Clinical trial results:
A Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Palifermin (Recombinant Human Keratinocyte Growth Factor) for Reduction of Oral Mucositis in Subjects With Stage 2B or 3 Locally Advanced, Colon Cancer Receiving 5-FU and Leucovorin as Adjuvant Therapy

Summary

EudraCT number	2004-005007-14
Trial protocol	HU CZ BE
Global end of trial date	31 March 2014

Results information

Result version number	v1 (current)
This version publication date	04 May 2017
First version publication date	04 May 2017

Trial information

Trial identification

Sponsor protocol code	20040122

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00393822
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of palifermin in reducing the incidence of grade ≥ 2 oral mucositis (OM) in subjects with stage 2B or stage 3 locally advanced colon cancer undergoing adjuvant chemotherapy with 5-fluorouracil (5-FU) and leucovorin (LV).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 August 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	Hungary: 38
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Czech Republic: 4
Worldwide total number of subjects	100
EEA total number of subjects	100

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	51
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 23 sites in 4 European Union (EU) countries, of which 14 sites randomized subjects.

Pre-assignment

Screening details:

Eligible subjects were randomized at a 1:1 ratio to receive palifermin or placebo through an Interactive Voice Response System (IVRS). The randomization was stratified by the following 4 disease stage/grade strata:
• 2B Low Grade, 3A Low Grade
• 2B High Grade, 3A High Grade
• Stage 3B – all grades
• Stage 3C – all grades

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received adjuvant chemotherapy with 20 mg/m² leucovorin administered by intravenous (IV) injection followed by an IV bolus infusion of 425 mg/m² 5-fluorouracil (5-FU) daily for 5 consecutive days beginning on day 1 of each 28-day treatment cycle, for a total of up to 6 cycles. A single dose of placebo to palifermin administered as a bolus IV injection was given three days prior to each cycle of chemotherapy for up to 6 doses. Starting in cycle 2, the 5-FU dose could have been decreased by 20% for toxicity.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Administered as a bolus intravenous (IV) injection over 15-20 seconds.

Arm title	Palifermin

Arm description:

Participants received adjuvant chemotherapy with 20 mg/m² leucovorin administered by intravenous (IV) injection followed by an IV bolus infusion of 425 mg/m² 5-fluorouracil (5-FU) daily for 5 consecutive days beginning on day 1 of each 28-day treatment cycle, for a total of up to 6 cycles. A single dose of 120 µg/kg palifermin administered as a bolus IV injection was given three days prior to each cycle of chemotherapy for up to 6 doses. Starting in cycle 2, the 5-FU dose could have been decreased by 20% for toxicity.

Arm type	Experimental
Investigational medicinal product name	Palifermin
Investigational medicinal product code	
Other name	Kepivance
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:
Palifermin 120 µg/kg administered as a bolus intravenous (IV) injection over 15-20 seconds.

Number of subjects in period 1	Placebo	Palifermin
Started	49	51
Received Treatment	47	49
Completed	41	43
Not completed	8	8
Consent withdrawn by subject	3	4
Administrative decision	-	1
Other	1	-
Adverse event	3	1
Ineligibility determined	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received adjuvant chemotherapy with 20 mg/m² leucovorin administered by intravenous (IV) injection followed by an IV bolus infusion of 425 mg/m² 5-fluorouracil (5-FU) daily for 5 consecutive days beginning on day 1 of each 28-day treatment cycle, for a total of up to 6 cycles. A single dose of placebo to palifermin administered as a bolus IV injection was given three days prior to each cycle of chemotherapy for up to 6 doses. Starting in cycle 2, the 5-FU dose could have been decreased by 20% for toxicity.	
Reporting group title	Palifermin
Reporting group description:	
Participants received adjuvant chemotherapy with 20 mg/m² leucovorin administered by intravenous (IV) injection followed by an IV bolus infusion of 425 mg/m² 5-fluorouracil (5-FU) daily for 5 consecutive days beginning on day 1 of each 28-day treatment cycle, for a total of up to 6 cycles. A single dose of 120 µg/kg palifermin administered as a bolus IV injection was given three days prior to each cycle of chemotherapy for up to 6 doses. Starting in cycle 2, the 5-FU dose could have been decreased by 20% for toxicity.	

