00, 66.00
Min, Max	[	]
Change from Baseline to Day -8		
n	93	126
Mean	-1.25	-3.15
SD	5.58	5.94
Median	-2.00	-4.00
Q1, Q3	-5.00, 2.00	-7.00, 0.00
Min, Max	[	]
Day -5		
n	157	238
Mean	60.13	60.72
SD	8.22	6.95
Median	59.00	60.00
Q1, Q3	56.00, 65.00	56.00, 65.00
Min, Max	[	]

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N=Number of subjects,n=non-missing values,SD=sample standard deviation

Table 16.6.b. Summary of Total Protein at Selected Time Points (Hematology Transplant: Safety Pool B)

Total Protein (g/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	151	234
Mean	-5.01	-5.21
SD	8.05	6.49
Median	-5.00	-5.00
Q1, Q3	-8.00, -1.00	-9.10, -1.00
Min, Max	[	]
Day 0		
n	142	208
Mean	57.10	57.34
SD	7.67	9.06
Median	57.00	57.50
Q1, Q3	53.00, 62.00	53.00, 63.00
Min, Max	[	]
Change from Baseline to Day 0		
n	138	201
Mean	-7.53	-8.91
SD	8.47	8.21
Median	-8.00	-8.00
Q1, Q3	-12.00, -3.00	-14.00, -4.00
Min, Max	[	]
Day 7		
n	178	263
Mean	54.93	56.78
SD	7.52	8.48
Median	55.00	56.00
Q1, Q3	50.00, 60.00	52.00, 62.00
Min, Max	[	]

Table 16.6.b. Summary of Total Protein at Selected Time Points (Hematology Transplant: Safety Pool B)

Total Protein (g/L)

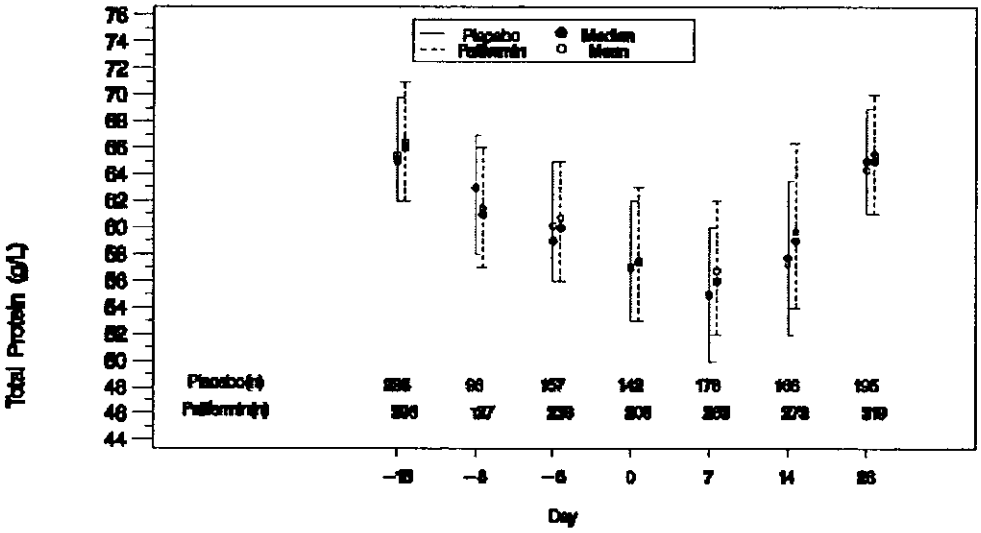
	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 7		
n	173	254
Mean	-10.02	-9.34
SD	8.69	8.78
Median	-9.00	-9.00
Q1, Q3	-15.00, -4.00	-15.00, -4.00
Min, Max	[	]
Day 14		
n	166	273
Mean	57.29	59.70
SD	9.19	10.54
Median	57.75	59.00
Q1, Q3	52.00, 63.50	54.00, 66.40
Min, Max	[	]
Change from Baseline to Day 14		
n	160	262
Mean	-8.35	-6.72
SD	8.90	10.44
Median	-8.00	-7.00
Q1, Q3	-13.75, -2.25	-11.00, -1.00
Min, Max	[	]
Day 28		
n	195	319
Mean	64.33	65.51
SD	7.76	6.59
Median	65.00	65.00
Q1, Q3	61.00, 69.00	61.00, 70.00
Min, Max	[	]

Table 16.6.b. Summary of Total Protein at Selected Time Points (Hematology Transplant: Safety Pool B)

Total Protein (g/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 28		
n	190	310
Mean	-1.20	-0.82
SD	8.77	7.14
Median	-1.00	-1.00
Q1, Q3	-6.00, 4.00	-5.00, 3.00
Min, Max	[	]

Figure 1.10.b. Median of Total Protein by Study Day (Hematology Transplant: Safety Pool B)



Chemistry - Albumin(range of normal in standard units used 24 –60 g/L):

Table 16.7.b. Summary of Albumin at Selected Time Points (Hematology Transplant: Safety Pool B)

Albumin (g/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	232	388
Mean	37.82	39.00
SD	4.94	4.85
Median	38.00	39.00
Q1, Q3	35.00, 41.00	36.00, 42.00
Min, Max	[	]
Day -8		
n	99	126
Mean	36.38	35.38
SD	4.61	4.37
Median	36.00	35.50
Q1, Q3	33.00, 40.00	32.00, 38.00
Min, Max	[	]
Change from Baseline to Day -8		
n	95	123
Mean	-0.55	-2.11
SD	3.79	4.21
Median	-1.00	-2.00
Q1, Q3	-3.00, 2.00	-5.00, 0.00
Min, Max	[	]
Day -5		
n	159	240
Mean	33.88	34.70
SD	4.97	4.34
Median	34.00	35.00
Q1, Q3	30.00, 38.00	32.00, 38.00
Min, Max	[	]

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N=Number of subjects;n=non-missing values;SD=sample standard deviation

Table 16.7.b. Summary of Albumin at Selected Time Points (Hematology Transplant: Safety Pool B)

Albumin (g/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	155	232
Mean	-2.90	-3.35
SD	4.11	4.33
Median	-3.00	-3.00
Q1, Q3	-6.00, 0.00	-6.00, 0.00
Min, Max	[	]
Day 0		
n	142	205
Mean	32.30	32.66
SD	5.28	5.30
Median	32.00	33.00
Q1, Q3	29.00, 36.00	30.00, 36.00
Min, Max	[	]
Change from Baseline to Day 0		
n	136	198
Mean	-4.55	-5.77
SD	4.36	4.75
Median	-5.00	-5.71
Q1, Q3	-8.00, -2.00	-9.00, -3.00
Min, Max	[	]
Day 7		
n	173	267
Mean	28.32	30.75
SD	5.19	5.18
Median	28.00	31.00
Q1, Q3	25.00, 32.00	27.00, 34.00
Min, Max	[	]

Table 16.7.b. Summary of Albumin at Selected Time Points (Hematology Transplant: Safety Pool B)

Albumin (g/L)

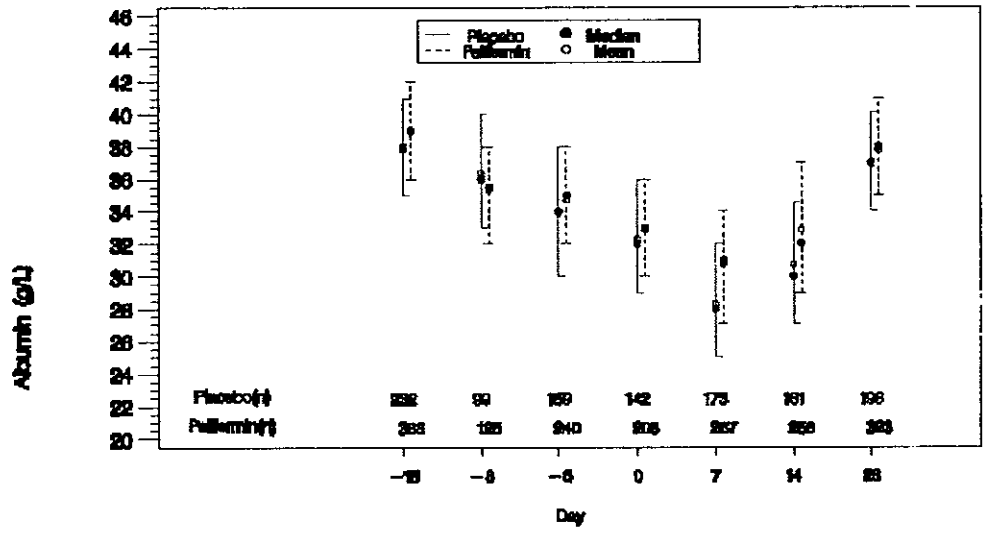
	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 7		
n	167	258
Mean	-9.25	-8.16
SD	5.17	4.80
Median	-9.00	-8.00
Q1, Q3	-13.00, -5.00	-11.00, -5.00
Min, Max	[	]
Day 14		
n	161	256
Mean	30.72	32.87
SD	6.28	6.02
Median	30.00	32.04
Q1, Q3	27.00, 34.55	29.00, 37.00
Min, Max	[	]
Change from Baseline to Day 14		
n	157	247
Mean	-7.15	-6.19
SD	6.05	5.94
Median	-8.00	-6.00
Q1, Q3	-11.00, -3.96	-10.00, -2.85
Min, Max	[	]
Day 28		
n	196	323
Mean	36.91	37.78
SD	5.42	5.19
Median	37.00	38.00
Q1, Q3	34.00, 40.14	35.00, 41.00
Min, Max	[	]

Table 16.7.b. Summary of Albumin at Selected Time Points (Hematology Transplant: Safety Pool B)

Albumin (g/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 28		
n	191	310
Mean	-1.05	-1.23
SD	5.41	4.84
Median	-1.00	-1.20
Q1, Q3	-4.00, 2.00	-4.00, 2.00
Min, Max		

Figure 1.11.b. Median of Albumin by Study Day (Hematology Transplant: Safety Pool B)



Chemistry - Creatinine(range of normal in standard units used 44 - 132 µmol/L):

Table 16.8.b. Summary of Creatinine at Selected Time Points (Hematology Transplant: Safety Pool B)

Creatinine (umol/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	241	407
Mean	79.29	79.71
SD	21.08	27.84
Median	79.00	79.56
Q1, Q3	63.00, 88.40	61.88, 88.40
Min, Max	[	]
Day -8		
n	107	145
Mean	82.46	77.36
SD	23.33	21.65
Median	79.56	70.72
Q1, Q3	70.72, 88.40	61.88, 88.40
Min, Max	[	]
Change from Baseline to Day -8		
n	107	145
Mean	3.29	-0.85
SD	15.43	12.91
Median	0.00	0.00
Q1, Q3	-8.84, 8.84	-8.84, 8.84
Min, Max	[	]
Day -5		
n	168	266
Mean	76.85	74.39
SD	24.48	24.60
Median	70.72	70.72
Q1, Q3	61.88, 88.40	61.88, 88.40
Min, Max	[	]

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N=Number of subjects,n=non-missing values,SD=sample standard deviation

Table 16.8.b. Summary of Creatinine at Selected Time Points (Hematology Transplant: Safety Pool B)

Creatinine (umol/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	168	265
Mean	-1.99	-5.11
SD	15.54	28.22
Median	0.00	-5.00
Q1, Q3	-8.84, 5.42	-8.93, 0.00
Min, Max	[	]
Day 0		
n	153	223
Mean	69.79	66.42
SD	21.77	24.00
Median	64.00	61.88
Q1, Q3	53.04, 79.56	53.04, 70.72
Min, Max	[	]
Change from Baseline to Day 0		
n	153	222
Mean	-10.06	-12.97
SD	14.12	15.40
Median	-8.84	-8.84
Q1, Q3	-17.68, 0.00	-19.00, -8.00
Min, Max	[	]
Day 7		
n	190	295
Mean	78.12	73.31
SD	57.32	43.12
Median	61.88	61.88
Q1, Q3	53.04, 80.00	53.04, 79.56
Min, Max	[	]

Table 16.8.b. Summary of Creatinine at Selected Time Points (Hematology Transplant: Safety Pool B)

Creatinine (umol/L)

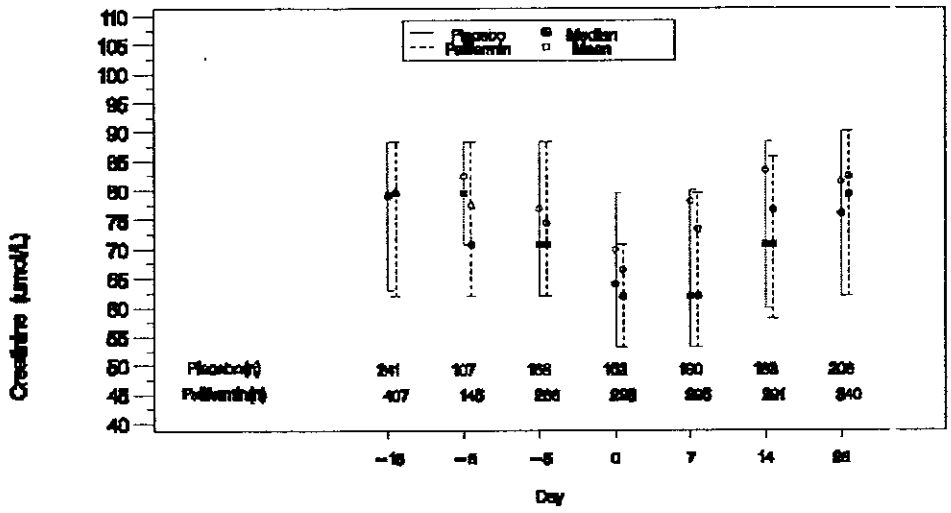
	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 7		
n	190	293
Mean	-1.08	-7.87
SD	50.07	45 24
Median	-8.84	-10 00
Q1, Q3	-17.68, 0.00	-18.00 -3.00
Min, Max		
Day 14		
n	183	291
Mean	83.38	76.69
SD	64.58	32 26
Median	70.72	70.72
Q1, Q3	60.00, 88.40	58.00, 85.75
Min, Max		
Change from Baseline to Day 14		
n	183	289
Mean	3.39	-2.54
SD	59.16	37.11
Median	-8.84	-8 84
Q1, Q3	-17.68, 8.84	-17.68, 6.00
Min, Max		
Day 28		
n	208	340
Mean	81.49	82 38
SD	31.87	35 86
Median	76.00	79 28
Q1, Q3	61.88, 90.00	61.88, 90.00
Min, Max		

Table 16.8.b. Summary of Creatinine at Selected Time Points (Hematology Transplant: Safety Pool B)

Creatinine (umol/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 28		
n	208	339
Mean	1.39	2.53
SD	25.65	38.75
Median	0.00	0.00
Q1, Q3	-9.00, 8.84	-8.84, 8.84
Min, Max	[illegible]	[illegible]

Figure 1.12.b. Median of Creatinine by Study Day (Hematology Transplant: Safety Pool B)



Chemistry - Lactate Dehydrogenase(range of normal in standard units used 60–537 U/L):

Table 16.9.b. Summary of LDH at Selected Time Points (Hematology Transplant: Safety Pool B)

LDH (U/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	223	377
Mean	383.10	434.95
SD	321.94	475.33
Median	279.00	299.00
Q1, Q3	177.00, 512.00	178.00, 501.00
Min, Max	[illegible]	[illegible]
Day -8		
n	96	126
Mean	405.17	365.91
SD	362.67	389.30
Median	270.00	216.50
Q1, Q3	170.00, 539.00	155.00, 478.00
Min, Max	[illegible]	[illegible]
Change from Baseline to Day -8		
n	91	120
Mean	-63.45	-169.71
SD	291.36	444.05
Median	-33.00	-38.50
Q1, Q3	-119.00, 20.00	-186.00, 9.00
Min, Max	[illegible]	[illegible]
Day -5		
n	149	232
Mean	308.18	330.41
SD	296.18	368.86
Median	224.00	208.00
Q1, Q3	155.00, 410.00	151.00, 425.50
Min, Max	[illegible]	[illegible]

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N=Number of subjects,n=non-missing values,SD=sample standard deviation

Table 16.9.b. Summary of LDH at Selected Time Points (Hematology Transplant: Safety Pool B)

LDH (U/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	137	215
Mean	-104.95	-162.49
SD	253.97	489.72
Median	-45.00	-54.00
Q1, Q3	-157.00, -5.00	-193.00, -7.00
Min, Max	[illegible]	
Day 0		
n	144	212
Mean	692.06	548.74
SD	1106.84	885.24
Median	252.50	222.80
Q1, Q3	147.00, 534.00	147.50, 447.00
Min, Max	[illegible]	[illegible]
Change from Baseline to Day 0		
n	134	192
Mean	281.19	80.34
SD	1108.91	907.76
Median	-33.50	-45.00
Q1, Q3	-154.00, 50.00	-185.00, 18.00
Min, Max	[illegible]	[illegible]
Day 7		
n	180	243
Mean	245.43	248.73
SD	171.02	178.54
Median	178.00	178.00
Q1, Q3	127.50, 318.50	132.00, 321.00
Min, Max	[illegible]	[illegible]

Table 16.9.b. Summary of LDH at Selected Time Points (Hematology Transplant: Safety Pool B)

LDH (U/L)