Reporting group values	Placebo	Palifermin	Total
Number of subjects	49	51	100
Age Categorical Units: Subjects			
Adults (18-64 years)	22	29	51
From 65-84 years	27	22	49
Age Continuous Units: years			
arithmetic mean	64.2	63.5	
standard deviation	± 9.4	± 8.1	-
Gender Categorical Units: Subjects			
Female	24	18	42
Male	25	33	58
Race Units: Subjects			
Caucasian	49	51	100

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received adjuvant chemotherapy with 20 mg/m² leucovorin administered by intravenous (IV) injection followed by an IV bolus infusion of 425 mg/m² 5-fluorouracil (5-FU) daily for 5 consecutive days beginning on day 1 of each 28-day treatment cycle, for a total of up to 6 cycles. A single dose of placebo to palifermin administered as a bolus IV injection was given three days prior to each cycle of chemotherapy for up to 6 doses. Starting in cycle 2, the 5-FU dose could have been decreased by 20% for toxicity.

Reporting group title	Palifermin

Reporting group description:

Participants received adjuvant chemotherapy with 20 mg/m² leucovorin administered by intravenous (IV) injection followed by an IV bolus infusion of 425 mg/m² 5-fluorouracil (5-FU) daily for 5 consecutive days beginning on day 1 of each 28-day treatment cycle, for a total of up to 6 cycles. A single dose of 120 µg/kg palifermin administered as a bolus IV injection was given three days prior to each cycle of chemotherapy for up to 6 doses. Starting in cycle 2, the 5-FU dose could have been decreased by 20% for toxicity.

Primary: Number of Participants with Grade ≥ 2 Oral Mucositis in Cycle 1

End point title	Number of Participants with Grade ≥ 2 Oral Mucositis in Cycle 1

End point description:

Oral mucositis (OM) assessments were performed by a trained evaluator according to the world health organization (WHO) Toxicity Criteria for grading oral mucositis:
- Grade 0: None;
- Grade 1: Soreness, erythema;
- Grade 2: Erythema, ulcers, ability to eat solids;
- Grade 3: Ulcers, requires liquid diet;
- Grade 4: Alimentation not possible.

This analysis was performed n the full analysis set which includes all randomized participants.

End point type	Primary

End point timeframe:

Cycle 1, 28 days

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	51		
Units: participants	7	7		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

The null hypothesis for this study was that the incidence of grade ≥ 2 OM (WHO scale) would be the same between the placebo group and the palifermin group. The alternative hypothesis was that the incidence of grade ≥ 2 OM (WHO scale) between palifermin and placebo group would be different.

Comparison groups	Placebo v Palifermin

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9149 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.14

Notes:

[1] - Generalized Cochran-Mantel-Haenszel test for general association with randomization strata as analysis stratification factor.

Secondary: Number of Participants with Grade ≥ 2 Oral Mucositis in Cycle 2

End point title	Number of Participants with Grade ≥ 2 Oral Mucositis in Cycle 2

End point description:

Oral mucositis assessments were performed by a trained evaluator according to the world health organization (WHO) Toxicity Criteria for grading oral mucositis:
Grade 0: None;
Grade 1: Soreness, erythema;
Grade 2: Erythema, ulcers, ability to eat solids;
Grade 3: Ulcers, requires liquid diet;
Grade 4: Alimentation not possible.
This analysis was performed in the Efficacy Evaluable Subset for Cycle 2 which includes all subjects who were randomized and received investigational product on day –3 and at least one dose of 5-FU in cycle 2.

End point type	Secondary

End point timeframe:

Cycle 2 (28 days)

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: participants	4	5		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Palifermin
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7189 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.14

Notes:

[2] - Generalized Cochran-Mantel-Haenszel test for general association with randomization strata as analysis stratification factor.

Secondary: Average Mouth and Throat Soreness (MTS) Score in Cycle 1

End point title	Average Mouth and Throat Soreness (MTS) Score in Cycle 1

End point description:

Mouth and throat soreness was assessed by Question 2 of the Oral Mucositis Daily Questionnaire (OMDQ): "During the past 24 hours, how much mouth and throat soreness did you have?" The question was answered using a verbal descriptive scale with 5 response categories from 0 (no soreness) to 4 (extreme soreness).
This endpoint was analyzed in the PRO Evaluable Subset for Cycle 1 which included all randomized subjects that had a valid baseline assessment for MTS (question 2 of the OMDQ) and either at least 2 assessments each week for MTS in cycles 1 and/or 2, or 70% or greater overall compliance for MTS in cycles 1 and/or 2.

End point type	Secondary

End point timeframe:

Cycle 1 (28 days)

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	47		
Units: units on a scale				
arithmetic mean (standard deviation)	0.32 (± 0.53)	0.26 (± 0.43)		

Statistical analyses

Statistical analysis title	Statistical Anlaysis
Comparison groups	Placebo v Palifermin
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9397 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in MTS Score
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.13

Notes:

[3] - Generalized Cochran-Mantel-Haenszel test for mean score difference using modified ridit score with randomization strata as analysis stratification factor.