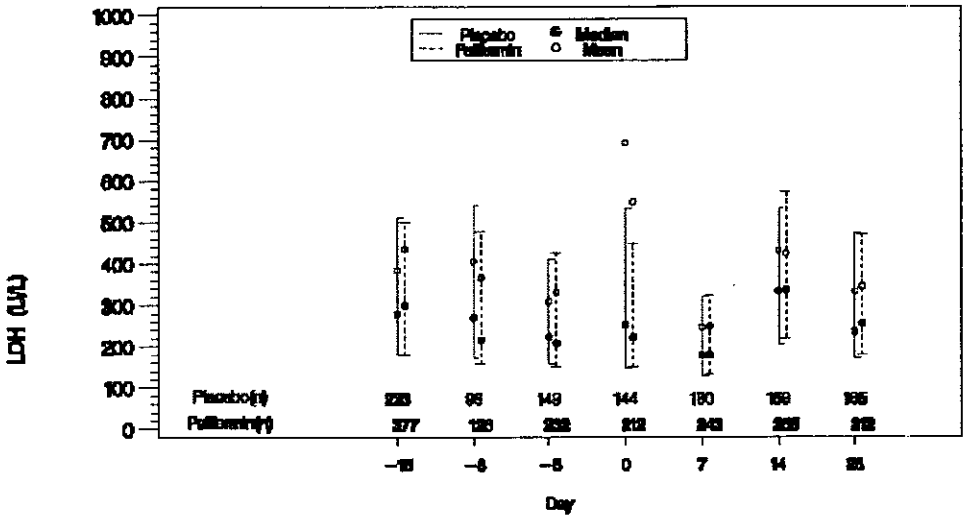
	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 7		
n	164	224
Mean	-162.16	-216.20
SD	282.36	467.15
Median	-94.00	-90.50
Q1, Q3	-229.50, -10.50	-238.50, -21.50
Min, Max	C	7
Day 14		
n	158	255
Mean	430.85	424.78
SD	346.26	277.73
Median	334.00	336.00
Q1, Q3	204.00, 531.00	220.00, 574.00
Min, Max	C	7
Change from Baseline to Day 14		
n	152	242
Mean	34.40	-16.19
SD	376.74	423.01
Median	27.00	42.00
Q1, Q3	-59.75, 117.50	-76.00, 112.00
Min, Max	C	]
Day 28		
n	185	312
Mean	331.82	344.63
SD	209.26	275.33
Median	236.00	255.50
Q1, Q3	173.00, 472.00	177.50, 470.00
Min, Max	C	]

Table 16.9.b. Summary of LDH at Selected Time Points (Hematology Transplant: Safety Pool B)

LDH (U/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 28		
n	171	291
Mean	-52.58	-80.16
SD	271.73	429.19
Median	2.00	7.00
Q1, Q3	-97.00, 54.00	-100.00, 67.00
Min, Max	[	]

Figure 1.13.b. Median of LDH by Study Day (Hematology Transplant: Safety Pool B)



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Chemistry- Aspartate aminotransferase(range of normal in standard units used 5-50 U/L):

Table 16.10.b. Summary of AST at Selected Time Points
(Hematology Transplant: Safety Pool B)

AST (U/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	236	399
Mean	25.45	26.68
SD	13.10	14.70
Median	23.00	24.60
Q1, Q3	17.00, 30.00	17.00, 32.00
Min, Max	[	]
Day -8		
n	96	130
Mean	28.34	25.47
SD	17.01	11.72
Median	23.00	22.50
Q1, Q3	20.00, 31.50	18.00, 31.00
Min, Max	[	]
Change from Baseline to Day -8		
n	94	127
Mean	0.44	-1.68
SD	13.94	11.85
Median	0.00	-1.00
Q1, Q3	-6.00, 5.00	-8 00, 4.00
Min, Max	[	]
Day -5		
n	160	240
Mean	24.78	27.01
SD	12.25	18.20
Median	22.00	23.50
Q1, Q3	17.00, 29.00	18.00, 31.50
Min, Max	[	]

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N=Number of subjects,n=non-missing values.SD=sample standard deviation

Table 16.10.b. Summary of AST at Selected Time Points (Hematology Transplant: Safety Pool B)

AST (U/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	156	236
Mean	-3.20	-2.57
SD	15.57	15.64
Median	-3.00	-2.00
Q1, Q3	-10.00, 3.50	-9.00, 4.00
Min, Max	[	]
Day 0		
n	148	217
Mean	23.42	22.09
SD	17.83	16.22
Median	16.00	17.00
Q1, Q3	13.50, 26.00	13.00, 24.00
Min, Max	[	]
Change from Baseline to Day 0		
n	144	210
Mean	-3.44	-5.39
SD	20.65	18.00
Median	-7.00	-6.00
Q1, Q3	-14.50, 2.50	-14.00, 0.00
Min, Max	[	]
Day 7		
n	184	275
Mean	14.97	21.99
SD	8.53	85.52
Median	12.00	14.00
Q1, Q3	9.00, 18.00	10.00, 19.00
Min, Max	[	]

Table 16.10.b. Summary of AST at Selected Time Points (Hematology Transplant: Safety Pool B)

AST (U/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 7		
n	180	267
Mean	-11.67	-5.76
SD	15.11	86.23
Median	-9.50	10.00
Q1, Q3	-17.50, -4.00	-17.00, -3.60
Min, Max	[	]
Day 14		
n	173	272
Mean	28.67	29.28
SD	20.51	19.41
Median	24.00	25.00
Q1, Q3	18.00, 32.00	17.00, 35.00
Min, Max	[	]
Change from Baseline to Day 14		
n	170	266
Mean	3.63	4.05
SD	22.04	20.16
Median	2.00	1.35
Q1, Q3	-4.00, 9.00	-6.00, 10.00
Min, Max	[	]
Day 28		
n	203	327
Mean	35.24	36.78
SD	16.94	28.80
Median	32.00	31.00
Q1, Q3	24.00, 42.00	23.00, 42.00
Min, Max	[	]

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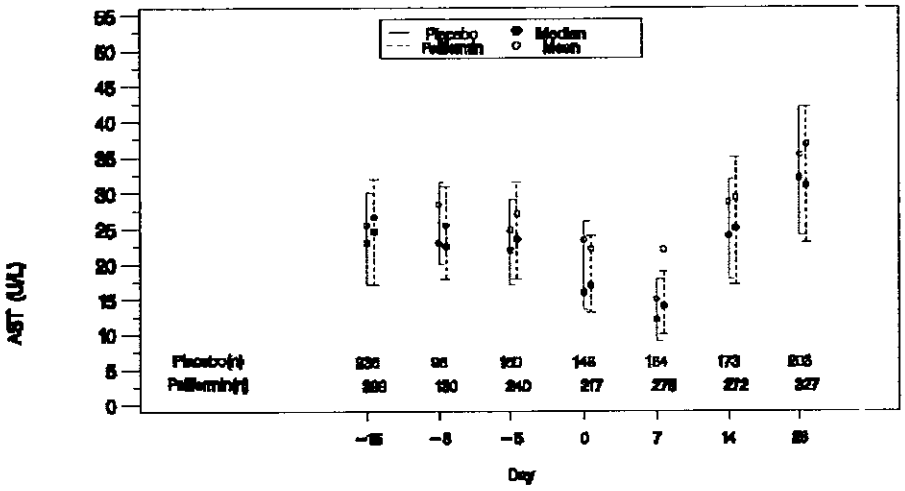
Table 16.10.b. Summary of AST at Selected Time Points (Hematology Transplant: Safety Pool B)

AST (U/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 28		
n	201	321
Mean	9.89	10.79
SD	17.20	28.14
Median	7.00	7.00
Q1, Q3	0.00, 16.00	0.00, 17.00
Min, Max		

Figure 1.7.b. Median of AST by Study Day (Hematology Transplant: Safety Pool B)



Chemistry - Alanine aminotransferase(range of normal in standard units used 4-50 U/L):

Table 16.11.b. Summary of ALT at Selected Time Points (Hematology Transplant: Safety Pool B)

ALT (U/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	227	388
Mean	29.85	28.48
SD	23.13	19.34
Median	23.00	23.00
Q1, Q3	15.00, 37.00	16.00, 36.00
Min, Max	[	]
Day -8		
n	99	133
Mean	35.63	27.92
SD	30.54	20.81
Median	25.00	22.00
Q1, Q3	17.00, 43.00	15.00, 34.80
Min, Max	[	]
Change from Baseline to Day -8		
n	96	131
Mean	2.44	0.13
SD	20.56	16.51
Median	0.00	-1.00
Q1, Q3	-9.00, 7.50	-6.00, 4.00
Min, Max	[	]
Day -5		
n	153	236
Mean	29.03	26.71
SD	23.01	20.85
Median	23.00	23.00
Q1, Q3	17.00, 32.00	16.00, 31.50
Min, Max	[	]

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N=Number of subjects,n=non-missing values,SD=sample standard deviation

Table 16.11.b. Summary of ALT at Selected Time Points (Hematology Transplant: Safety Pool B)

ALT (U/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	145	225
Mean	-5.04	-3.28
SD	25.59	17.04
Median	-3.00	-2.00
Q1, Q3	-13.00, 3.00	-9.00, 3.00
Min, Max	[illegible]	[illegible]
Day 0		
n	145	219
Mean	19.74	21.20
SD	12.58	18.17
Median	16.00	16.00
Q1, Q3	12.00, 23.00	12.00, 23.00
Min, Max	[illegible]	[illegible]
Change from Baseline to Day 0		
n	140	206
Mean	-11.30	-7.22
SD	22.46	18.77
Median	-7.50	-7.00
Q1, Q3	-18.00, 1.00	-16.00, 1.00
Min, Max	[illegible]	[illegible]
Day 7		
n	178	267
Mean	16.60	18.09
SD	8.98	21.30
Median	15.00	14.00
Q1, Q3	10.00, 21.00	9.00, 21.00
Min, Max	[illegible]	[illegible]

Table 16.11.b. Summary of ALT at Selected Time Points (Hematology Transplant: Safety Pool B)

ALT (U/L)

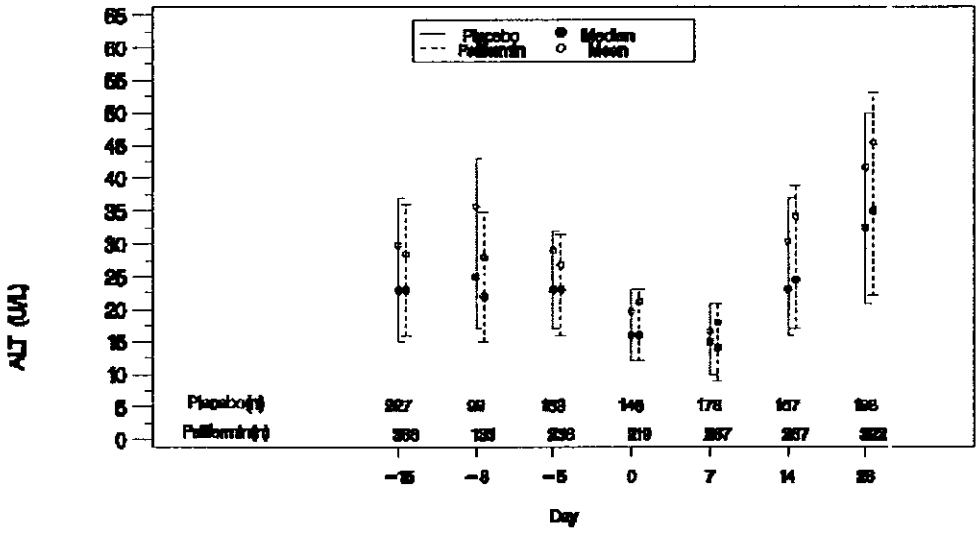
	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 7		
n	169	249
Mean	-14.71	-10.38
SD	22.95	20.84
Median	-9.00	-9.00
Q1, Q3	-23.00, 0.00	-19.00, -2.00
Min, Max	[	]
Day 14		
n	167	267
Mean	30.34	34 14
SD	25.22	32 91
Median	23.00	24 50
Q1, Q3	16.00, 37.00	17.00, 39.00
Min, Max	[	]
Change from Baseline to Day 14		
n	163	259
Mean	0.52	6.54
SD	31.64	34 38
Median	1.00	1.00
Q1, Q3	-10.00, 12.00	-10.00, 13.00
Min, Max	[	]
Day 28		
n	198	322
Mean	41.61	45 48
SD	30.77	45 22
Median	32.50	35 00
Q1, Q3	21.00, 50.00	22.00, 53.00
Min, Max	[	]

Table 16.11.b. Summary of ALT at Selected Time Points (Hematology Transplant: Safety Pool B)

ALT (U/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 28		
n	191	309
Mean	12.37	17.30
SD	30.43	42.45
Median	9.00	9.60
Q1, Q3	-1.00, 21.00	0.00, 27.00
Min, Max		

Figure 1.8.b. Median of ALT by Study Day (Hematology Transplant: Safety Pool B)



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Hematology - Absolute Neutrophil Count:

Table 15.1.b. Summary of Absolute Neutrophil Count at Selected Time Points (Hematology Transplant: Safety Pool B)

ANC (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	235	402
Mean	7.70	7.32
SD	11.41	10.81
Median	3.52	3.76
Q1, Q3	2.18, 6.25	2.44, 6.39
Min, Max	[	]
Day -8		
n	114	242
Mean	3.54	3.38
SD	2.29	2.20
Median	3.06	2.82
Q1, Q3	1.94, 4.40	1.95, 4.23
Min, Max	[	]
Change from Baseline to Day -8		
n	112	239
Mean	-0.58	-1.24
SD	2.69	4.91
Median	-0.10	-0.31
Q1, Q3	-0.96, 0.45	-1.21, 0.27
Min, Max	[	]
Day -5		
n	230	397
Mean	4.14	3.94
SD	3.11	2.99
Median	3.13	2.93
Q1, Q3	2.05, 5.18	2.00, 4.97
Min, Max	[	]

N=Number of subjects;n=non-missing values;SD=sample standard deviation

Table 15.1.b. Summary of Absolute Neutrophil Count at Selected Time Points (Hematology Transplant: Safety Pool B)

ANC (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	226	390
Mean	-3.75	-3.36
SD	12.08	10.96
Median	0.01	-0.36
Q1, Q3	-2.27, 1.39	-2.34, 0.85
Min, Max	[	]
Day 0		
n	214	370
Mean	1.34	1.54
SD	1.40	1.62
Median	0.88	0.90
Q1, Q3	0.25, 1.88	0.31, 2.31
Min, Max	[	]
Change from Baseline to Day 0		
n	208	364
Mean	-6.09	-5.58
SD	11.35	10.67
Median	-2.10	-2.12
Q1, Q3	-4.72, -0.58	-4.81, -0.57
Min, Max	[	]
Day 7		
n	184	317
Mean	0.32	0.42
SD	0.58	0.75
Median	0.10	0.09
Q1, Q3	0.02, 0.30	0.02, 0.44
Min, Max	[	]

Table 15.1.b. Summary of Absolute Neutrophil Count at Selected Time Points (Hematology Transplant: Safety Pool B)

ANC (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 7		
n	181	311
Mean	-6.81	-6.34
SD	11.01	9.35
Median	-3.24	-3.54
Q1, Q3	-5.87, -2.02	-5.67, -2.22
Min, Max	[	]
Day 10		
n	221	376
Mean	3.51	4.01
SD	4.54	5.44
Median	1.58	2.24
Q1, Q3	0.76, 5.02	0.71, 5.10
Min, Max	[	]
Change from Baseline to Day 10		
n	217	369
Mean	-3.78	-3.32
SD	12.05	11.88
Median	-1.51	-1.28
Q1, Q3	-3.94, 0.84	-3.64, 0.81
Min, Max	[	]
Day 14		
n	190	316
Mean	5.53	5.41
SD	4.27	3.66
Median	4.12	4.66
Q1, Q3	2.59, 6.73	2.73, 7.27
Min, Max	[	]

Table 15.1.b. Summary of Absolute Neutrophil Count at Selected Time Points (Hematology Transplant: Safety Pool B)

ANC (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 14		
n	185	312
Mean	-1.57	-1.32
SD	11.80	11.31
Median	0 71	0.89
Q1, Q3	-2.02, 3.66	-2.04, 3.72
Min, Max	[	]
Day 28		
n	202	337
Mean	2.86	3.11
SD	2.04	2.68
Median	2 41	2.42
Q1, Q3	1.63, 3.69	1.62, 3.70
Min, Max	[	]
Change from Baseline to Day 28		
n	197	331
Mean	-4.90	-4.09
SD	11.75	11.04
Median	-1.04	-1.09
Q1, Q3	-3.58, 0.09	-3.14, 0.26
Min, Max	[	]

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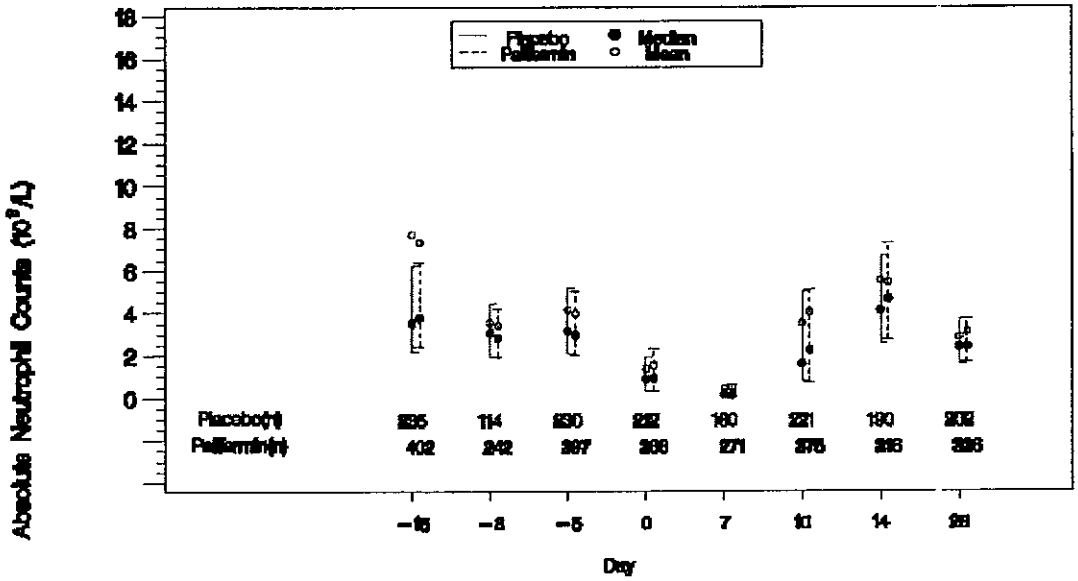
Figure 1.2.b. Median of ANC by Study Day (Hematology Transplant: Safety Pool B)



Hematology – White Blood Count:

Table 15.3.b. Summary of White Blood Count at Selected Time Points (Hematology Transplant: Safety Pool B)

WBC (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	241	408
Mean	9.91	9.47
SD	12.85	12.76
Median	5.20	5.45
Q1, Q3	3.60, 8.50	3.80, 8.10
Min, Max		
Day -8		
n	123	260
Mean	5.55	5.05
SD	4.28	2.72
Median	4.70	4.35
Q1, Q3	3.40, 6.30	3.30, 6.10
Min, Max		
Change from Baseline to Day -8		
n	123	259
Mean	-0.78	-1.32
SD	2.92	5.65
Median	-0.20	-0.30
Q1, Q3	-1.30, 0.40	-1.30, 0.30
Min, Max		
Day -5		
n	238	405
Mean	4.91	4.77
SD	3.30	3.30
Median	3.80	3.90
Q1, Q3	2.70, 6.00	2.60, 6.00
Min, Max		

N=Number of subjects,n=non-missing values SD=sample standard deviation

Table 15.3.b Summary of White Blood Count at Selected Time Points (Hematology Transplant: Safety Pool B)

WBC (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	238	404
Mean	-5.05	-4.71
SD	13.51	13.04
Median	-0.50	-1.00
Q1, Q3	-3.40, 0.90	-3.59, 0.50
Min, Max	[	]
Day 0		
n	237	405
Mean	1.23	1.47
SD	1.51	1.72
Median	0.40	0.60
Q1, Q3	0.20, 2.00	0.20, 2.40
Min, Max	[	]
Change from Baseline to Day 0		
n	237	404
Mean	-8.69	-8.03
SD	13.32	13.21
Median	-3.60	-3.90
Q1, Q3	-7.70, -2.25	-7.20, -1.88
Min, Max	[	]
Day 7		
n	238	406
Mean	0.19	0.32
SD	0.20	1.08
Median	0.10	0.20
Q1, Q3	0.10, 0.20	0.10, 0.20
Min, Max	[	]

Table 15.3.b Summary of White Blood Count at Selected Time Points (Hematology Transplant: Safety Pool B)

WBC (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 7		
n	238	405
Mean	-9.72	-9.16
SD	12.90	12.78
Median	-5.05	-5.30
Q1, Q3	-8.40, -3.30	-7.80, -3.40
Min, Max	[	]
Day 10		
n	233	399
Mean	4.61	5.19
SD	6.40	7.16
Median	1.90	2.70
Q1, Q3	0.90, 5.70	1.00, 6.40
Min, Max	[	]
Change from Baseline to Day 10		
n	233	398
Mean	-5.37	-4.32
SD	14.43	14.12
Median	-2.90	-2.30
Q1, Q3	-5.42, 0.13	-5.15, 0.10
Min, Max	[	]
Day 14		
n	194	333
Mean	7.65	7.58
SD	5.46	4.86
Median	6.30	6.50
Q1, Q3	3.90, 10.10	4.30, 9.90
Min, Max	[	]

Table 15.3.b Summary of White Blood Count at Selected Time Points (Hematology Transplant: Safety Pool B)

WBC (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 14		
n	194	332
Mean	-1.90	-1.27
SD	14.28	13.72
Median	0.60	1.40
Q1, Q3	-2.40, 4.90	-1.90, 4.90
Min, Max	[	]
Day 28		
n	212	349
Mean	5.49	6.16
SD	2.62	7.36
Median	5.10	5.30
Q1, Q3	3.60, 6.58	3.70, 7.00
Min, Max	[	]
Change from Baseline to Day 28		
n	212	348
Mean	-4.73	-3.23
SD	13.52	14.56
Median	-0.10	-0.25
Q1, Q3	-3.27, 1.70	-2.68, 1.74
Min, Max	[	]

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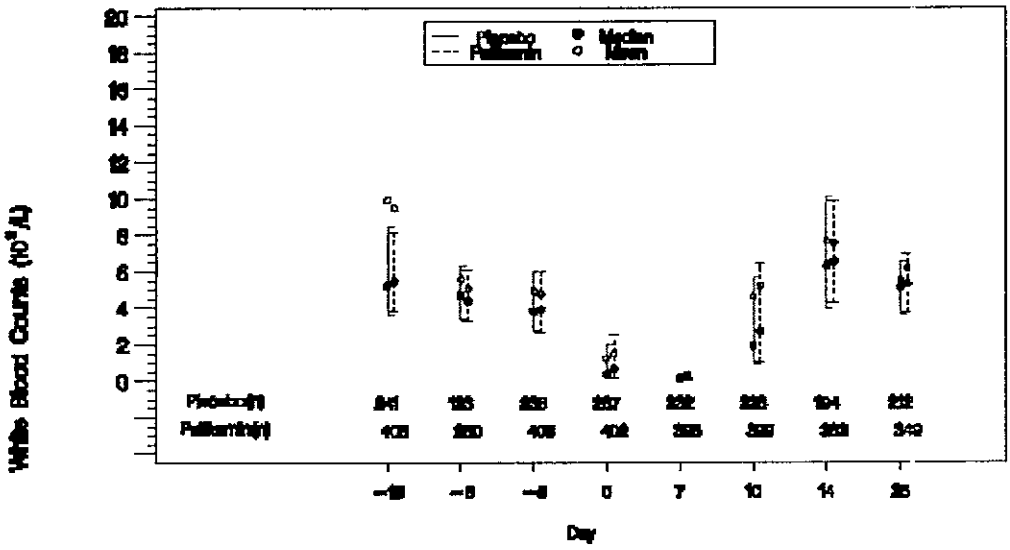
Figure 1.1.b. Median of WBC by Study Day (Hematology Transplant: Safety Pool B)



Hematology – Hemoglobin:

Table 15.4.b. Summary of Hemoglobin at Selected Time Points (Hematology Transplant: Safety Pool B)

Hemoglobin (g/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	241	408
Mean	109.94	109.18
SD	15.36	17.29
Median	108.00	107.00
Q1, Q3	99.00, 120.00	97.00, 121.00
Min, Max	[illegible]	[illegible]
Day -8		
n	123	260
Mean	110.64	109.15
SD	14.43	15.68
Median	109.00	107.00
Q1, Q3	101.00, 119.00	98.00, 120.00
Min, Max	[illegible]	[illegible]
Change from Baseline to Day -8		
n	123	259
Mean	-0.78	-0.31
SD	8.29	8.96
Median	0.00	0.00
Q1, Q3	-5.00, 4.00	-5.00, 4.00
Min, Max	[illegible]	[illegible]
Day -5		
n	238	405
Mean	105.04	102.75
SD	12.85	13.30
Median	104.00	102.00
Q1, Q3	95.00, 113.00	93.46, 111.00
Min, Max	[illegible]	[illegible]

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N=Number of subjects;n=non-missing values;SD=sample standard deviation

Table 15.4.b. Summary of Hemoglobin at Selected Time Points (Hematology Transplant: Safety Pool B)

Hemoglobin (g/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	238	404
Mean	-4.87	-6.47
SD	11.82	13.06
Median	-6.00	-8.00
Q1, Q3	-11.00, 1.00	-15.00, 0.00
Min, Max	[illegible]	[illegible]
Day 0		
n	239	405
Mean	98.69	97.53
SD	12.44	12.44
Median	98.00	97.00
Q1, Q3	90.00, 108.00	89.00, 106.00
Min, Max	[illegible]	[illegible]
Change from Baseline to Day 0		
n	239	404
Mean	-11.20	-11.66
SD	15.05	16.16
Median	-12.00	-13.00
Q1, Q3	-21.00, -2.00	-23.00, -1.31
Min, Max	[illegible]	[illegible]
Day 7		
n	238	406
Mean	90.23	92.28
SD	10.24	10.94
Median	90.00	92.00
Q1, Q3	82.00, 97.00	85.00, 98.00
Min, Max	[illegible]	[illegible]

Table 15.4.b. Summary of Hemoglobin at Selected Time Points (Hematology Transplant: Safety Pool B)

Hemoglobin (g/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 7		
n	238	405
Mean	-19.61	-16.94
SD	16.02	18.01
Median	-20.50	-17.00
Q1, Q3	-31.00, -9.00	-28.00, -5.00
Min, Max	[	]
Day 10		
n	233	399
Mean	94.13	96.11
SD	10.85	11.28
Median	94.00	96.00
Q1, Q3	87.00, 101.00	88.00, 104.00
Min, Max	[	]
Change from Baseline to Day 10		
n	233	398
Mean	-15.82	-13.25
SD	16.47	18.14
Median	-15.00	-12.00
Q1, Q3	-28.00, -4.00	-26.00, -1.00
Min, Max	[	]
Day 14		
n	194	333
Mean	100.63	101.80
SD	12.19	12.43
Median	99.50	101.00
Q1, Q3	92.00, 110.00	93.00, 110.00
Min, Max	[	]

Table 15.4.b. Summary of Hemoglobin at Selected Time Points (Hematology Transplant: Safety Pool B)

Hemoglobin (g/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 14		
n	194	332
Mean	-9.23	-6.60
SD	17.00	18.40
Median	-8.00	-7.00
Q1, Q3	-20.00, 3.00	-18.00, 4.42
Min, Max	[	]
Day 28		
n	212	348
Mean	110.65	109 73
SD	13.94	14.29
Median	110.00	110.00
Q1, Q3	100.00, 119.00	100.00, 119.00
Min, Max	[	]
Change from Baseline to Day 28		
n	212	347
Mean	0.65	0 73
SD	16.23	18.00
Median	1.00	1 00
Q1, Q3	-10.00, 11.00	-10.00, 13.00
Min, Max	[	]

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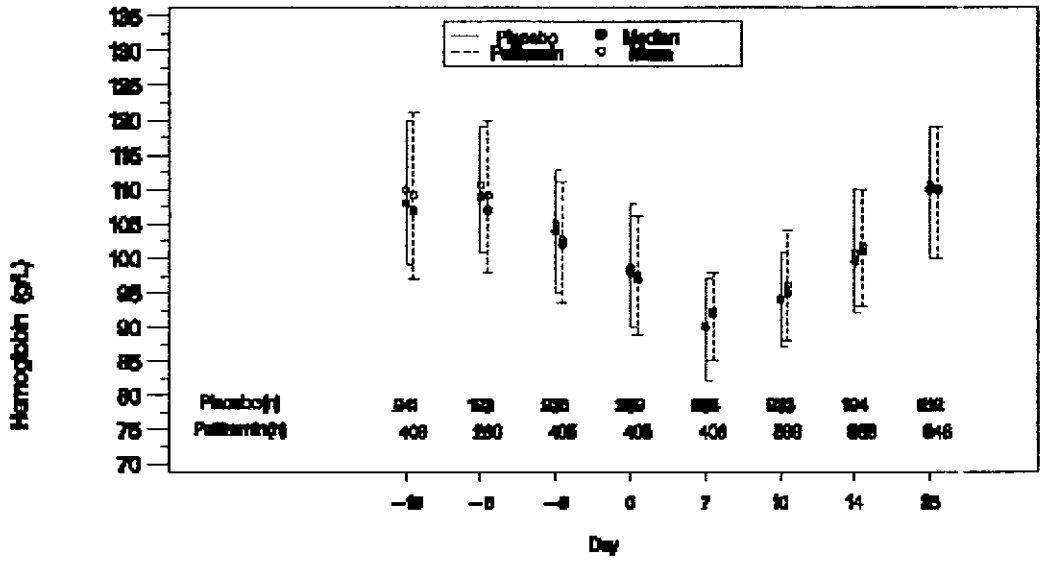
Figure 1.3.b. Median of Hemoglobin by Study Day (Hematology Transplant: Safety Pool B)



Hematology – Platelet:

Table 15.5.b. Summary of Platelets at Selected Time Points (Hematology Transplant: Safety Pool B)

Platelets (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Baseline		
n	241	408
Mean	204.85	198.53
SD	116.38	111.53
Median	180.00	188.00
Q1, Q3	129.00, 260.00	120.00, 247.00
Min, Max	[	]
Day -8		
n	123	260
Mean	205.69	213.60
SD	91.00	104.93
Median	192.00	197.00
Q1, Q3	153.00, 240.00	145.00, 257.00
Min, Max	[	]
Change from Baseline to Day -8		
n	123	259
Mean	-5.50	-2.96
SD	36.84	55.62
Median	-3.00	-3.00
Q1, Q3	-28.00, 10.00	-22.00, 17.00
Min, Max	[	]
Day -5		
n	238	405
Mean	195.52	190.84
SD	91.17	88.58
Median	183.00	176.00
Q1, Q3	140.00, 237.00	130.00, 232.00
Min, Max	[	]

N=Number of subjects,n=non-missing values;SD=sample standard deviation

Table 15.5.b. Summary of Platelets at Selected Time Points (Hematology Transplant: Safety Pool B)

Platelets (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day -5		
n	238	404
Mean	-9.37	-6.94
SD	82.76	92.03
Median	-15.50	-13.00
Q1, Q3	-46.00, 33.00	-46.50, 29.00
Min, Max	[	]
Day 0		
n	239	405
Mean	108.90	111.04
SD	58.63	62.86
Median	98.00	104.00
Q1, Q3	67.00, 140.00	65.00, 143.00
Min, Max	[	]
Change from Baseline to Day 0		
n	239	404
Mean	-94.67	-87.48
SD	96.18	97.47
Median	-80.00	-75.50
Q1, Q3	-131.00, -42.00	-129.50, -31.00
Min, Max	[	]
Day 7		
n	238	406
Mean	23.66	23.12
SD	15.27	17.53
Median	19.50	19.00
Q1, Q3	13.00, 30.00	13.00, 28.00
Min, Max	[	]

Table 15.5.b. Summary of Platelets at Selected Time Points (Hematology Transplant: Safety Pool B)

Platelets (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 7		
n	238	405
Mean	-179.91	-175.45
SD	115.60	110.96
Median	-154.50	-167.00
Q1, Q3	-236.00, -100.00	-224.00, -98.00
Min, Max	[	]
Day 10		
n	233	399
Mean	29.28	28.67
SD	16.32	17.91
Median	27.00	24.00
Q1, Q3	18.00, 36.00	16.00, 36.00
Min, Max	[	]
Change from Baseline to Day 10		
n	233	398
Mean	-174.64	-168.34
SD	111.32	105.83
Median	-151.00	-162.50
Q1, Q3	-227.00, -100.00	-215.00, -94.00
Min, Max	[	]
Day 14		
n	194	334
Mean	46.36	49.83
SD	37.91	42.24
Median	38.00	37.00
Q1, Q3	23.00, 55.00	24.00, 62.00
Min, Max	[	]

Table 15.5.b. Summary of Platelets at Selected Time Points (Hematology Transplant: Safety Pool B)

Platelets (10^9/L)

	Placebo (N=241)	Palifermin (N=409)
Change from Baseline to Day 14		
n	194	333
Mean	-153.86	-146.90
SD	102.71	99.64
Median	-140.00	-134.00
Q1, Q3	-201.00, -88.00	-193.00, -80.00
Min, Max	[	]
Day 28		
n	212	348
Mean	134.37	134.77
SD	86.24	84.45
Median	124.00	129.50
Q1, Q3	69.00, 186.50	70.00, 189.50
Min, Max	[	]
Change from Baseline to Day 28		
n	212	347
Mean	-64.92	-61.82
SD	101.42	101.56
Median	-57.00	-55.00
Q1, Q3	-108.00, -8.50	-107.00, -9.00
Min, Max	[	]

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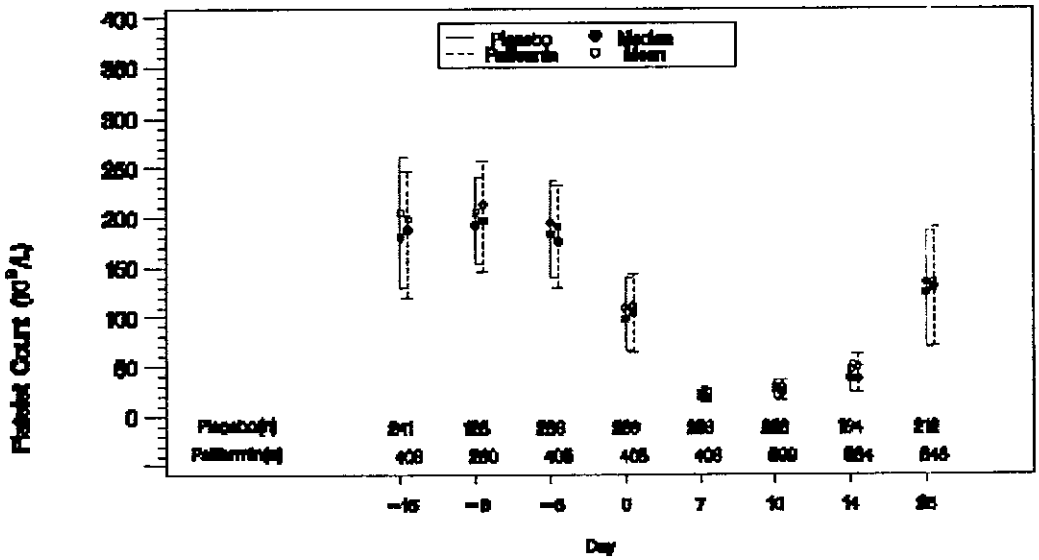
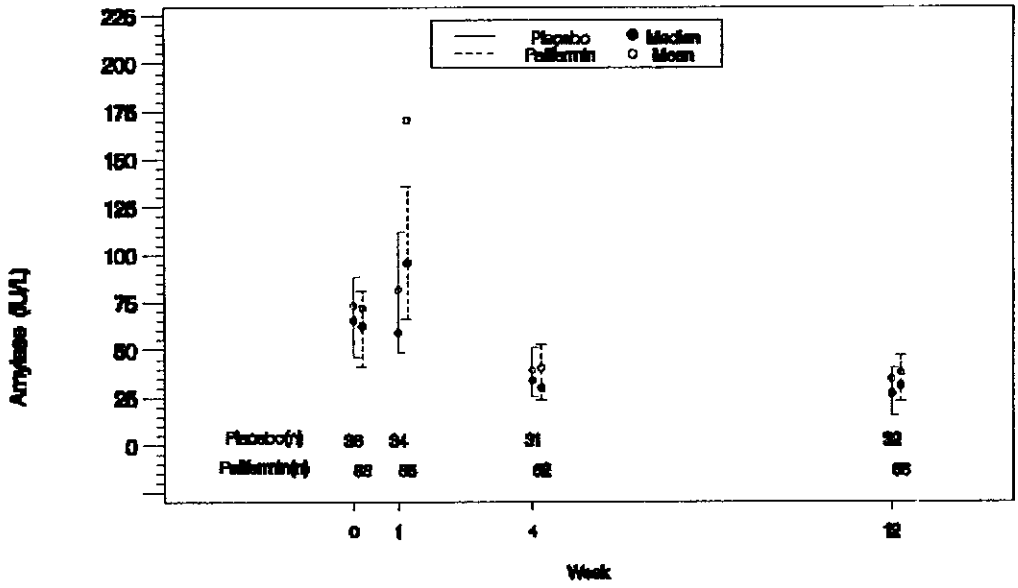
Figure 1.4.b. Median of Platelets by Study Day (Hematology Transplant: Safety Pool B)



Solid Tumor Setting
Head and Neck Cancer

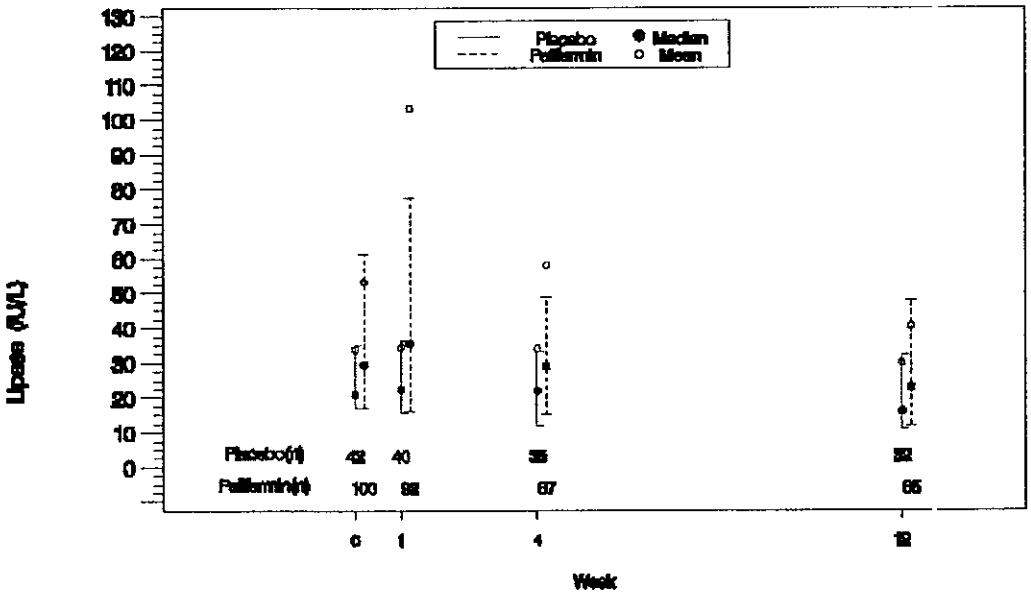
Chemistry – Amylase(range of normal in standard units used 1-88 /L)::

Figure 1.5.d. Median of Amylase by Week (Head and Neck Cancer: Safety Pool D)



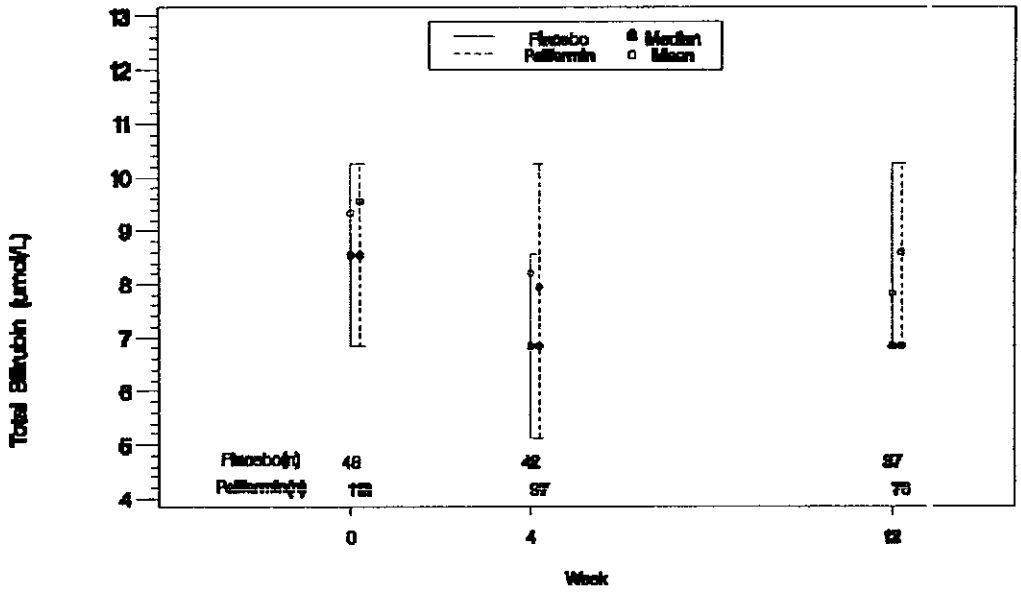
Chemistry - Lipase(range of normal in standard units used 0 – 63 IU/L):

Figure 1.6.d. Median of Lipase by Week (Head and Neck Cancer: Safety Pool D)



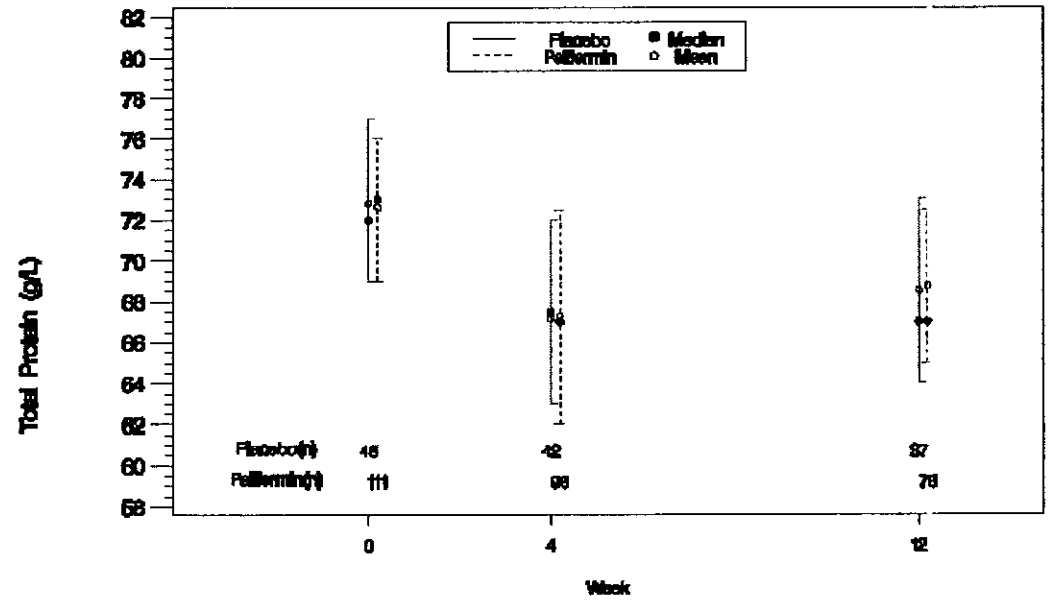
Chemistry – Bilirubin(range of normal in standard units used 0 – 25.6 µmol/L):

Figure 1.9.d. Median of Total Bilirubin by Week (Head and Neck Cancer: Safety Pool D)



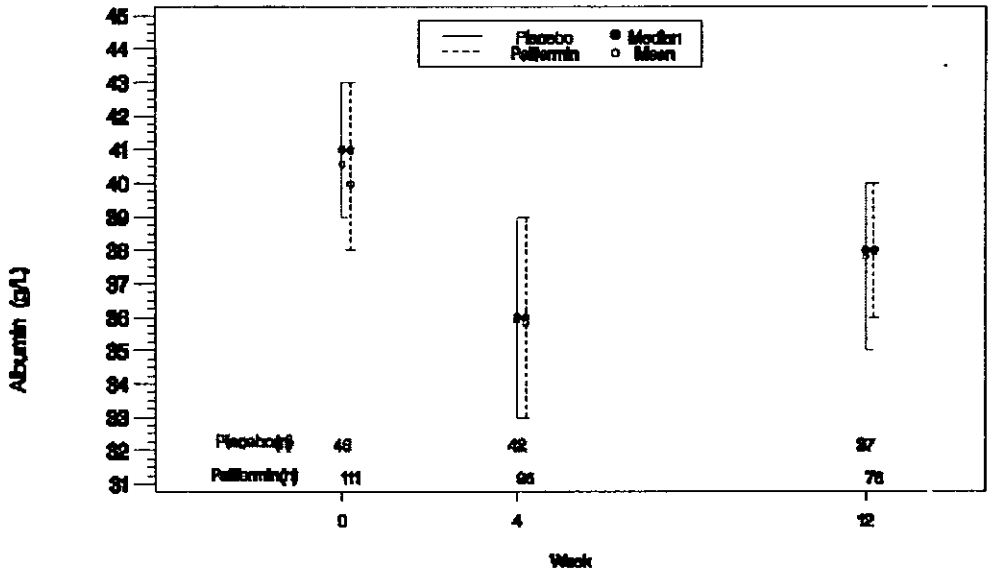
Chemistry – Total Protein(range of normal in standard units used 58-85 g/L):

Figure 1.10.d. Median of Total Protein by Week (Head and Neck Cancer: Safety Pool D)



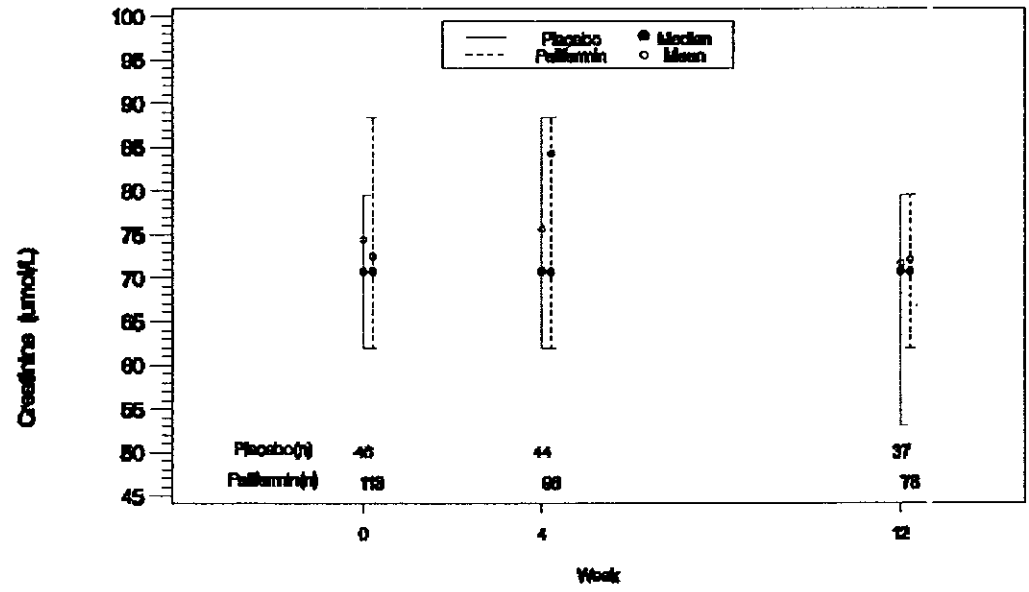
Chemistry – Albumin(range of normal in standard units used 30 – 50 g/L):

Figure 1.11.d. Median of Albumin by Week (Head and Neck Cancer: Safety Pool D)



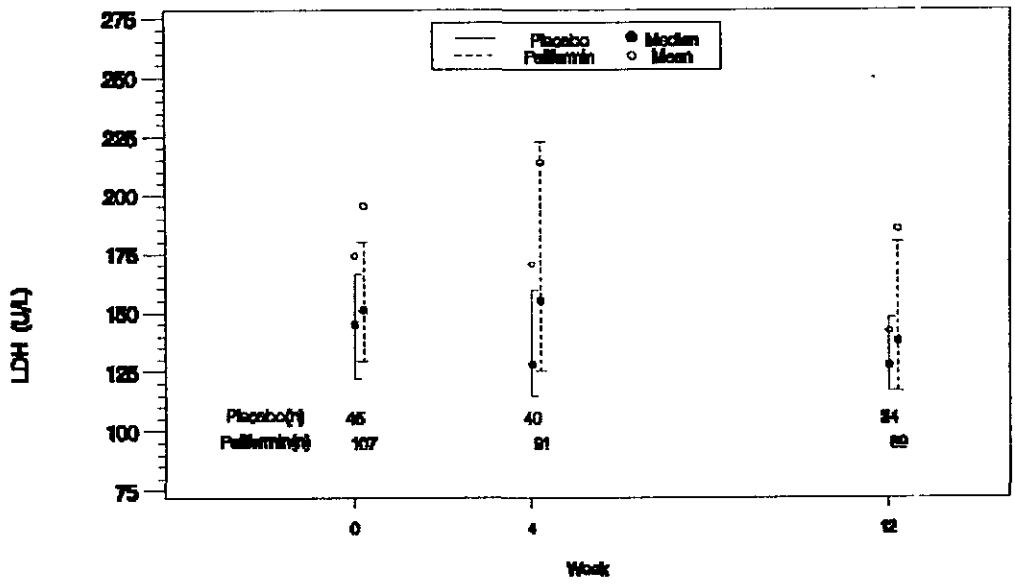
Chemistry – Creatinine(range of normal in standard units used 35-132 μmol/L):

Figure 1.12.d. Median of Creatinine by Week (Head and Neck Cancer: Safety Pool D)



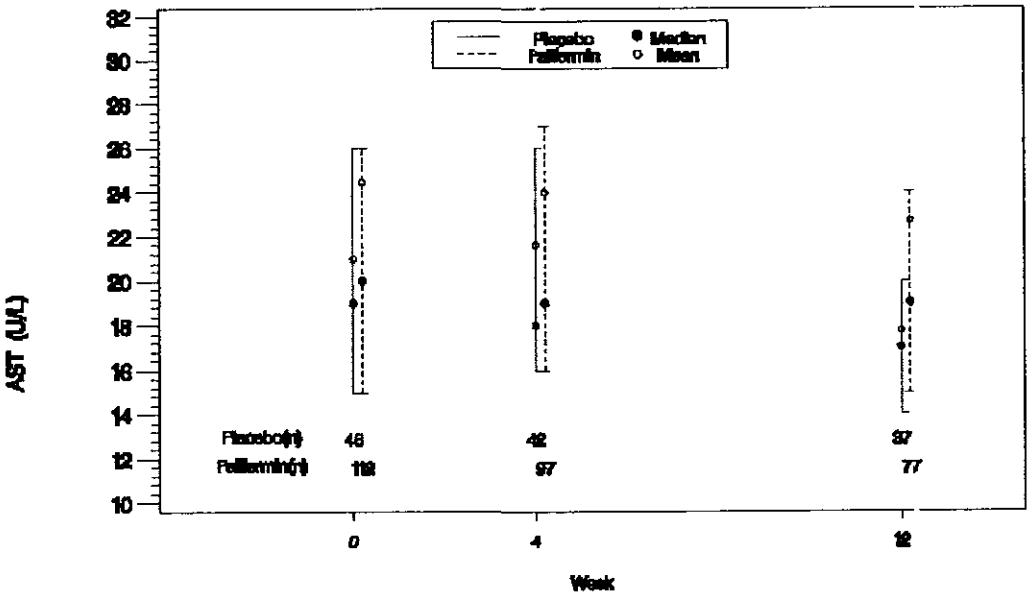
Chemistry - Lactate Dehydrogenase(range of normal in standard units used 0-618 U/L):

Figure 1.13.d. Median of LDH by Week (Head and Neck Cancer: Safety Pool D)



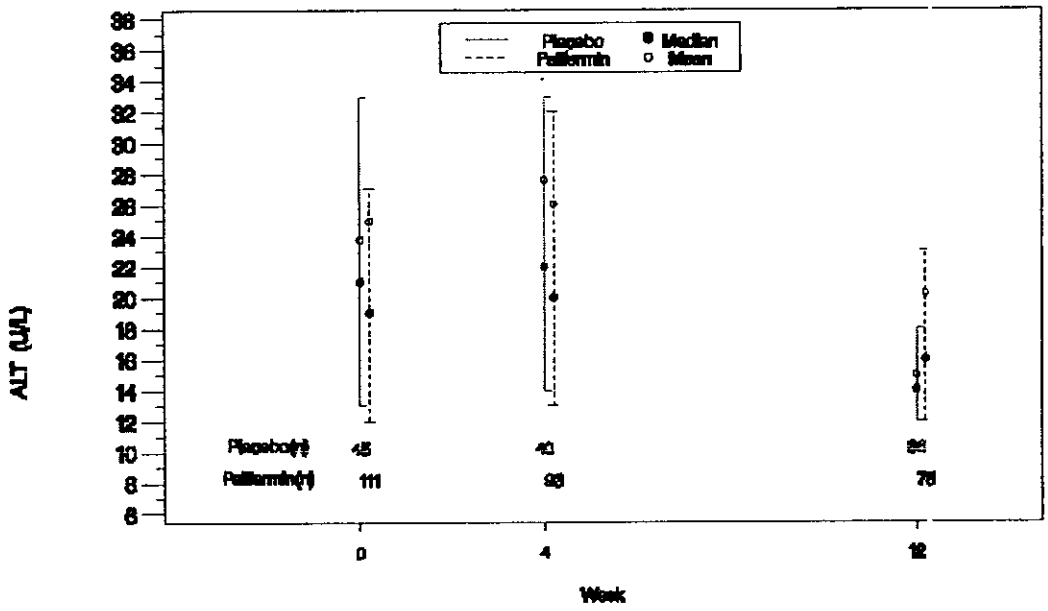
Chemistry - Aspartate aminotransferase(range of normal in standard units used 0 – 60 U/L):

Figure 1.7.d. Median of AST by Week (Head and Neck Cancer: Safety Pool D)



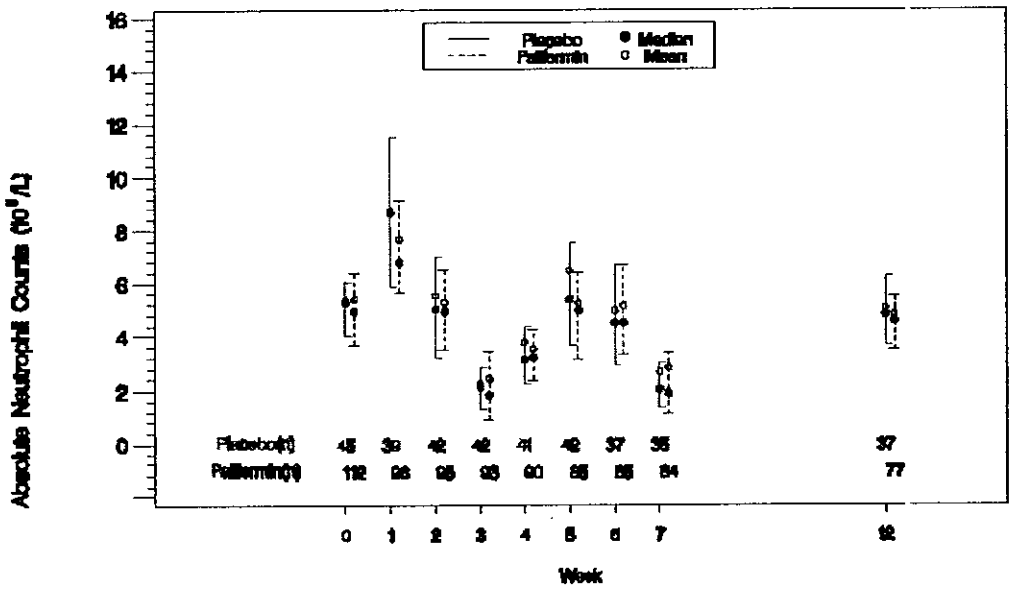
Chemistry – Alanine aminotransferase(range of normal in standard units used 0-72 U/L):

Figure 1.8.d. Median of ALT by Week (Head and Neck Cancer: Safety Pool D)



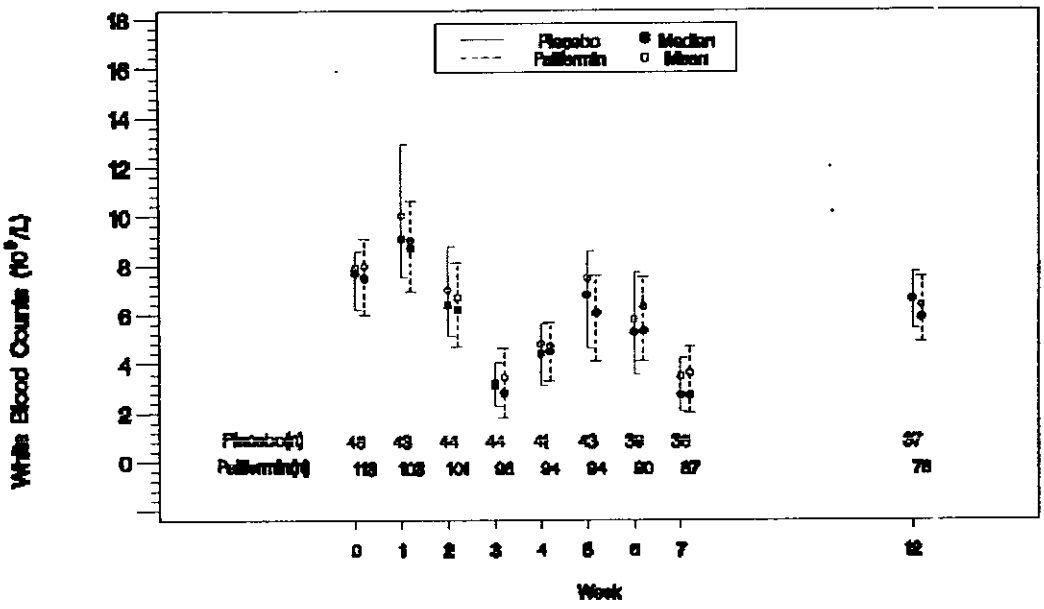
Hematology – Absolute Neutrophil Count:

Figure 1.2.d. Median of ANC by Week (Head and Neck Cancer: Safety Pool D)



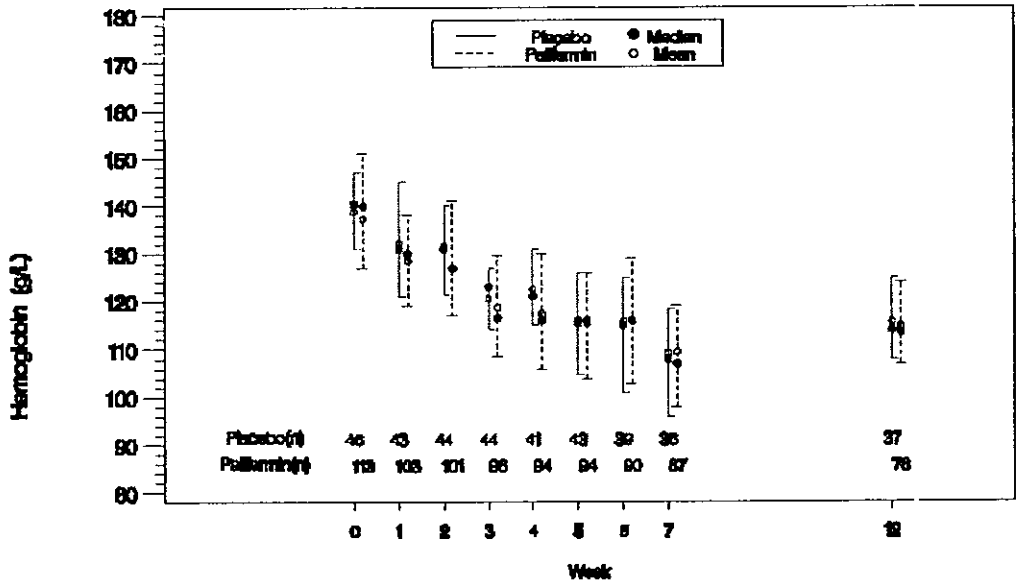
Hematology – White Blood Count:

Figure 1.1.d. Median of WBC by Week (Head and Neck Cancer: Safety Pool D)



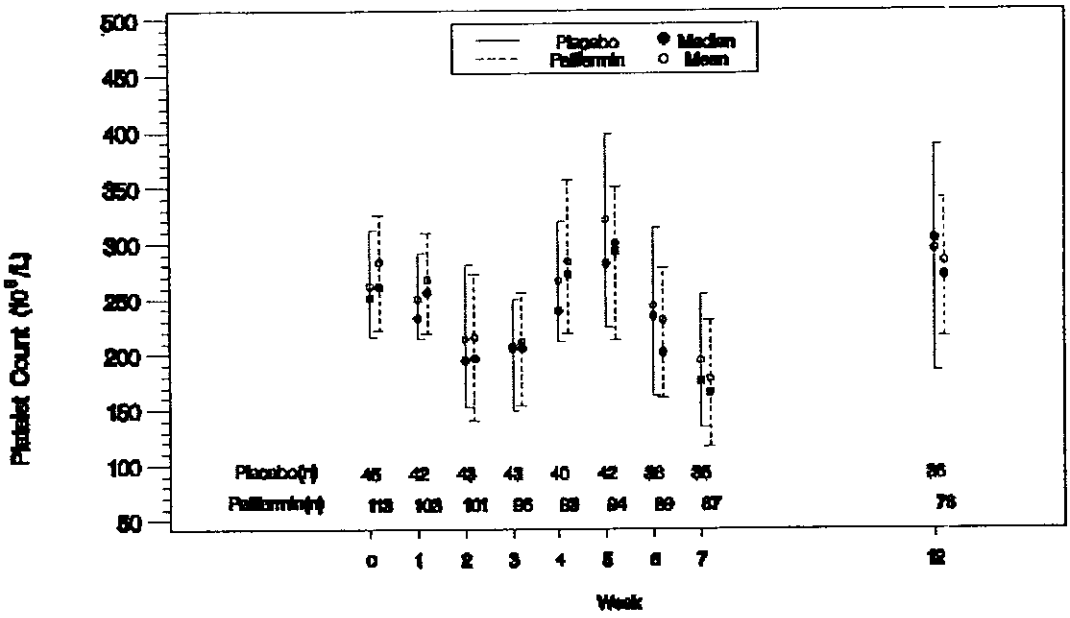
Hematology – Hemoglobin:

Figure 1.3.d. Median of Hemoglobin by Week (Head and Neck Cancer: Safety Pool D)



Hematology – Platelet:

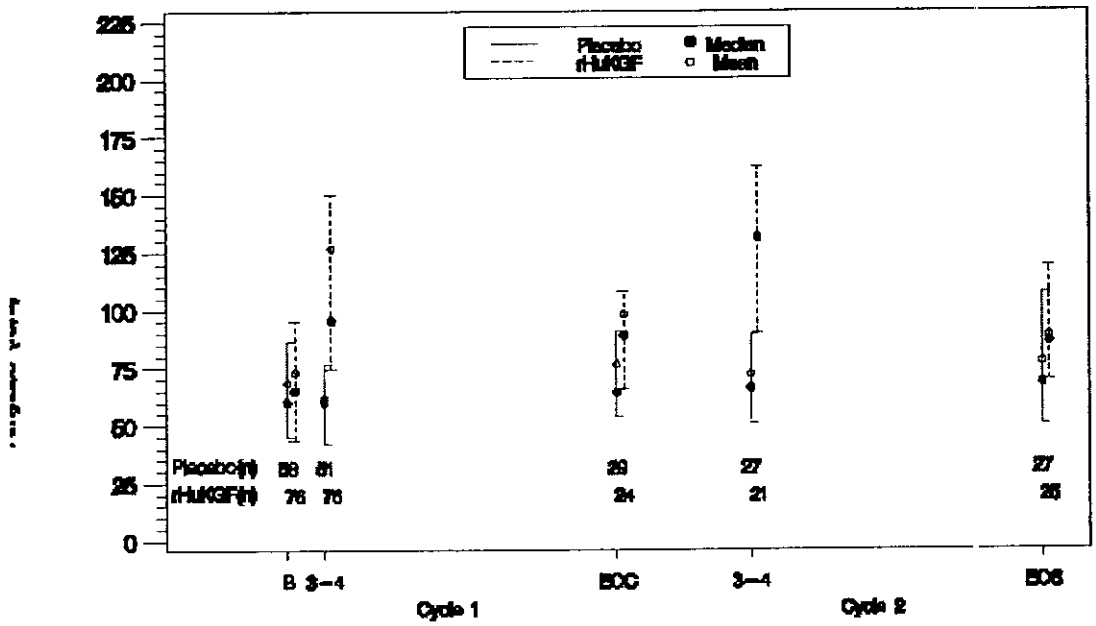
Figure 1.4.d. Median of Platelets by Week (Head and Neck Cancer: Safety Pool D)



Colorectal Cancer Safety Pool F

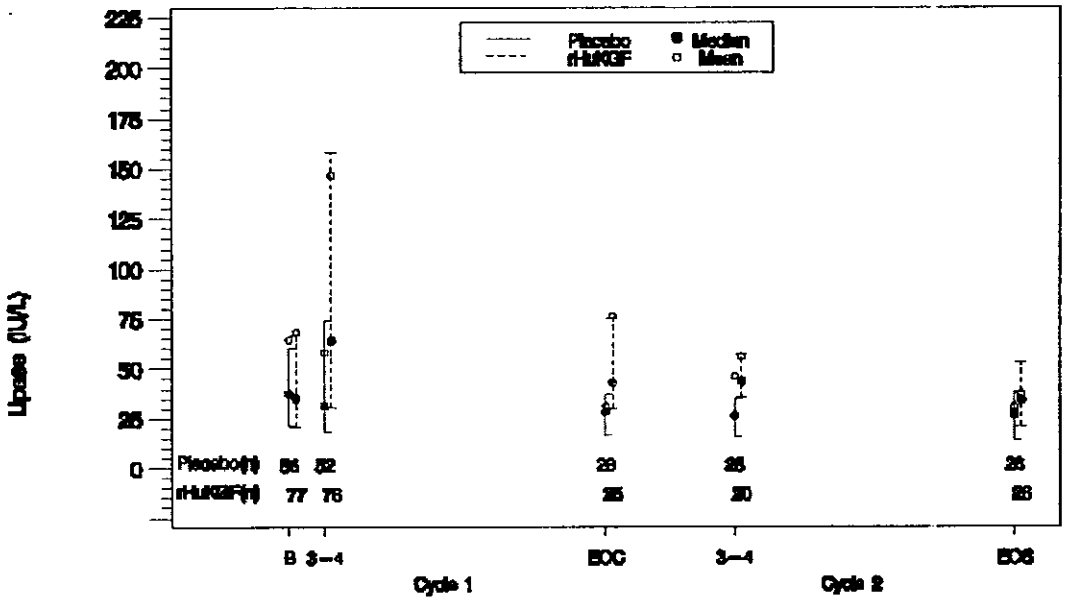
Chemistry – Amylase(range of normal in standard units used 1-88 /L):

Figure 14.6.2c Summary Plot for Amylase by Study Day, Study 960226 Part A and Part B (Safety Population)



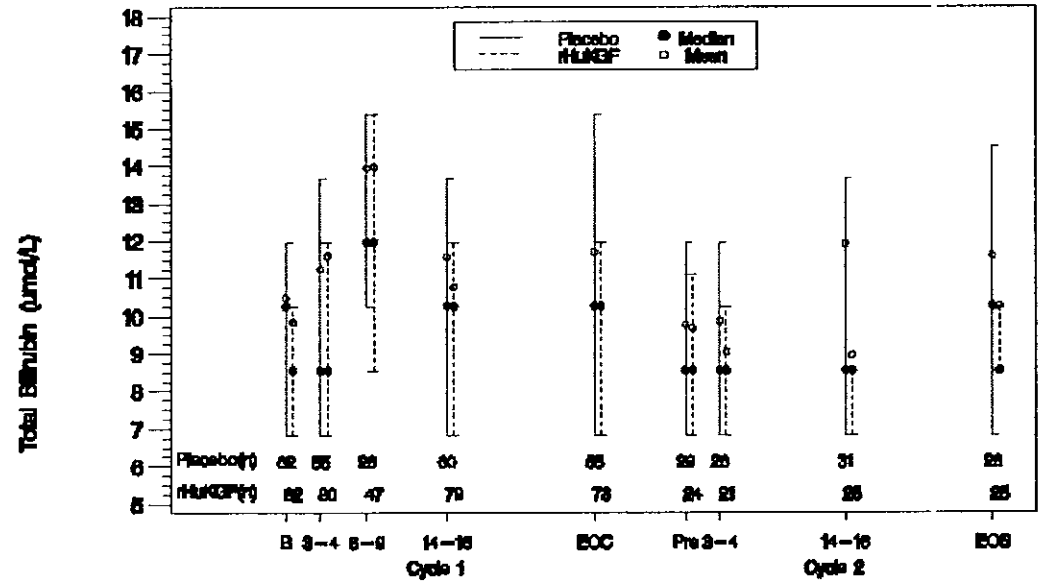
Chemistry - Lipase(range of normal in standard units used 0 – 63 IU/L):

Figure 14.6.3c Summary Plot for Lipase by Study Day, Study 950225 Part A and Part B (Safety Population)



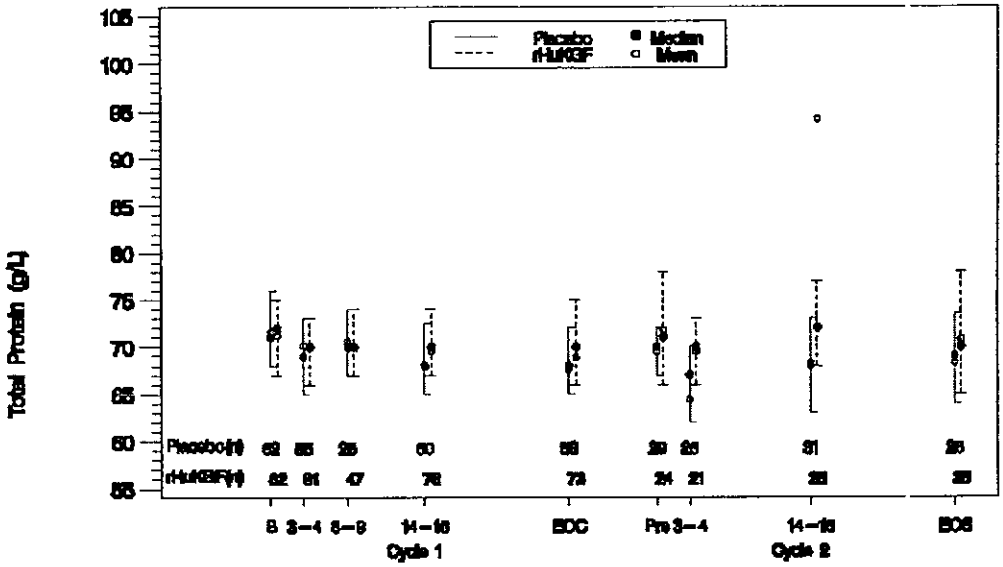
Chemistry – Bilirubin(range of normal in standard units used 0 – 25.6 µmol/L):

Figure 14.6.6c Summary Plot for Total Bilirubin by Study Day, Study 950225 Part A and Part B (Safety Population)



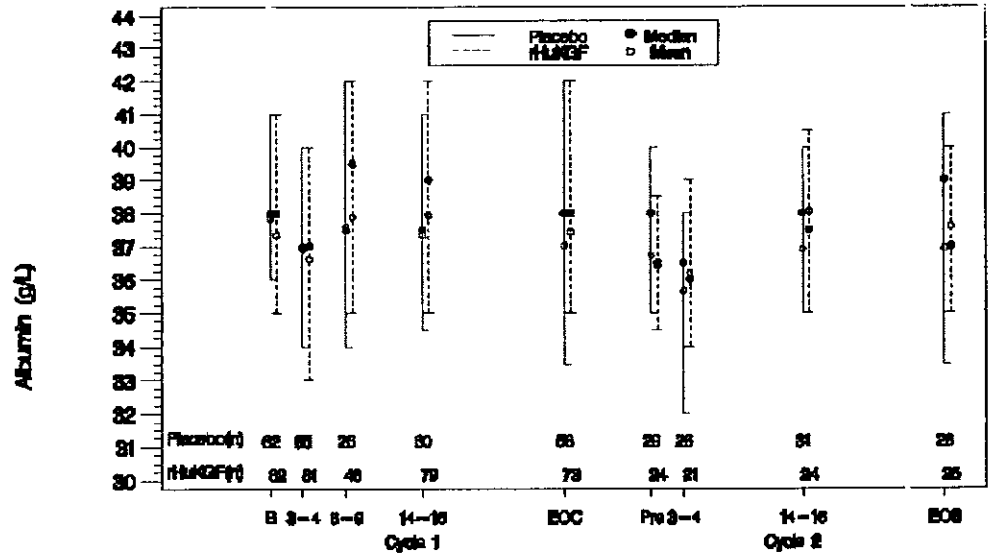
Chemistry – Total Protein(range of normal in standard units used 58-85 g/L).

Figure 14.6.7c Summary Plot for Total Protein by Study Day, Study 950225 Part A and Part B (Safety Population)



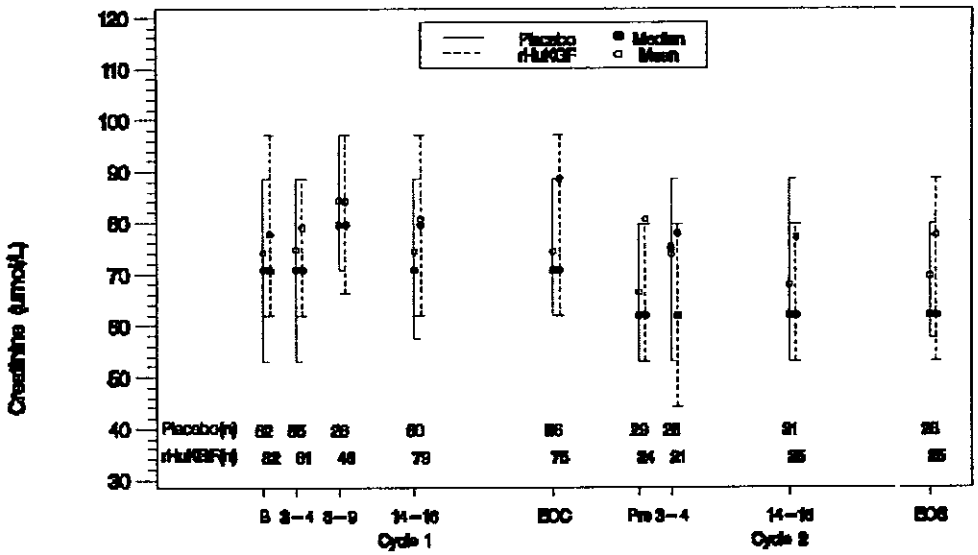
Chemistry – Albumin(range of normal in standard units used 30 – 50 g/L):

Figure 14.6.8c Summary Plot for Albumin by Study Day, Study 950225 Part A and Part B (Safety Population)



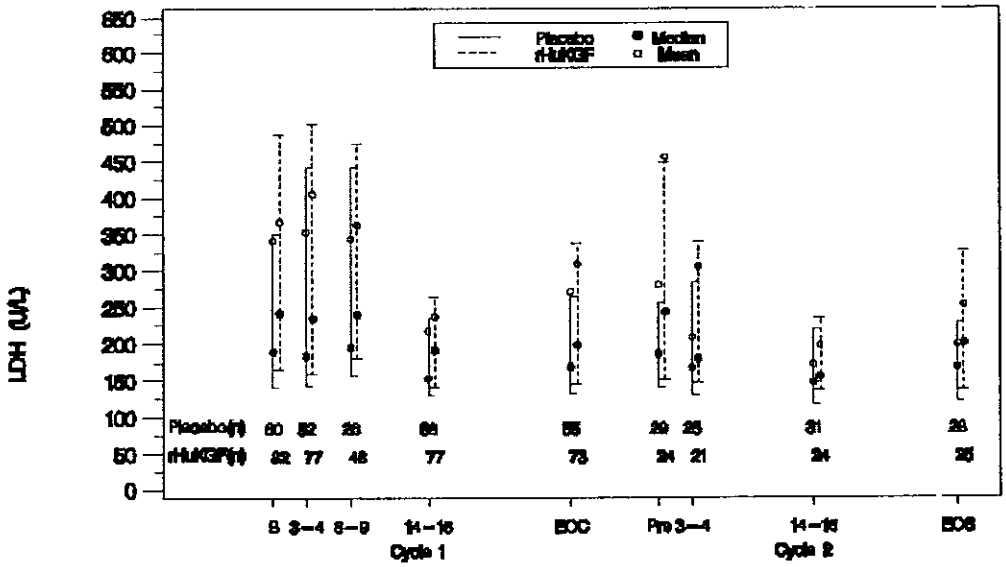
Chemistry – Creatinine(range of normal in standard units used 35-132 µmol/L):

Figure 14.6.9o Summary Plot for Creatinine by Study Day, Study 960226 Part A and Part B
(Safety Population)

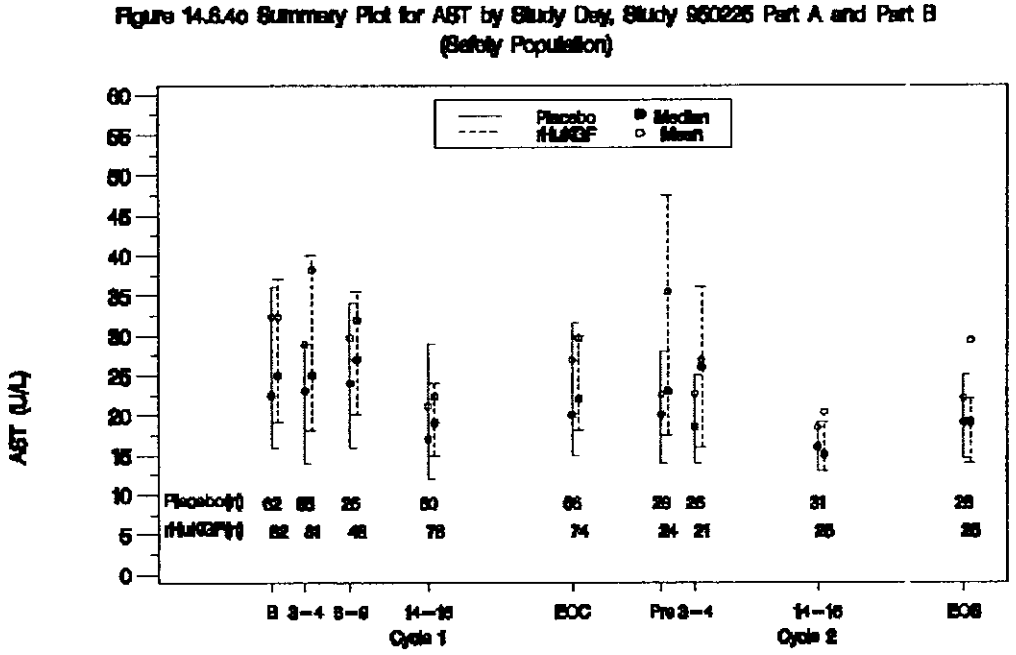


Chemistry - Lactate Dehydrogenase(range of normal in standard units used 0-618 U/L):

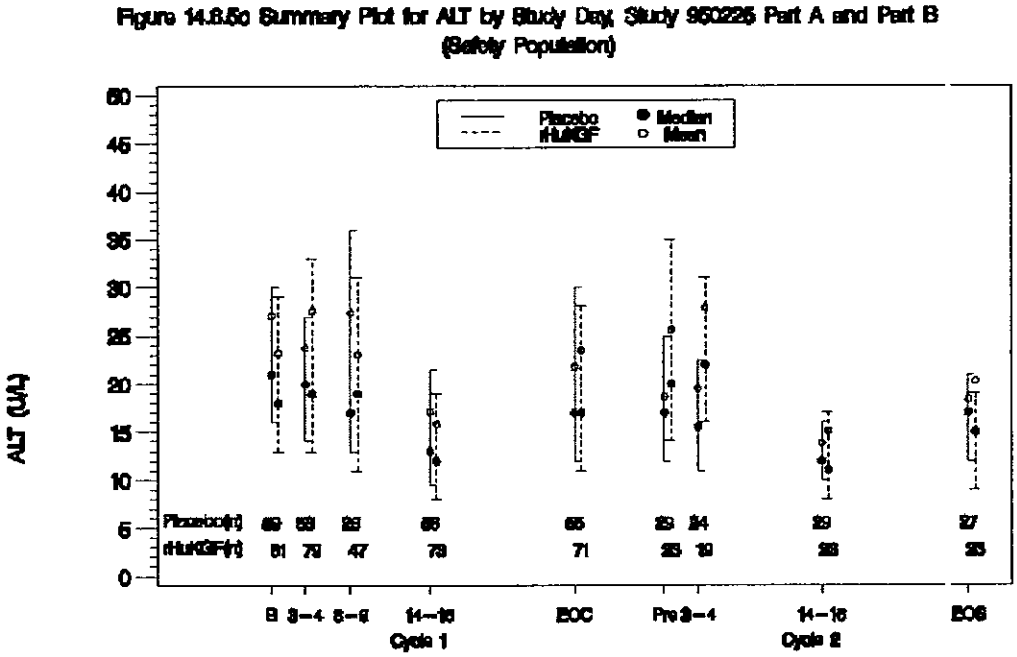
Figure 14.6.10o Summary Plot for LDH by Study Day, Study 960226 Part A and Part B
(Safety Population)



Chemistry - Aspartate aminotransferase(range of normal in standard units used 0 – 60 U/L):

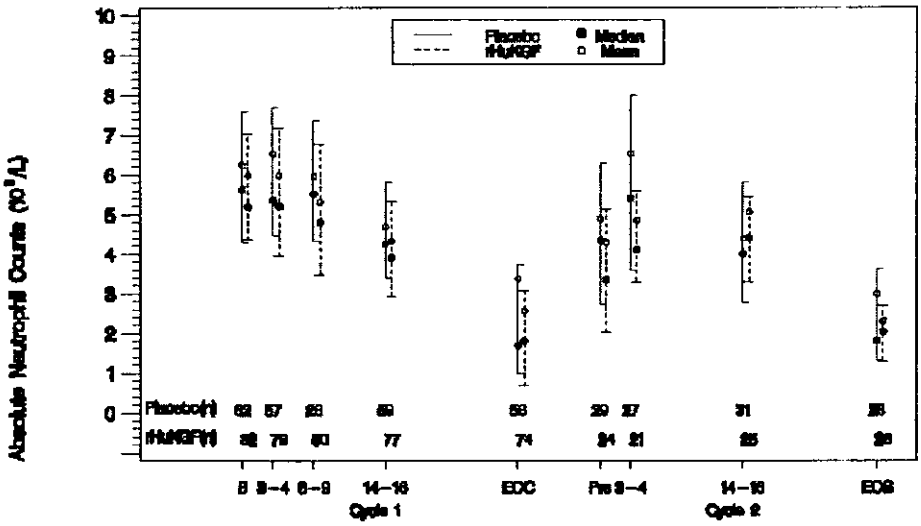


Chemistry – Alanine aminotransferase(range of normal in standard units used 0-72 U/L):



Hematology – Absolute Neutrophil Count:

Figure 14.5.2c Summary Plot for Absolute Neutrophil Count by Study Day, Study 950225 Part A and Part B (Safety Population)



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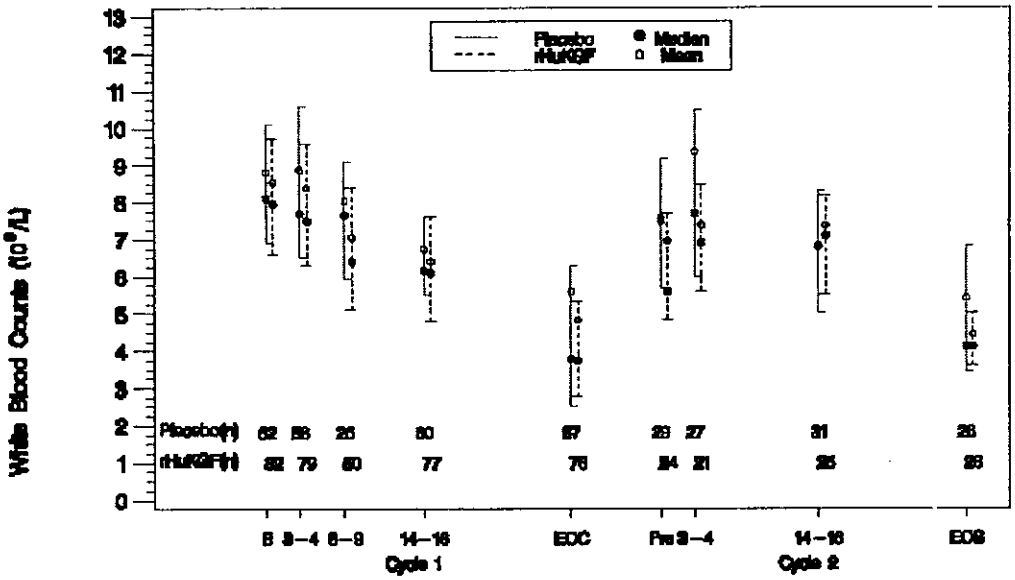
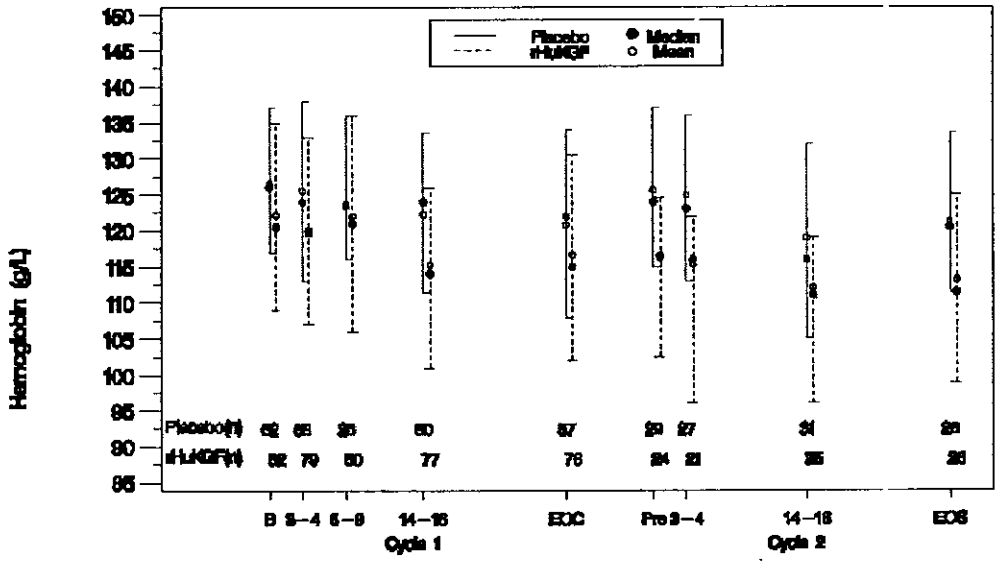
Hematology – White Blood Count:

Figure 14.5.1c Summary Plot for White Blood Count by Study Day, Study 950225 Part A and Part B (Safety Population)



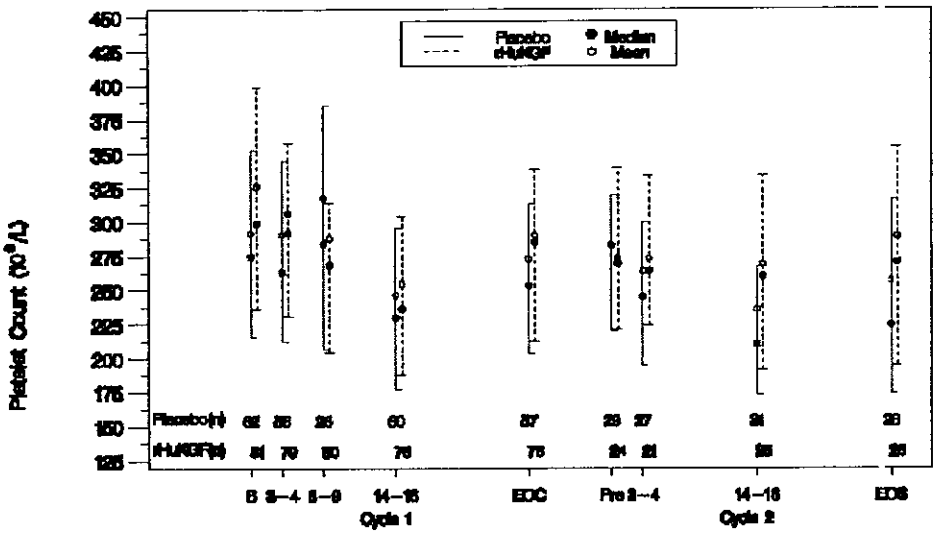
Hematology – Hemoglobin:

Figure 14.5.3c Summary Plot for Hemoglobin by Study Day, Study 950225 Part A and Part B (Safety Population)



Hematology – Platelet:

Figure 14.5.5c Summary Plot for Platelet Count by Study Day, Study 950225 Part A and Part B (Safety Population)



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7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Amgen's Shift tables for Amylase, Lipase, and Absolute Neutrophil Count follow.

Hematologic Malignancy Patient Population:

Chemistry - Amylase:

Table 16.2.b. Shifts in CTC Toxicity Grade from Baseline in Amylase (Increase)
(Hematology Transplant: Safety Pool B)

	Placebo (N=241) Baseline							Palifermin (N=409) Baseline						
Maximum Post-Baseline	N/A	0	1	2	3	4	Total	N/A	0	1	2	3	4	Total
N/A	44	4	0	0	0	0	48	85	4	1	0	0	0	90
0	3	82 (44)	0	0	0	0	85	9	113 (38)	1 (0)	0	0	0	123
1	0	25 (13)	3 (2)	0	0	0	28	4	40 (13)	0	0	0	0	44
2	0	14 (8)	2 (1)	0	0	0	16	2	21 (7)	1 (0)	0	0	0	24
3	3	34 (18)	1 (1)	0	0	0	38	5	59 (20)	5 (2)	0	0	0	69
4	1	21 (11)	3 (2)	1 (1)	0	0	26	1	52 (17)	3 (1)	2 (1)	1 (0)	0	59
Total	51	180	9	1	0	0	241	106	289	11	2	1	0	409

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Note. N/A = not available

Chemistry - Lipase:

Table 16.4.b. Shifts in CTC Toxicity Grade from Baseline in Lipase (Increase)
(Hematology Transplant: Safety Pool B)

	Placebo (N=241) Baseline							Palifermin (N=409) Baseline						
Maximum Post-Baseline	N/A	0	1	2	3	4	Total	N/A	0	1	2	3	4	Total
N/A	60	3	0	0	0	0	63	117	3	0	0	0	0	120
0	6	126 (74)	2 (1)	0	0	0	134	13	183 (67)	2 (1)	2 (1)	2 (1)	0	202
1	1	21 (12)	2 (1)	0	0	0	24	2	23 (8)	3 (1)	1 (0)	0	0	29
2	1	7 (4)	1 (1)	0	0	0	9	0	21 (8)	1 (0)	2 (1)	0	1 (0)	25
3	0	8 (5)	1 (1)	0	0	1 (1)	10	0	25 (9)	0	2 (1)	1 (0)	0	28
4	0	1 (1)	0	0	0	0	1	0	3 (1)	1 (0)	0	0	1 (0)	5
Total	68	166	6	0	0	1	241	132	258	7	7	3	2	409

Hematology – Absolute Neutrophil Count:

Table 15.2.b. Shifts in CTC Toxicity Grade from Baseline in ANC (Decrease)
(Hematology Transplant: Safety Pool B)

	Placebo (N=241) Baseline							Palifermin (N=409) Baseline						
Maximum Post-Baseline	N/A	0	1	2	3	4	Total	N/A	0	1	2	3	4	Total
N/A	0	0	0	0	0	0	0	0	1	0	0	0	0	1
0	0	2 (1)	1 (0)	0	0	0	3	0	9 (2)	0	0	0	0	9
1	0	2 (1)	0	1 (0)	0	0	3	1	4 (1)	0	0	0	0	5
2	0	12 (5)	3 (1)	0	2 (1)	0	17	0	19 (5)	1 (0)	0	1 (0)	0	21
3	2	21 (9)	0	1 (0)	0	0	24	0	29 (7)	5 (1)	4 (1)	2 (0)	0	40
4	4	158 (67)	8 (3)	13 (6)	6 (3)	5 (2)	194	6	290 (72)	12 (3)	19 (5)	5 (1)	1 (0)	333
Total	6	195	12	15	8	5	241	7	352	18	23	8	1	409

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Note. N/A = not available

Solid Tumor Setting
Head and Neck Cancer
Chemistry - Amylase:

Table 28. Shifts in CTC Toxicity Grade from Baseline in Amylase (Increase) (Safety Pool D)

	Placebo (N=46) Baseline							Palifermin (N=113) Baseline						
Maximum Post-Baseline	N/A	0	1	2	3	4	Total	N/A	0	1	2	3	4	Total
N/A	4	2	0	0	0	0	6	15	1	0	0	0	0	16
0	6	29 (85)	1 (3)	0	0	0	36	10	64 (74)	0	0	1 (1)	0	75
1	0	3 (9)	0	0	0	0	3	0	11 (13)	0	0	0	0	11
2	0	1 (3)	0	0	0	0	1	0	4 (5)	0	0	0	0	4
3	0	0	0	0	0	0	0	0	3 (3)	1 (1)	0	0	0	4
4	0	0	0	0	0	0	0	0	2 (2)	1 (1)	0	0	0	3
Total	10	35	1	0	0	0	46	25	85	2	0	1	0	113

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Note: N/A = not available

Table 29. Shifts in CTC Toxicity Grade from Baseline in Lipase (Increase) (Safety Pool D)

	Placebo (N=46) Baseline							Palifermin (N=113) Baseline						
Maximum Post-Baseline	N/A	0	1	2	3	4	Total	N/A	0	1	2	3	4	Total
N/A	2	0	0	0	0	0	2	9	2	0	0	0	0	11
0	2	36 (86)	0	0	0	0	38	3	68 (69)	3 (3)	0	0	0	74
1	0	4 (10)	0	0	0	0	4	1	8 (8)	2 (2)	1 (1)	0	0	12
2	0	1 (2)	0	0	0	0	1	0	2 (2)	3 (3)	0	0	0	5
3	0	0	0	0	1 (2)	0	1	0	5 (5)	1 (1)	0	2 (2)	0	8
4	0	0	0	0	0	0	0	0	3 (3)	0	0	0	0	3
Total	4	41	0	0	1	0	46	13	88	9	1	2	0	113

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Note: N/A = not available

Colorectal Cancer
Chemistry - Amylase:

Table 14-6.12c. Shifts in CTC Grade from Baseline in Amylase (Increase), Study 950225 Part A and Part B (Safety Population)

	Placebo: n (%) (N=63) Baseline							rHuKGF: n (%) (All Doses) (N=82) Baseline						
Maximum Post-Baseline Toxicity Grade	N/A	0	1	2	3	4	Total	N/A	0	1	2	3	4	Total
N/A	1	2	0	0	0	0	3	0	2	0	0	0	0	2
0	4	53(95)	1(2)	0	0	0	58	6	56(76)	3(4)	0	0	0	65
1	0	1(2)	0	0	0	0	1	0	11(15)	0	0	0	0	11
2	0	0	1(2)	0	0	0	1	0	1(1)	0	0	0	0	1
3	0	0	0	0	0	0	0	0	2(3)	1(1)	0	0	0	3
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	5	56	2	0	0	0	63	6	72	4	0	0	0	82

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Table 14-6.12c. Shifts in CTC Grade from Baseline in Amylase (Increase), Study 950225 Part A and Part B (Safety Population)

	rHuKGF: n (%) 1-20 µg/kg/day (N=25) Baseline							rHuKGF: n (%) 40-80 µg/kg/day (N=57) Baseline						
Maximum Post-Baseline Toxicity Grade	N/A	0	1	2	3	4	Total	N/A	0	1	2	3	4	Total
N/A	0	1	0	0	0	0	1	0	1	0	0	0	0	1
0	1	20(87)	2(9)	0	0	0	23	5	36(71)	1(2)	0	0	0	42
1	0	1(4)	0	0	0	0	1	0	10(20)	0	0	0	0	10
2	0	0	0	0	0	0	0	0	1(2)	0	0	0	0	1
3	0	0	0	0	0	0	0	0	2(4)	1(2)	0	0	0	3
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	1	22	2	0	0	0	25	5	50	2	0	0	0	57

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Chemistry - Lipase:

Table 14-6.13c. Shifts in CTC Grade from Baseline in Lipase (Increase), Study 950225 Part A and Part B (Safety Population)

Maximum Post-Baseline Toxicity Grade	Placebo, n (%) (N=63) Baseline							rHuKGF n (%) (All Doses) (N=82) Baseline						
	N/A	0	1	2	3	4	Total	N/A	0	1	2	3	4	Total
N/A	1	1	0	0	1	0	3	0	2	0	0	0	0	2
0	5	34(63)	0	0	0	0	39	4	26(35)	5(7)	0	0	0	35
1	1	2(4)	2(4)	1(2)	1(2)	0	7	0	11(15)	1(1)	0	1(1)	0	13
2	0	3(6)	0	1(2)	1(2)	0	5	0	3(4)	1(1)	1(1)	0	0	5
3	0	2(4)	2(4)	1(2)	1(2)	1(2)	7	0	9(12)	1(1)	0	6(8)	1(1)	17
4	0	1(2)	0	0	1(2)	0	2	1	4(5)	1(1)	0	2(3)	2(3)	10
Total	7	43	4	3	5	1	63	5	55	9	1	9	3	82

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Table 14-6.13c. Shifts in CTC Grade from Baseline in Lipase (Increase), Study 950225 Part A and Part B (Safety Population)

Maximum Post-Baseline Toxicity Grade	rHuKGF: n (%) 1-20 µg/kg/day (N=25) Baseline							rHuKGF: n (%) 40-80 µg/kg/day (N=57) Baseline						
	N/A	0	1	2	3	4	Total	N/A	0	1	2	3	4	Total
N/A	0	1	0	0	0	0	1	0	1	0	0	0	0	1
0	0	9(38)	3(13)	0	0	0	12	4	17(33)	2(4)	0	0	0	23
1	0	2(8)	1(4)	0	1(4)	0	4	0	9(18)	0	0	0	0	9
2	0	3(13)	1(4)	0	0	0	4	0	0	0	1(2)	0	0	1
3	0	2(8)	0	0	1(4)	1(4)	4	0	7(14)	1(2)	0	5(10)	0	13
4	0	0	0	0	0	0	0	1	4(8)	1(2)	0	2(4)	2(4)	10
Total	0	17	5	0	2	1	25	5	38	4	1	7	2	57

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Hematology – Absolute Neutrophil Count:

Table 14-5.6c. Shifts in CTC Grade from Baseline in Absolute Neutrophil Counts (Decrease) Study 950225 Part A and Part B

Maximum Post-Baseline Toxicity Grade	Placebo, n (%) (N=63) Baseline							rHuKGF n (%) (All Doses) (N=82) Baseline						
	N/A	0	1	2	3	4	Total	N/A	0	1	2	3	4	Total
N/A	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	1	26(42)	0	0	0	0	27	0	34(41)	0	0	0	0	34
1	0	3(5)	1(2)	0	0	0	4	0	8(10)	0	0	0	0	8
2	0	11(18)	0	0	0	0	11	0	11(13)	0	0	0	0	11
3	0	11(18)	0	0	0	0	11	0	13(16)	0	0	0	0	13
4	0	10(16)	0	0	0	0	10	0	16(20)	0	0	0	0	16
Total	1	61	1	0	0	0	63	0	82	0	0	0	0	82

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Table 14-5.6c. Shifts in CTC Grade from Baseline in Absolute Neutrophil Counts (Decrease) Study 950225 Part A and Part B

Maximum Post-Baseline Toxicity Grade	rHuKGF: n (%) 1-20 µg/kg/day (N=25) Baseline							rHuKGF: n (%) 40-80 µg/kg/day (N=57) Baseline						
	N/A	0	1	2	3	4	Total	N/A	0	1	2	3	4	Total
N/A	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	11(44)	0	0	0	0	11	0	23(40)	0	0	0	0	23
1	0	4(16)	0	0	0	0	4	0	4(7)	0	0	0	0	4
2	0	2(8)	0	0	0	0	2	0	9(16)	0	0	0	0	9
3	0	3(12)	0	0	0	0	3	0	10(18)	0	0	0	0	10
4	0	5(20)	0	0	0	0	5	0	11(19)	0	0	0	0	11
Total	0	25	0	0	0	0	25	0	57	0	0	0	0	57

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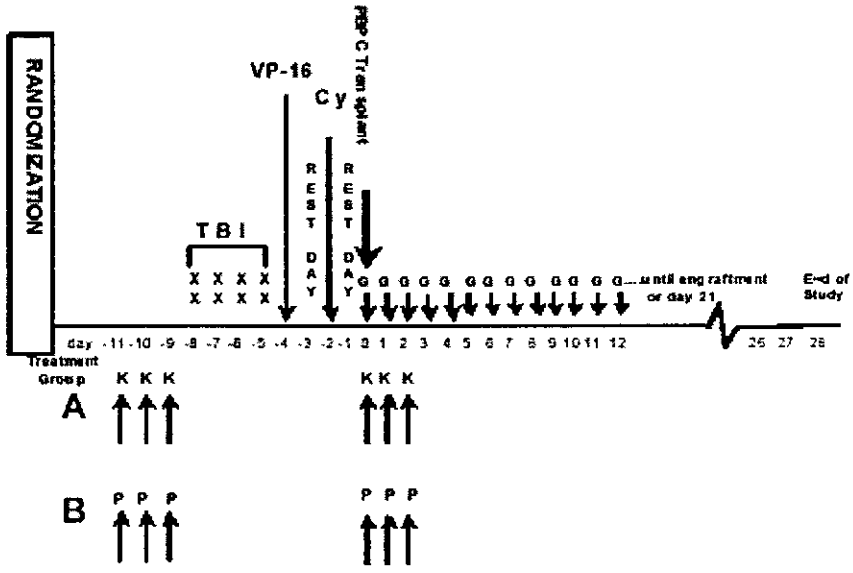
APPENDIX 10.4 Protocol Schemas

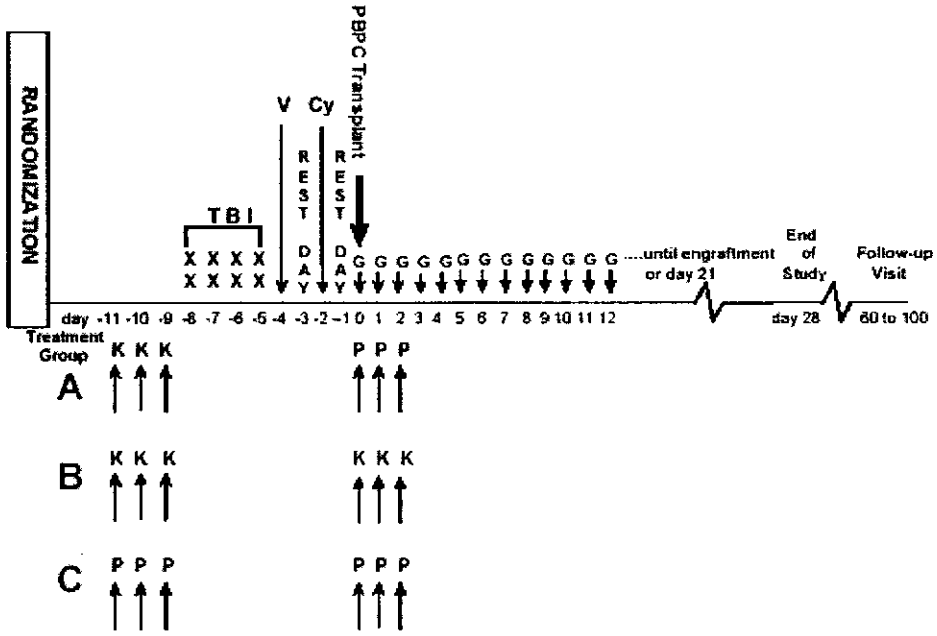
Hematologic Malignancy Patient Population:

20000162 A Phase 3, Randomized, Double-blind, Placebo-controlled Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) for Reduction of Mucositis in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation (TBI) and High-dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell (PBPC) Transplantation. (eCTD 5.3.5.1.1, Clinical Study Report 20000162 page 43)

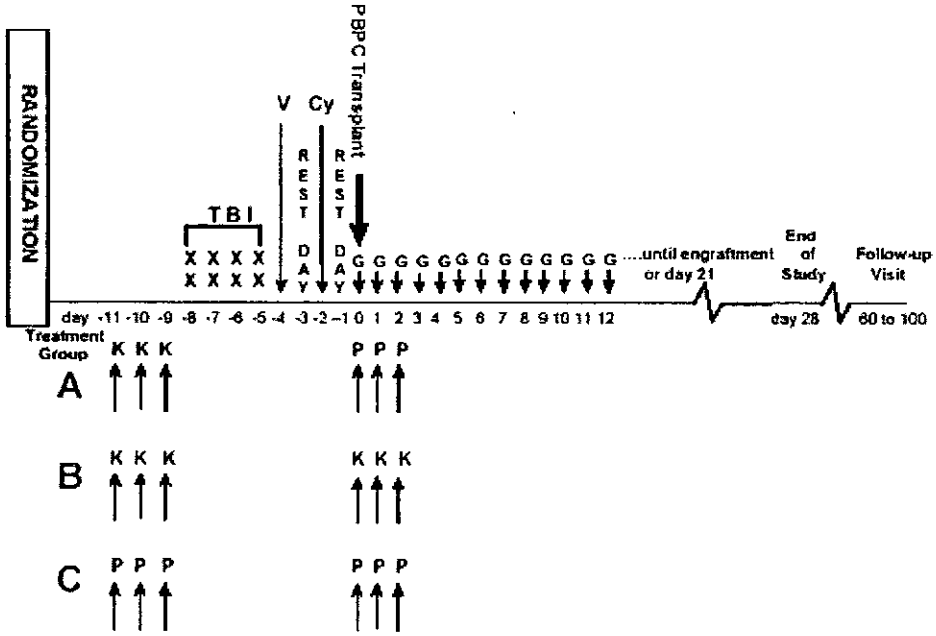


K – palifermin
P - placebo

980231 A Randomized, Double-blind, Placebo controlled Trial of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation (TBI) and High-dose Chemotherapy with Autologous Peripheral Bloor Progenitor Cell (PBPC) Transplantation. (eCTD 5.3.5.1.3, Clinical Study Report 990231 page 63, 64)

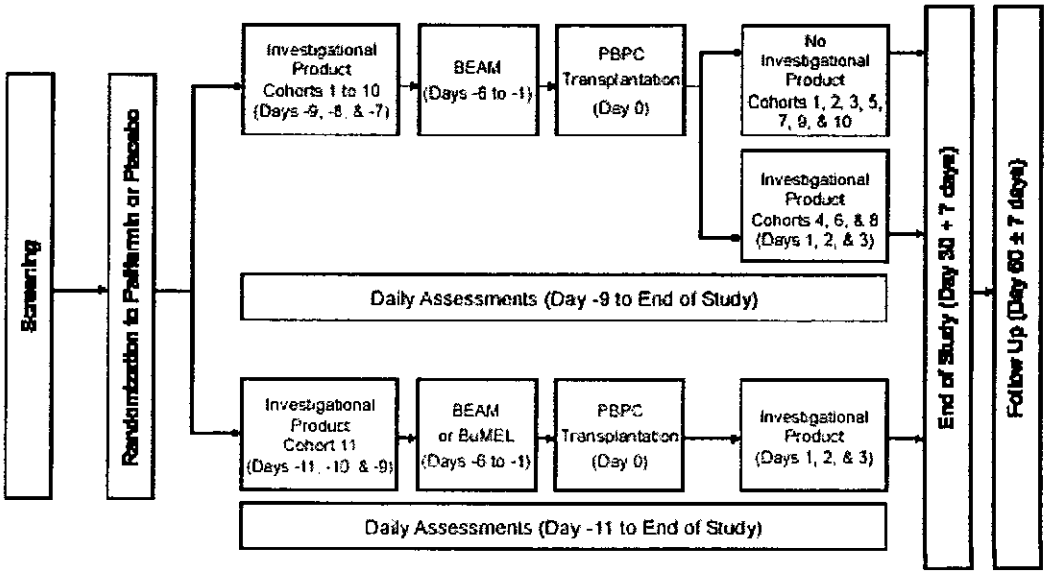


Appendix 10.4 Protocol Schemas
Patricia Dinndorf, M.D.
125103 Palifermin Kepivance™



K – palifermin
P - placebo

960189 A Randomized, Double Blind, Placebo Controlled, Dose Escalation Trial of the Safety of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Hodgkin's Disease and Non-Hodgkin's Lymphoma Patients Undergoing High Dose Chemotherapy with Autologous Peripheral Blood Progenitor Cell Transplantation (eCTD 5.3.5.1.2, Clinical Study Report 960189 page 51)



20010182 An open-Label Study of the Pharmacokinetics (PK) of Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Subjects with Hematologic Malignancies Undergoing Total Body Irradiation and High-Dose Chemotherapy Followed by Peripheral Blood Progenitor Cell (PBPC) Transplantation. (eCTD 5.3.3.2.1, Clinical Study Report 20010182 page 31)

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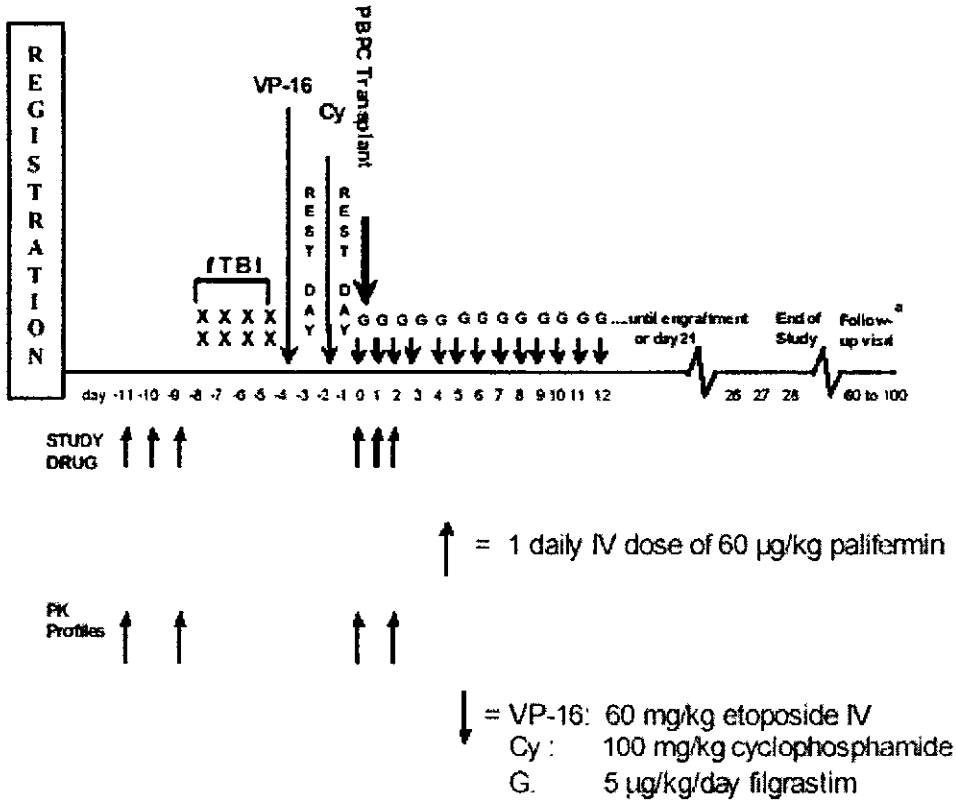


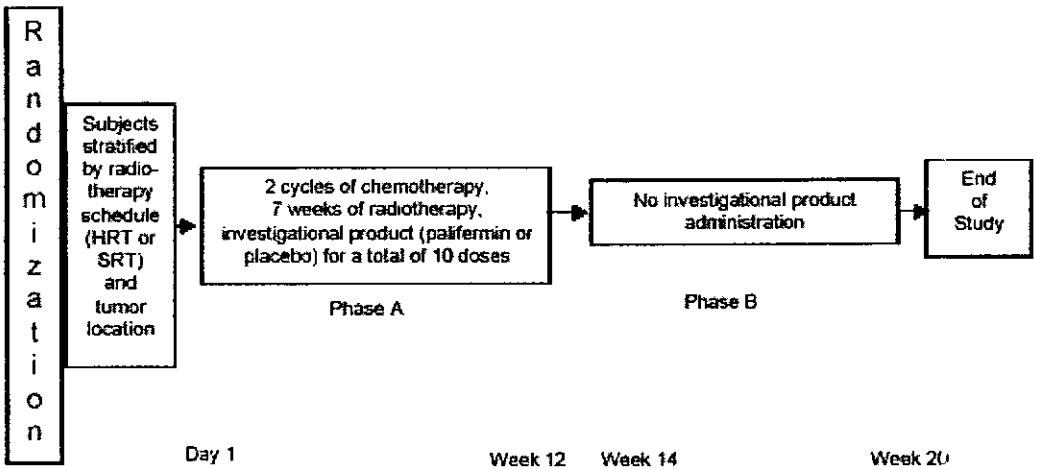
Blood draws (2 mL) for PK specimens on days -11, -9, 0, and 2 occurred before the palifermin dose; at 2, 5, 15, and 30 minutes postdose; and 1, 1.5, 2, 4, 6, 8, 12, and 24 hours postdose. Additional 48-hour samples were taken after the third and sixth doses of palifermin (ie. days -7 and 4).

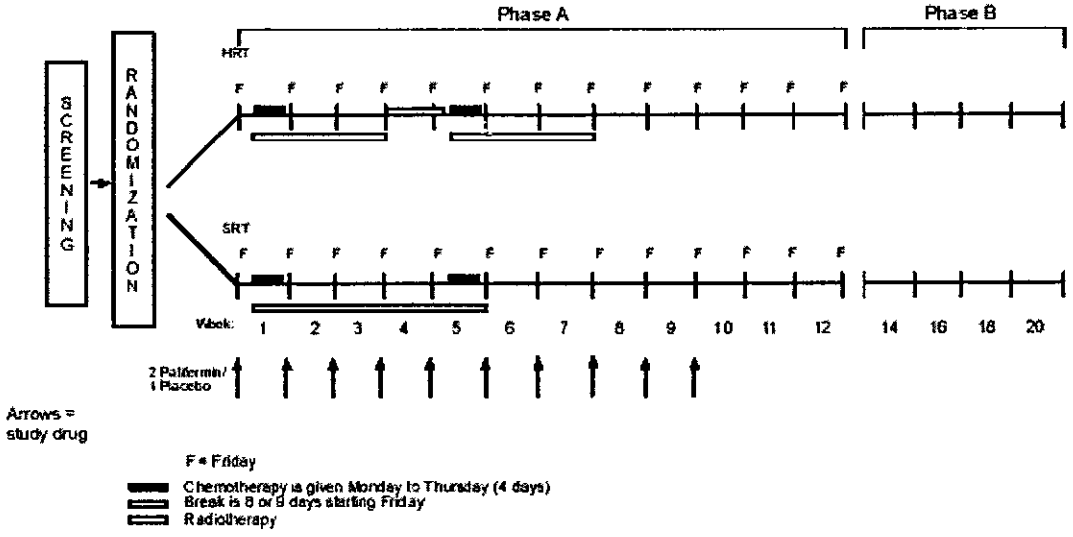
* The day after the end of study (day 28 post-transplant or as soon as possible thereafter) was defined as the start of the palifermin long-term follow-up Study 960226. In this study, subjects were monitored for disease status and survival. The visit expected between days 60 and 100 was the initial visit under the palifermin Protocol 960226.

Solid Tumor Setting:

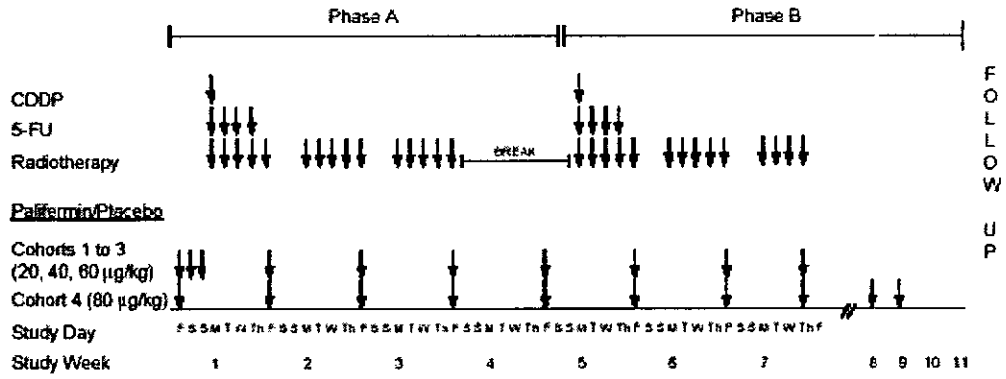
990119 A Phase 2 Study of Recombinant Keratinocyte Growth Factor (rHuKGF) in Head and Neck Cancer Patients Receiving Concurrent Chemotherapy with Standard or

Hyperfractionated Radiation Therapy Investigational Product: recombinant human keratinocyte growth factor(rHuKGF; palifermin) (eCTD 5.3.5.4.4, Clinical Study Report 990119 page 44, 59)





970149 A Phase 1-2 Study of Escalating Doses of Recombinant Keratinocyte Growth Factor (rHuKGF) in Head and Neck Cancer Patients Undergoing Chemoradiotherapy (eCTD 5.3.5.4.3, Clinical Study Report 970149 page 36)



CDDP = cisplatin (100 mg/m^2/day for 1 day or 25 mg/m^2/day for 4 days)
5-FU = 5-fluorouracil (1000 mg/m^2/day for 4 days)
Radiotherapy = 125 cGy twice daily
Note: Subjects were randomized in a 3:1 allocation to receive palifermin or placebo.

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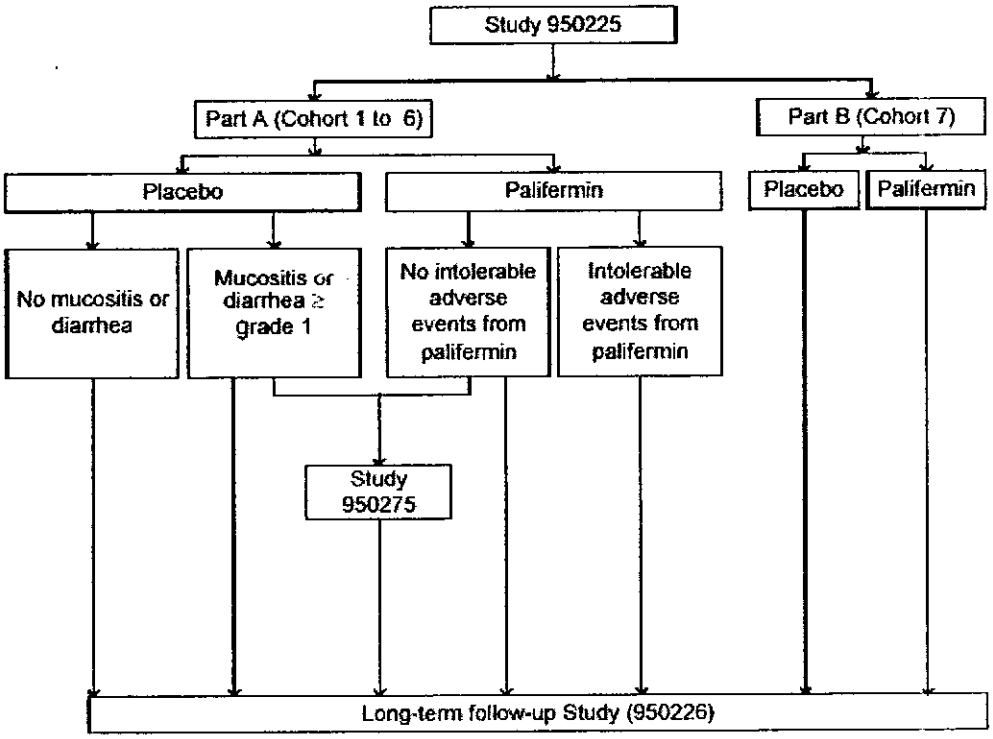
950225: Randomized, Double-blind, Placebocontrolled, Phase 1 Trial of Intravenously Administered Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Colorectal Carcinoma Patients Treated with 5-Fluorouracil and Leucovorin: rHuKGF Dosing Before Chemotherapy

950275: Extension Study to KGF 950225: Open-label Study of Intravenously Administered Recombinant Human Keratinocyte Growth Factor (rHuKGF) in Colorectal Carcinoma Patients Treated With 5-Fluorouracil and Leucovorin: Cycle 2 Through 7 - rHuKGF Dosing Before Chemotherapy (eCTD 5.3.5.4.1, Clinical Study Report 950225 page 80 - 84)

Figure 7-1. Relationship Between Studies 950225 and 950275



Further information on eligibility requirements for continuation into the open-label extension Study 950275 is provided in Section 7.5. An intolerable adverse event was defined as a grade 2 adverse event that required discontinuation of the study.

Figure 7-2. Planned Dose Escalation for Study 950225

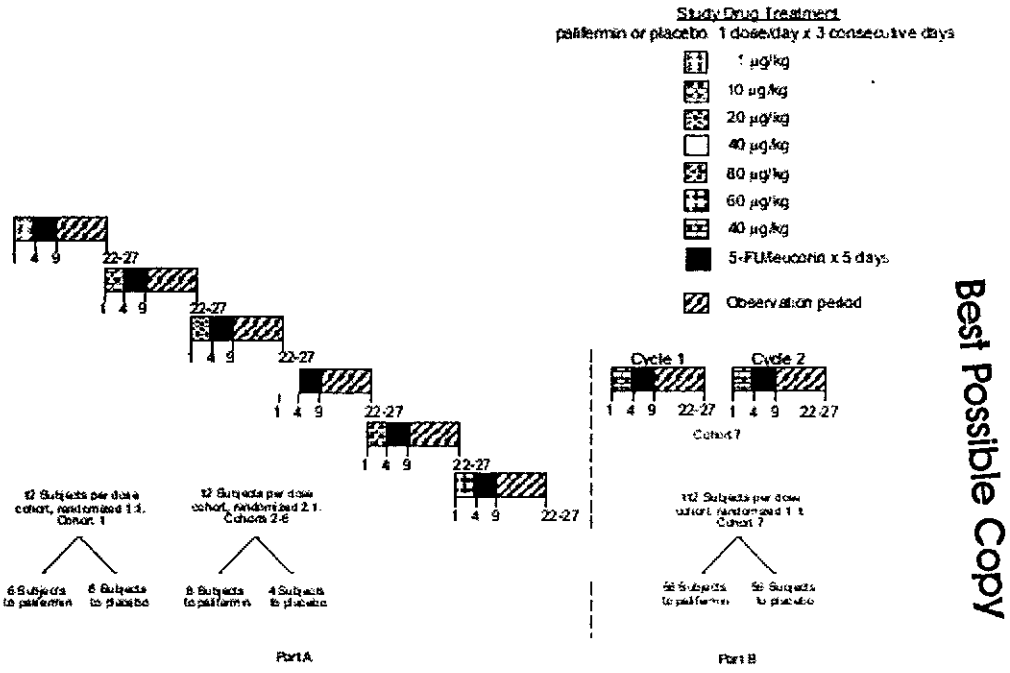


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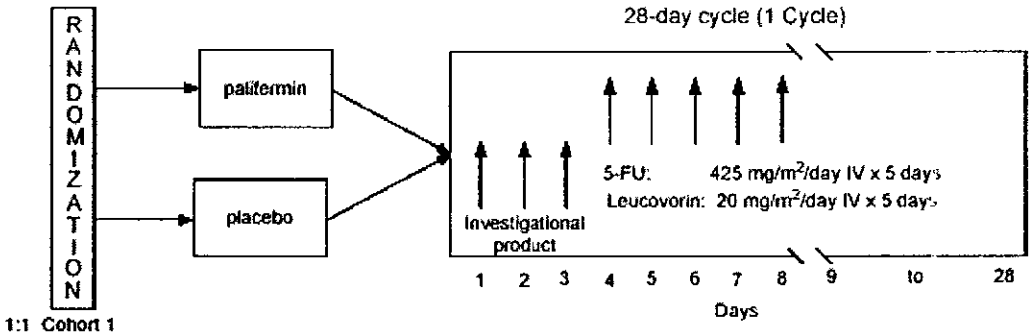
Figure 7-3. Schema for Study 950225 Part A

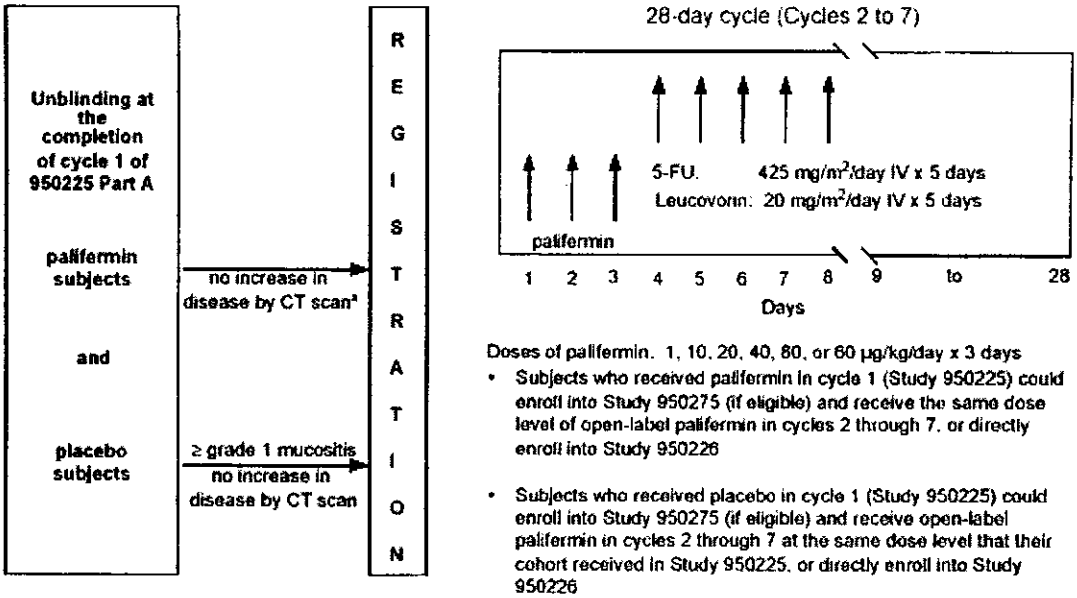


1:1 Cohort 1
2:1* Cohorts 2 to 6

*palifermin:placebo

Palifermin or placebo doses in sequentially enrolling cohorts. 1, 10, 20, 40, 60, or 60 µg/kg

Figure 7-5. Schema for Study 950275



* Eligible subjects also were required to have no intolerable (required discontinuation of the study) grade 2 adverse events related to palifermin.