Secondary: Average Mouth and Throat Soreness (MTS) Score in Cycle 2

End point title	Average Mouth and Throat Soreness (MTS) Score in Cycle 2

End point description:

Mouth and throat soreness was assessed by Question 2 of the Oral Mucositis Daily Questionnaire (OMDQ): "During the past 24 hours, how much mouth and throat soreness did you have?" The question was answered using a verbal descriptive scale with 5 response categories from 0 (no soreness) to 4 (extreme soreness).
This endpoint was analyzed in the PRO Evaluable Subset for Cycle 2 which included all randomized subjects who
received investigational product on Day –3 and at least one dose of 5-FU in that cycle 2 that had a valid baseline assessment for MTS (question 2 of the OMDQ) and either at least 2 assessments each week for MTS in cycles 1 and/or 2, or 70% or greater overall compliance for MTS in cycles 1 and/or 2.

End point type	Secondary

End point timeframe:

Cycle 2 (28 days)

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: units on a scale				
arithmetic mean (standard deviation)	0.23 (± 0.35)	0.26 (± 0.53)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Palifermin
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4569 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in MTS Score
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.21

Notes:

[4] - Generalized Cochran-Mantel-Haenszel test for mean score difference using modified ridit score with randomization strata as analysis stratification factor.

Secondary: Number of Participants with 5-FU Dose Changes, Dose Delays, or Not Receiving a Dose in Cycle 2

End point title	Number of Participants with 5-FU Dose Changes, Dose Delays,

	or Not Receiving a Dose in Cycle 2

End point description:

End point type	Secondary

End point timeframe:

Cycle 2 (28 days)

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	51		
Units: participants	26	28		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v Palifermin
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8461 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.21

Notes:

[5] - Generalized Cochran-Mantel-Haenszel test for general association with randomization strata as analysis stratification factor.

Secondary: Duration of Grade ≥ 2 Oral Mucositis in Cycle 1

End point title	Duration of Grade ≥ 2 Oral Mucositis in Cycle 1

End point description:

Duration of grade ≥ 2 oral mucositis was calculated from the onset of grade ≥ 2 OM (first time WHO grade 2, 3 or 4 was observed) to the resolution of this event (first time WHO grade 0 or 1 was observed after last WHO grade 2, 3 or 4).
This endpoint was analyzed in participants who experienced a grade 2, 3 or 4 oral mucositis event in cycle 1.

End point type	Secondary

End point timeframe:

Cycle 1 (28 days)

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: days				
median (full range (min-max))	11 (4 to 19)	10.8 (4 to 27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Grade ≥ 2 Oral Mucositis in Cycle 2

End point title	Duration of Grade ≥ 2 Oral Mucositis in Cycle 2

End point description:

Duration of grade ≥ 2 oral mucositis was calculated from the onset of grade ≥ 2 OM (first time WHO grade 2, 3 or 4 was observed) to the resolution of this event (first time WHO grade 0 or 1 was observed after last WHO grade 2, 3 or 4).
This endpoint was analyzed in participants who experienced a grade 2, 3 or 4 oral mucositis event in cycle 2.

End point type	Secondary

End point timeframe:

Cycle 2 (28 days)

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: days				
median (full range (min-max))	12 (5 to 16)	11 (5 to 26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events During the Treatment Period

End point title	Number of Participants with Adverse Events During the Treatment Period

End point description:

The severity of adverse events (AEs) was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.
The relationship of adverse events to the investigational product was assessed by the investigator.
A protocol-specific limiting toxicity (PSLT) was defined as any non-hematologic grade ≥ 3 (CTCAE v3.0) adverse event considered related to investigational product (IP) that prompts discontinuation of investigational product with the exception of non-symptomatic elevated amylase and/or lipase serum levels.

End point type	Secondary

End point timeframe:

From the first dose of investigational drug (placebo or palifermin) until 30 days after last dose (approximately 7 months)

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: participants				
All adverse events	40	40		
Serious adverse events	9	6		
Severe adverse events (CTCAE grade 3, 4 or 5)	22	21		
Treatment-related adverse events (TRAEs)	6	15		
Serious treatment-related adverse events	0	1		
Severe treatment-related adverse events	0	0		
AE leading to study withdrawal	3	1		
AE leading to IP discontinuation	1	2		
Protocol-specific limiting toxicity (PSLT)	0	0		
Fatal adverse events	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-Palifermin Antibody Formation

End point title	Number of Participants with Anti-Palifermin Antibody Formation

End point description:

This endpoint was analyzed in participants who received investigational product and who had measurements at each time point.

End point type	Secondary

End point timeframe:

Samples for antibody analysis were collected on cycle 1 day -3, cycle 3, day -3 and at the end of treatment visit

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: participants				
Cycle 1 day -3 (n = 46, 43)	1	2		
Cycle 3 day -3 (n = 43, 40)	1	0		
End of treatment (n = 38, 33)	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Progression-free Survival at the End of Treatment

End point title	Number of Participants with Progression-free Survival at the End of Treatment

End point description:

Disease progression was assessed by computed tomography (CT) scans of the chest abdomen and pelvis.
The number of participants with progression-free survival is the number of subjects alive and progression free at the end of treatment visit.

End point type	Secondary

End point timeframe:

6 months

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: participants	46	44		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Second Primary Tumors at the End of Long-term Follow-up

End point title	Number of Participants with Second Primary Tumors at the End of Long-term Follow-up

End point description:

End point type	Secondary

End point timeframe:

From first dose of investigational product until the end of the long-term follow-up period; the median (minimum, maximum) follow-up duration was 313 (47, 436) weeks for the placebo group and 321 (8, 430) weeks for the palifermin group.

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: participants	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Other Malignancies at the End of Long-term Follow-up

End point title	Number of Participants with Other Malignancies at the End of Long-term Follow-up

End point description:

End point type	Secondary

End point timeframe:

From first dose of investigational product until the end of the long-term follow-up period; the median (minimum, maximum) follow-up duration was 313 (47, 436) weeks for the placebo group and 321 (8, 430) weeks for the palifermin group.

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: participants	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Tumor Progression or Recurrence of Primary Disease at the End of Long-term Follow-up

End point title	Number of Participants with Tumor Progression or Recurrence of Primary Disease at the End of Long-term Follow-up

End point description:

End point type	Secondary

End point timeframe:

From first dose of investigational product until the end of the long-term follow-up period; the median (minimum, maximum) follow-up duration was 313 (47, 436) weeks for the placebo group and 321 (8, 430) weeks for the palifermin group.

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: participants	14	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Deaths at the End of Long-term Follow-up

End point title	Number of Deaths at the End of Long-term Follow-up

End point description:

End point type	Secondary

End point timeframe:

From first dose of investigational product until the end of the long-term follow-up period; The median (minimum, maximum) follow-up duration was 313 (47, 436) weeks for the placebo group and 321 (8, 430) weeks for the palifermin group.

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: participants	9	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of investigational drug (placebo or palifermin) until 30 days after last dose (approximately 7 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received adjuvant chemotherapy with 20 mg/m² leucovorin administered by intravenous (IV) injection followed by an IV bolus infusion of 425 mg/m² 5-fluorouracil (5-FU) daily for 5 consecutive days beginning on day 1 of each 28-day treatment cycle, for a total of up to 6 cycles. A single dose of placebo to palifermin administered as a bolus IV injection was given three days prior to each cycle of chemotherapy for up to 6 doses. Starting in cycle 2, the 5-FU dose could have been decreased by 20% for toxicity.

Reporting group title	Palifermin

Reporting group description:

Participants received adjuvant chemotherapy with 20 mg/m² leucovorin administered by intravenous (IV) injection followed by an IV bolus infusion of 425 mg/m² 5-fluorouracil (5-FU) daily for 5 consecutive days beginning on day 1 of each 28-day treatment cycle, for a total of up to 6 cycles. A single dose of 120 µg/kg palifermin administered as a bolus IV injection was given three days prior to each cycle of chemotherapy for up to 6 doses. Starting in cycle 2, the 5-FU dose could have been decreased by 20% for toxicity.

Serious adverse events	Placebo	Palifermin	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 47 (19.15%)	6 / 49 (12.24%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	1 / 47 (2.13%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 47 (0.00%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Obstructive airways disorder			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mania			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Starvation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Palifermin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 47 (74.47%)	36 / 49 (73.47%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 47 (2.13%)	7 / 49 (14.29%)	
occurrences (all)	1	7	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 47 (4.26%)	3 / 49 (6.12%)	
occurrences (all)	2	4	
Headache			

subjects affected / exposed	3 / 47 (6.38%)	1 / 49 (2.04%)	
occurrences (all)	3	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 47 (23.40%)	12 / 49 (24.49%)	
occurrences (all)	21	22	
Neutropenia			
subjects affected / exposed	20 / 47 (42.55%)	16 / 49 (32.65%)	
occurrences (all)	39	44	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 47 (17.02%)	7 / 49 (14.29%)	
occurrences (all)	10	13	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 47 (8.51%)	5 / 49 (10.20%)	
occurrences (all)	8	7	
Abdominal pain upper			
subjects affected / exposed	3 / 47 (6.38%)	0 / 49 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	5 / 47 (10.64%)	4 / 49 (8.16%)	
occurrences (all)	6	4	
Diarrhoea			
subjects affected / exposed	11 / 47 (23.40%)	15 / 49 (30.61%)	
occurrences (all)	30	58	
Dry mouth			
subjects affected / exposed	1 / 47 (2.13%)	6 / 49 (12.24%)	
occurrences (all)	3	7	
Dyspepsia			
subjects affected / exposed	1 / 47 (2.13%)	3 / 49 (6.12%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	8 / 47 (17.02%)	10 / 49 (20.41%)	
occurrences (all)	13	16	
Oral pain			

subjects affected / exposed	0 / 47 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	3	
Vomiting			
subjects affected / exposed	6 / 47 (12.77%)	1 / 49 (2.04%)	
occurrences (all)	10	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 47 (8.51%)	1 / 49 (2.04%)	
occurrences (all)	4	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 47 (0.00%)	4 / 49 (8.16%)	
occurrences (all)	0	4	
Pruritus			
subjects affected / exposed	1 / 47 (2.13%)	3 / 49 (6.12%)	
occurrences (all)	1	10	
Rash			
subjects affected / exposed	6 / 47 (12.77%)	5 / 49 (10.20%)	
occurrences (all)	9	6	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 47 (4.26%)	3 / 49 (6.12%)	
occurrences (all)	2	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 47 (4.26%)	3 / 49 (6.12%)	
occurrences (all)	2	3	
Oral herpes			
subjects affected / exposed	0 / 47 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	6	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	5 / 47 (10.64%)	5 / 49 (10.20%)	
occurrences (all)	6	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2005	Amendment 1 instituted the following changes: • Following a data monitoring committee (DMC) review of available safety data from subjects who received the 180 µg/kg dose in the setting of radiation therapy with concomitant chemotherapy, the dose was reduced to 120 µg/kg in patients with advanced head and neck cancer post-surgery as recommended by the DMC. This recommendation was made based on the review of safety data after application of palifermin at a weekly dose of 180 µg/kg, which has been associated with limited local swelling in areas of previous surgery or epithelial injury (eg, tracheotomy or tumor surgery). A previous pharmacokinetic-pharmacodynamics study in young, male adults receiving single palifermin doses of 60 to 250 µg/kg (study 20010192) showed a dose-response in palifermin biological activity (as measured by buccal mucosal epithelial cell proliferation) with a plateau between the doses of 160 µg/kg and 210 µg/kg. Based on our commitment first and foremost to patient safety, Amgen followed the DMC recommendation and also made the decision to implement the same dose reduction in this study in colon cancer post-surgery. All 100 subjects enrolled into this study (20040122) received the 120 µg/kg dose. • The safety section of the Subject Informed Consent Template was updated with additional information. • The patient reported outcomes (PRO) sections were clarified to ensure consistency across the palifermin program. • Additional laboratory parameters (hematocrit and blood urea nitrogen or urea) were added. • At the time when all subjects completed the first 2 cycles of chemotherapy (ie, completed all efficacy assessments), the data were unblinded and the final analysis of all efficacy endpoints was performed.
30 January 2008	Amendment 2 was written to clarify and reduce the study objectives and the corresponding analyses as follows: • The primary objective wording was changed to specify the incidence of Grade ≥ 2 OM in cycle 1. • The secondary objectives “To evaluate the effect of palifermin on patient reported diarrhea” and “To validate the OMDQ instrument in the colon cancer patient setting” were removed. • The secondary objective “To evaluate the incidence of Grade ≥ 2 OM in cycle 2” was added. • The efficacy analysis after all subjects have completed Cycle 2 was deleted. • The majority of exploratory analysis were removed. • The analysis of all endpoints was changed to occur after the End of Treatment visit. • The clinical study report includes data up to the End of Treatment visit (6 month time point). As a result, Kaplan-Meier estimates of 6 month progression rates were replaced with summaries of observed rates. The first long term follow-up (LTFU) visit for this study was at year 1 (month 12), and then annually thereafter, thus the time delay, while awaiting LTFU data, has been removed. • The frequency of DMC meetings was changed so that the LTFU review follows evaluation of all palifermin solid tumor studies. The DMC were in agreement that the reduction in frequency of data reviewed would not have a significant impact on the assessment of safety in this patient population. As a result, DMC and Amgen reviews were aligned across the palifermin solid tumor program.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported