Clinical trial results:
A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Weekly Doses of Palifermin (Recombinant Human Keratinocyte Growth Factor, rHuKGF) for the Reduction of Oral Mucositis in Subjects With Advanced Head and Neck Cancer ReceivingAdjuvant Radiotherapy and Chemotherapy (RT/CT)

Summary

EudraCT number	2004-002016-28
Trial protocol	DE GB AT IT ES
Global end of trial date	11 July 2016

Results information

Result version number	v1 (current)
This version publication date	26 July 2017
First version publication date	26 July 2017

Trial information

Trial identification

Sponsor protocol code	20040118

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00131638
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	11 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 July 2016
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 administered weekly at the dose of 120 µg/kg intravenously (IV) in reducing the incidence of severe (World Health Organization [WHO] grade 3 or 4) oral mucositis (OM) in subjects with locally advanced head and neck cancer (HNC) receiving radiotherapy with concurrent chemotherapy as an adjuvant treatment for their disease (postoperative setting).

Protection of trial subjects:

This study was conducted in accordance with the principles that have their origin in the Declaration of Helsinki and in compliance with Food and Drug Administration (FDA), the Canadian Health Protection Branch (HPB), and 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.
An independent data monitoring committee of oncologists and a statistician reviewed safety and efficacy data according to a prespecified schedule.

Background therapy:

Conventional or three-dimensional radiation planning techniques and standard fractionation (5 × 2.0 Gy/wk) were followed. The total dose was 60 Gy or 66 Gy (allowable range, ± 15%) after R0 or R1 resection, respectively. Spinal cord dose was restricted to 48 Gy. The radiation volume included the tumor bed with a 2 to 3 cm safety margin and regional nodal areas. Radiation breaks were not allowed and were considered to be a major deviation when 5 or more consecutive days or 10 or more total treatment days were missed.
Cisplatin 100 mg/m² was given intravenously on days 1 and 22 after appropriate hydration. Patients irradiated beyond week 6 (boost or catch-up radiation) received an additional 100 mg/m² cisplatin (day 43).
Local supportive care, including normal saline rinses, topical anesthetics, feeding tubes, and hematopoietic growth factors were allowed according to each center's procedures.

Evidence for comparator: -

Actual start date of recruitment	27 January 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 62

Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Italy: 32
Country: Number of subjects enrolled	Austria: 30
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Canada: 4
Worldwide total number of subjects	224
EEA total number of subjects	205

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)	184
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled between January 27, 2005, and August 17, 2007 at 38 study centers in Germany, Spain, France, Italy, Austria, Australia, the United Kingdom, and Canada.

Pre-assignment

Screening details:

The original protocol included 3 treatment groups randomized in a 1:1:1 ratio: placebo, 7-dose palifermin and 4-dose palifermin. Protocol Amendment 3 removed the 4-dose palifermin group. Subjects were stratified by postsurgical residual tumor stage (R0 versus R1) and anatomical tumor location (oral cavity/oropharynx versus hypopharynx/larynx).

Period 1

Period 1 title	Oral Mucositis Evaluation Phase (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 a single dose of placebo administered intravenously 3 days before the start of radiotherapy, and 6 once-weekly doses during a 6-week course of radio/chemotherapy.

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 by bolus intravenous injection

Arm title	Palifermin 4-dose

Arm description:

Participants received a single dose of 120 µg/kg palifermin administered intravenously 3 days before the start of radiotherapy, and 3 once-weekly doses during a 6-week course of radio/chemotherapy. This treatment group was removed with implementation of protocol amendment 3.

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:

Administered by bolus intravenous injection

Arm title	Palifermin 7-dose

Arm description:

Participants received a single dose of 120 µg/kg palifermin administered intravenously 3 days before the start of radiotherapy, and 6 once-weekly doses during a 6-week course of radio/chemotherapy.

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:

Administered by bolus intravenous injection

Number of subjects in period 1	Placebo	Palifermin 4-dose	Palifermin 7-dose
Started	94	38	92
Received Study Drug	93	38	92
Completed	82	34	79
Not completed	12	4	13
Consent withdrawn by subject	4	1	2
Administrative decision	-	-	1
Other	2	1	5
Death	-	1	1
Adverse event	5	-	3
Lost to follow-up	1	-	1
Ineligibility determined	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received a single dose of placebo administered intravenously 3 days before the start of radiotherapy, and 6 once-weekly doses during a 6-week course of radio/chemotherapy.	
Reporting group title	Palifermin 4-dose
Reporting group description:	
Participants received a single dose of 120 µg/kg palifermin administered intravenously 3 days before the start of radiotherapy, and 3 once-weekly doses during a 6-week course of radio/chemotherapy. This treatment group was removed with implementation of protocol amendment 3.	
Reporting group title	Palifermin 7-dose
Reporting group description:	
Participants received a single dose of 120 µg/kg palifermin administered intravenously 3 days before the start of radiotherapy, and 6 once-weekly doses during a 6-week course of radio/chemotherapy.	

Reporting group values	Placebo	Palifermin 4-dose	Palifermin 7-dose
Number of subjects	94	38	92
Age Categorical Units: Subjects			
Adults (18-64 years)	73	33	78
From 65-84 years	21	5	14
Age Continuous Units: years			
arithmetic mean	56.7	54.2	56.3
standard deviation	± 8.7	± 8.7	± 8.4
Gender Categorical Units: Subjects			
Female	19	5	14
Male	75	33	78
Race Units: Subjects			
Caucasian	94	38	91
Asian	0	0	1
Distribution of Subjects by Randomization Strata			
Stratification factors for randomization were: postsurgical residual tumor: no residual tumor (R0) versus microscopic residual tumor only (R1) and Anatomical tumor location: oral cavity / oropharynx versus hypopharynx / larynx).			
Units: Subjects			
R0 - oral cavity or oropharynx	47	19	46
R0 - hypopharynx or larynx	14	6	15
R1 - oral cavity or oropharynx	25	10	25
R1 - hypopharynx or larynx	8	3	6

Reporting group values	Total		
Number of subjects	224		
Age Categorical Units: Subjects			
Adults (18-64 years)	184		

From 65-84 years	40		

Age Continuous Units: years arithmetic mean standard deviation	- 		
Gender Categorical Units: Subjects			
Female Male	38 186		
Race Units: Subjects			
Caucasian Asian	223 1		
Distribution of Subjects by Randomization Strata			
Stratification factors for randomization were: postsurgical residual tumor: no residual tumor (R0) versus microscopic residual tumor only (R1) and Anatomical tumor location: oral cavity / oropharynx versus hypopharynx / larynx).			
Units: Subjects			
R0 - oral cavity or oropharynx R0 - hypopharynx or larynx R1 - oral cavity or oropharynx R1 - hypopharynx or larynx	112 35 60 17		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received a single dose of placebo administered intravenously 3 days before the start of radiotherapy, and 6 once-weekly doses during a 6-week course of radio/chemotherapy.

Reporting group title	Palifermin 4-dose

Reporting group description:

Participants received a single dose of 120 µg/kg palifermin administered intravenously 3 days before the start of radiotherapy, and 3 once-weekly doses during a 6-week course of radio/chemotherapy. This treatment group was removed with implementation of protocol amendment 3.

Reporting group title	Palifermin 7-dose

Reporting group description:

Participants received a single dose of 120 µg/kg palifermin administered intravenously 3 days before the start of radiotherapy, and 6 once-weekly doses during a 6-week course of radio/chemotherapy.

Subject analysis set title	Palifermin 7-dose
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received a single dose of 120 µg/kg administered intravenously 3 days before the start of radiotherapy, and 6 once-weekly doses during a 6-week course of radio/chemotherapy. Includes 1 participant randomized to placebo who received 1 dose of palifermin in error.

Subject analysis set title	Overall Palifermin
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received a single dose of 120 µg/kg administered intravenously 3 days before the start of radiotherapy, and 3 or 6 once-weekly doses during a 6-week course of radio/chemotherapy.

Primary: Percentage of Participants with Severe Oral Mucositis

End point title	Percentage of Participants with Severe Oral Mucositis

End point description:

Oral mucositis (OM) was assessed twice a week during the radio/chemotherapy period. Severity was assessed according to the World Health Organization (WHO) criteria:
Grade 1: may include buccal mucosal scalloping with or without erythema. No ulcers. Patient can swallow solid diet.
Grade 2: must include ulcers with or without erythema. Patient can swallow solid diet.
Grade 3: must include ulcers with or without (extensive) erythema. Patient is able to swallow liquid, but not solid diet.
Grade 4: mucositis to the extent that alimentation is not possible.
Participants with at least one OM assessment with a grade of 3 or 4 during the evaluation period were considered to have had an incidence of severe OM; partiipants with no post-randomization oral mucositis assessments were assumed to have severe oral mucositis.
This endpoint was assessed using the full analysis set which included all randomized participants.

End point type	Primary

End point timeframe:

The Acute Oral Mucositis Evaluation Phase was defined as lasting from the date of randomization through Week 12 (or up to Week 15 if OM was not resolved to ≤ WHO Grade 2 by Week 12).

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	38	92	
Units: percentage of participants				
number (not applicable)	66	68	51	

Statistical analyses

Statistical analysis title	Analysis of Incidence of Severe Oral Mucositis
Comparison groups	Placebo v Palifermin 7-dose
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0269 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Proportions
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	-0.02

Notes:

[1] - Generalized Cochran-Mantel-Haenszel test for general association stratified by post surgical residual tumor stage and anatomical tumor location.

Secondary: Duration of Severe Oral Mucositis

End point title	Duration of Severe Oral Mucositis

End point description:

Duration of severe OM was calculated as the number of days from the onset of severe OM (first grade 3 or 4 OM) to the day when severe OM was resolved (first time grade 2 or less was observed after last grade 3 or 4). Participants who did not experience severe OM were assigned a duration of severe OM of 0 days. Participants with no post-randomization oral mucositis assessments were assumed to have severe oral mucositis with an assumed duration equal to the grand mean of all participants experiencing the event.

End point type	Secondary

End point timeframe:

Mucositis was assessed 2 times weekly throughout RT/CT, and then until severe mucositis returned to grade ≤ 2 or until week 15. Thereafter, subjects with OM WHO ≥ Grade 2 were assessed once weekly until OM resolved to WHO Grade ≤ 1, or until week 24.

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	38	92	
Units: days				
arithmetic mean (standard deviation)	22.6 (± 22.2)	20.3 (± 19.5)	17.9 (± 25.9)	

Statistical analyses

Statistical analysis title	Analysis of Duration of Severe Oral Mucositis
Comparison groups	Placebo v Palifermin 7-dose
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.1871 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Mean Duration
Point estimate	-4.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.34
upper limit	1.98

Notes:

[2] - The type I error for the secondary efficacy endpoints was controlled using the Hochberg procedure.

[3] - Generalized Cochran-Mantel-Haenszel test for mean score difference stratified by post surgical residual tumor stage and anatomical tumor location.

Secondary: Average Patient-reported Mouth and Throat Soreness Score

End point title	Average Patient-reported Mouth and Throat Soreness Score

End point description:

The Oral Mucositis Weekly Questionnaire for Head and Neck Cancer (OMWQ-HN) is a 12 item questionnaire administered to participants twice weekly. The mouth and throat soreness (MTS) score was calculated from Question 3 "How much mouth and throat soreness did you experience in the past 24 hours?" answered on a scale from 0 (no soreness) to 4 (extreme soreness).
For each participant an average patient-reported mouth and throat soreness score was calculated by dividing the sum of the MTS scores at each assessment by the total number of assessments possible. This endpoint was assessed using the Patient Reported Outcomes (PRO) evaluable subset which included all randomized participants with a valid baseline assessment for MTS question 3 of the OMWQ-HN and at least 1 completed assessment each week for MTS up to withdrawal or the end of study week 7, or ≥ 70% overall compliance for MTS until withdrawal or the end of study week 7.

End point type	Secondary

End point timeframe:

Acute Oral Mucositis Evaluation Phase

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	32	84	
Units: units on a scale				
arithmetic mean (standard deviation)	1.57 (± 0.63)	1.51 (± 0.57)	1.52 (± 0.69)	

Statistical analyses

Statistical analysis title	Analysis of Mouth and Throat Soreness Score
Comparison groups	Placebo v Palifermin 7-dose
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.789 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Means
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.16

Notes:

[4] - The type I error for the secondary efficacy endpoints was controlled using the Hochberg procedure.

[5] - Generalized Cochran-Mantel-Haenszel test for mean score difference using modified ridit score stratified by post surgical residual tumor stage and anatomical tumor location.

Secondary: Time to Onset of Severe Oral Mucositis

End point title	Time to Onset of Severe Oral Mucositis

End point description:

Time to onset of severe oral mucositis was calculated as the number of days from randomization to date of first onset of severe (WHO grade 3 or 4) OM using the Kaplan-Meier procedure. Participants without an assessed event by the end of the acute OM evaluation phase were censored at the date of last assessment for OM. If the end of the OM evaluation phase assessment had not occurred the last OM assessment date was used as the censoring date.
"99999" indicates data not estimable.

End point type	Secondary

End point timeframe:

The Acute Oral Mucositis Evaluation Phase was defined as lasting from the date of subject randomization through Week 12 (or up to Week 15 if OM is not resolved to ≤ WHO Grade 2 by Week 12).

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	38	92	
Units: days				
median (inter-quartile range (Q1-Q3))	32 (22 to 99999)	36 (26 to 99999)	45 (28 to 99999)	

Statistical analyses

Statistical analysis title	Analysis of Time to Onset of Severe Oral Mucositis
Comparison groups	Placebo v Palifermin 7-dose
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.1535 [7]
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.95

Notes:

[6] - The type I error for the secondary efficacy endpoints was controlled using the Hochberg procedure.

[7] - Log rank test stratified by post surgical residual tumor stage and anatomical tumor location.

Secondary: Total Dose of Opioid Analgesic Used

End point title	Total Dose of Opioid Analgesic Used

End point description:

The total dose of opioid analgesics was the sum of all opioid analgesic administrations converted to intravenous (IV) morphine equivalents. Participants withdrawing before the first dose of study drug were assumed to have used opioid analgesics, and to have a total dose equal to the grand median of all participants using opioid analgesics.
This endpoint was assessed using the full analysis set.

End point type	Secondary

End point timeframe:

Acute Oral Mucositis Evaluation Phase

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	38	92	
Units: mg of IV morphine equivalents				
median (inter-quartile range (Q1-Q3))	171.23 (0 to 1100.21)	61.17 (0 to 354.27)	60.8 (0 to 837.5)	

Statistical analyses

Statistical analysis title	Analysis of Total Dose of Opioid Analgesic Used
Comparison groups	Placebo v Palifermin 7-dose

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.789 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Mean Total Dose
Point estimate	146.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-250.75
upper limit	544.64

Notes:

[8] - The type I error for the secondary efficacy endpoints was controlled using the Hochberg procedure.

[9] - Generalized Cochran-Mantel-Haenszel test for mean score difference using modified ridit score stratified by post surgical residual tumor stage and anatomical tumor location.

Secondary: Percentage of Participants with Breaks In Radiotherapy of ≥ 5 Consecutive Fractions of Scheduled Radiotherapy

End point title	Percentage of Participants with Breaks In Radiotherapy of ≥ 5 Consecutive Fractions of Scheduled Radiotherapy

End point description:

Participants who missed 5 or more consecutive fractions of planned radiotherapy or who discontinued radiotherapy prior to completion of planned radiotherapy were considered to have an unplanned break in radiotherapy.
This endpoint was assessed using the full analysis set.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	38	92	
Units: percentage of participants				
number (not applicable)	14	21	15	

Statistical analyses

Statistical analysis title	Analysis of Breaks in Radiotherapy
Comparison groups	Placebo v Palifermin 7-dose
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.789 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Proportions
Point estimate	0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.11

Notes:

[10] - The type I error for the secondary efficacy endpoints was controlled using the Hochberg procedure.
[11] - Generalized Cochran-Mantel-Haenszel test for general association stratified by post surgical residual tumor stage and anatomical tumor location.

Secondary: Percentage of Participants with Unplanned Delays in Chemotherapy for Cisplatin Administration

End point title	Percentage of Participants with Unplanned Delays in Chemotherapy for Cisplatin Administration

End point description:

An unplanned delay in chemotherapy for cisplatin administration was defined as day 22 chemotherapy administered on day 25 or later (i.e. 3 or more days delay), or no chemotherapy dose scheduled for day 22 at all.
This endpoint was assessed using the full analysis set.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	38	92	
Units: percentage of participants				
number (not applicable)	40	37	30	

Statistical analyses

Statistical analysis title	Analysis of Delays in Cisplatin Administration
Comparison groups	Placebo v Palifermin 7-dose
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.6543 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Proportions
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.04

Notes:

[12] - The type I error for the secondary efficacy endpoints was controlled using the Hochberg procedure.
[13] - Generalized Cochran-Mantel-Haenszel test for general association stratified by post surgical residual tumor stage and anatomical tumor location.

Secondary: Percentage of Participants with Xerostomia at the Month 4 Visit

End point title	Percentage of Participants with Xerostomia at the Month 4 Visit

End point description:

Xerostomia is an abnormal dryness of mouth. Dry mouth/xerostomia was assessed using weighted saliva volume determination and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, where
Grade 1 = Symptomatic (dry or thick saliva) without significant dietary alteration; Unstimulated saliva flow > 0.2 ml/min.
Grade 2 = Symptomatic and significant oral intake alteration (eg, copious water, other lubricants, diet limited to purees and/or soft, moist foods); Unstimulated saliva 0.1 to 0.2 ml/min.
Grade 3 = Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or total parenteral nutrition indicated; Unstimulated saliva < 1 ml/min.
Participants with a grade of 2 or higher CTCAE xerostomia assessment at the month 4 visit were considered to have had xerostomia.
This endpoint was assessed using the full analysis set. Participants with no month 4 xerostomia assessment results were assumed to have xerostomia grade ≥ 2.

End point type	Secondary

End point timeframe:

Month 4

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	94	38	92	
Units: percentage of participants				
number (not applicable)	35	47	43	

Statistical analyses

Statistical analysis title	Analysis of Incidence of Xerostomia
Comparison groups	Placebo v Palifermin 7-dose
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.1871 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Proportions
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.27

Notes:

[14] - The type I error for the secondary efficacy endpoints was controlled using the Hochberg procedure.
[15] - Generalized Cochran-Mantel-Haenszel test for general association stratified by post surgical residual tumor stage anatomical and tumor location.

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events[16]

End point description:

The severity of adverse events (AEs) was graded according to CTCAE version 3. The possible relationship of each AE to study drug was assessed by the investigator.
Serious adverse events include, but were not be limited to any event that
- was fatal
- was life threatening
- required in-patient hospitalization or prolongation of existing hospitalization
- was a persistent or significant disability/incapacity
- was a congenital anomaly/birth defect.

A protocol-specific limiting toxicity (PSLT) was defined as any grade ≥ 3 AE considered related to study drug that prompted discontinuation of study drug.
This endpoint was analyzed using the safety subset which included all participants who were randomized and received at least one dose of study drug, with participants analyzed according to the treatment they actually received. One participant randomized to placebo received one dose of palifermin and is included in the Palifermin 7-dose group for safety endpoints.

End point type	Secondary

End point timeframe:

From first dose of study drug until the end of the acute oral mucositis evaluation phase (up to 15 weeks).

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported for the safety subset

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	92	38	93	
Units: participants				
Any adverse event	89	35	91	
Serious adverse events	41	18	31	
Severe adverse events (CTCAE grade 3, 4, or 5)	51	23	46	
Treatment-related adverse events	10	11	27	
Treatment-related serious adverse events	0	3	1	
Severe treatment-related adverse events	0	4	6	
Leading to discontinuation from study	5	0	3	
Leading to discontinuation of study drug	5	2	11	
Protocol-specific limiting toxicity	0	0	4	
On-study deaths	1	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Developed Anti-palifermin Antibodies

End point title	Number of Participants who Developed Anti-palifermin Antibodies[17]

End point description:

The antibody testing utilized a tiered assay approach. Samples were first screened for anti-palifermin binding antibodies in a validated electrochemiluminescence (ECL) based immunoassay. If the immunoassay yielded any positive samples, they were tested in a validated cell-based bioassay to test for neutralizing antibodies to palifermin. If a sample was positive in both assays, the participant was defined as positive for neutralizing antibodies.
This endpoint was analyzed in the safety subset; participants who received palifermin were combined in the analysis.

End point type	Secondary

End point timeframe:

Samples for antibody testing were collected at baseline and weeks 4, 8 and 12.

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Palifermin dose groups were combined for antibody analyses.

End point values	Placebo	Overall Palifermin		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	91	132		
Units: participants				
Binding antibody positive	5	7		
Neutralizing antibody positive	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Disease Progression at Week 12

End point title	Number of Participants with Disease Progression at Week 12[18]

End point description:

Disease progression is the recurrence of tumor post-surgery in the anatomical region of the primary tumor (ie within the radiation field) or distant metastases.
Disease progression was analyzed in the safety population.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported for the safety subset

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	92	38	93	
Units: participants	1	0	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival[19]

End point description:

Overall survival was analyzed using Kaplan-Meier methods and was defined as the time from the date of first dose of study drug to the date of death, regardless of cause. Participants who did not die were censored at the date the participant was last known to be alive.
Overall survival was analyzed in the safety subset. "99999" indicates data not estimable.

End point type	Secondary

End point timeframe:

From randomization until the final analysis data cut-off date of 11 July 2016. The median duration of follow-up was 70.2 months in the placebo group and 58.8 months in the overall palifermin group.

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported for the safety subset

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	Overall Palifermin
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	92	38	93	131
Units: months				
median (confidence interval 95%)	112 (81.8 to 99999)	99999 (58.3 to 99999)	109.2 (61.5 to 99999)	114.2 (71.8 to 99999)

Statistical analyses

Statistical analysis title	Analysis of Overall Survival
Comparison groups	Placebo v Overall Palifermin
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.943 [20]
Method	Stratified Cox Proportional Hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	0.985

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.492

Notes:

[20] - The Cox proportional hazard model is stratified by disease stage (III vs. IV) and anatomical tumor location (oral cavity or oropharynx vs. nasopharynx vs. hypopharynx or larynx).

Statistical analysis title	Analysis of Overall Survival
Comparison groups	Placebo v Palifermin 7-dose
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7 [21]
Method	Stratified Cox Proportional Hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	1.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.701
upper limit	1.698

Notes:

[21] - The Cox proportional hazard model is stratified by disease stage (III vs. IV) and anatomical tumor location (oral cavity or oropharynx vs. nasopharynx vs. hypopharynx or larynx)

Secondary: Time to Disease Progression

End point title	Time to Disease Progression[22]

End point description:

Disease progression is the recurrence of tumor post-surgery in the anatomical region of the primary tumor (ie within the radiation field) or distant metastases. Time to disease progression was analyzed using Kaplan-Meier methods and was defined as the time from randomization to the date when disease progression was determined. Participants with no assessment of disease progression were censored at the date of last disease assessment. If a participant who had evidence of complete response (at least one assessment indicating complete response) died without evidence of tumor progression, the date of death was used as the censoring date.
Time to disease progression was analyzed in the safety subset. "99999" indicates data not estimable.

End point type	Secondary

End point timeframe:

From randomization until the final analysis data cut-off date of 11 July 2016. The median duration of follow-up was 70.2 months in the placebo group and 58.8 months in the overall palifermin group.

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported for the safety subset

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	Overall Palifermin
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	92	38	93	131
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (117.8 to 99999)	99999 (99999 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival[23]

End point description:

Progression free survival (PFS) was analyzed using Kaplan-Meier methods and was defined as the time between the date of first dose of study drug and the date of physical or radiological evidence of disease progression or death (regardless of cause). Participants who were still alive without disease progression were censored at the date of last disease response assessment. If the participant did not have a disease response assessment, then the date the participant was last known to be alive was used as the censoring date.
Progression-free survival was analyzed in the safety subset. "99999" indicates data not estimable.

End point type	Secondary

End point timeframe:

From randomization until the final analysis data cut-off date of 11 July 2016. The median duration of follow-up was 70.2 months in the placebo group and 58.8 months in the overall palifermin group.

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported for the safety subset

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	Overall Palifermin
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	92	38	93	131
Units: months				
median (confidence interval 95%)	88.5 (52.7 to 99999)	99999 (56.2 to 99999)	109.2 (43.4 to 99999)	109.2 (62.6 to 99999)

Statistical analyses

Statistical analysis title	Analysis of Progression-free Survival
Comparison groups	Placebo v Overall Palifermin
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.555 [24]
Method	Stratified Cox Proportional Hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	0.889

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.601
upper limit	1.315

Notes:

[24] - The Cox proportional hazard model is stratified by disease stage (III vs. IV) and anatomical tumor location (oral cavity or oropharynx vs. nasopharynx vs. hypopharynx or larynx)

Statistical analysis title	Analysis of Progression-free Survival
Comparison groups	Placebo v Palifermin 7-dose
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.948 [25]
Method	Stratified Cox Proportional Hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	0.986
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.648
upper limit	1.5

Notes:

[25] - The Cox proportional hazard model is stratified by disease stage (III vs. IV) and anatomical tumor location (oral cavity or oropharynx vs. nasopharynx vs. hypopharynx or larynx)

Secondary: Number of Participants with Second Primary Tumors

End point title	Number of Participants with Second Primary Tumors[26]

End point description:

End point type	Secondary

End point timeframe:

From first dose of study drug until the final analysis data cut-off date of 11 July 2016. The median duration of follow-up was 70.2 months in the placebo group and 58.8 months in the overall palifermin group.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported for the safety subset

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	Overall Palifermin
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	92	38	93	131
Units: participants	7	6	8	14

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Other Malignancies

End point title	Number of Participants with Other Malignancies[27]

End point description:

End point type	Secondary

End point timeframe:

From first dose of study drug until the final analysis data cut-off date of 11 July 2016. The median duration of follow-up was 70.2 months in the placebo group and 58.8 months in the overall palifermin group.

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported for the safety subset

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	Overall Palifermin
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	92	38	93	131
Units: participants	9	4	8	12

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Leukoplakia

End point title	Number of Participants with Leukoplakia[28]

End point description:

End point type	Secondary

End point timeframe:

From first dose of study drug until the final analysis data cut-off date of 11 July 2016. The median duration of follow-up was 70.2 months in the placebo group and 58.8 months in the overall palifermin group.

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported for the safety subset

End point values	Placebo	Palifermin 4-dose	Palifermin 7-dose	Overall Palifermin
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	92	38	93	131
Units: participants	1	0	4	4

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until the end of the acute oral mucositis evaluation phase (up to 15 weeks).

Adverse event reporting additional description:

The safety subset includes all participants who were randomized and received at least one dose of investigational product, with subjects analyzed according to the treatment they actually received. One participant randomized to placebo received one dose of palifermin in error and is included in the Palifermin 7-dose group for safety.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received a single dose of placebo administered intravenously 3 days before the start of radiotherapy, and 6 once-weekly doses during a 6-week course of radio/chemotherapy.

Reporting group title	Palifermin 7-dose

Reporting group description:

Participants received a single dose of 120 µg/kg administered intravenously 3 days before the start of radiotherapy, and 6 once-weekly doses during a 6-week course of radio/chemotherapy.

Reporting group title	Palifermin 4-dose

Reporting group description:

Participants received a single dose of 120 µg/kg palifermin administered intravenously 3 days before the start of radiotherapy, and 3 once-weekly doses during a 6-week course of radio/chemotherapy. This treatment group was removed with implementation of protocol amendment 3.

Serious adverse events	Placebo	Palifermin 7-dose	Palifermin 4-dose
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 92 (44.57%)	31 / 93 (33.33%)	18 / 38 (47.37%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lymph nodes			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pharyngeal neoplasm			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 92 (0.00%)	2 / 93 (2.15%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Tracheostomy			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Face oedema			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	3 / 92 (3.26%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	10 / 92 (10.87%)	4 / 93 (4.30%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 10	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 92 (2.17%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 92 (2.17%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal fistula			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngolaryngeal pain			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			

subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 92 (1.09%)	4 / 93 (4.30%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	2 / 92 (2.17%)	1 / 93 (1.08%)	2 / 38 (5.26%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Post procedural fistula			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation associated pain			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation mucositis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 92 (2.17%)	1 / 93 (1.08%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	2 / 92 (2.17%)	2 / 93 (2.15%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 92 (1.09%)	1 / 93 (1.08%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 92 (0.00%)	2 / 93 (2.15%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	3 / 92 (3.26%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	3 / 92 (3.26%)	7 / 93 (7.53%)	5 / 38 (13.16%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	8 / 92 (8.70%)	1 / 93 (1.08%)	2 / 38 (5.26%)
occurrences causally related to treatment / all	0 / 9	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal perforation			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral pain			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	4 / 92 (4.35%)	0 / 93 (0.00%)	3 / 38 (7.89%)
occurrences causally related to treatment / all	0 / 4	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	7 / 92 (7.61%)	2 / 93 (2.15%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 8	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin necrosis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			
subjects affected / exposed	1 / 92 (1.09%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 92 (2.17%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	1 / 92 (1.09%)	3 / 93 (3.23%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure chronic			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Pain in jaw			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess of salivary gland			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candidiasis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Clostridium difficile colitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes virus infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal candidiasis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	3 / 92 (3.26%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 92 (2.17%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superinfection oral			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Anorexia			
subjects affected / exposed	3 / 92 (3.26%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	6 / 92 (6.52%)	4 / 93 (4.30%)	3 / 38 (7.89%)
occurrences causally related to treatment / all	0 / 6	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 93 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 92 (1.09%)	1 / 93 (1.08%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Palifermin 7-dose	Palifermin 4-dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 92 (92.39%)	84 / 93 (90.32%)	34 / 38 (89.47%)
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 92 (2.17%)	2 / 93 (2.15%)	2 / 38 (5.26%)
occurrences (all)	2	3	2
Hypertension			
subjects affected / exposed	2 / 92 (2.17%)	3 / 93 (3.23%)	2 / 38 (5.26%)
occurrences (all)	2	4	2
Hypotension			
subjects affected / exposed	1 / 92 (1.09%)	1 / 93 (1.08%)	2 / 38 (5.26%)
occurrences (all)	1	1	2
Lymphoedema			
subjects affected / exposed	2 / 92 (2.17%)	2 / 93 (2.15%)	3 / 38 (7.89%)
occurrences (all)	3	3	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 92 (7.61%)	12 / 93 (12.90%)	3 / 38 (7.89%)
occurrences (all)	9	12	3
Face oedema			

subjects affected / exposed	5 / 92 (5.43%)	9 / 93 (9.68%)	3 / 38 (7.89%)
occurrences (all)	5	13	3
Fatigue			
subjects affected / exposed	13 / 92 (14.13%)	6 / 93 (6.45%)	0 / 38 (0.00%)
occurrences (all)	17	7	0
General physical health deterioration			
subjects affected / exposed	1 / 92 (1.09%)	0 / 93 (0.00%)	2 / 38 (5.26%)
occurrences (all)	1	0	3
Localised oedema			
subjects affected / exposed	2 / 92 (2.17%)	5 / 93 (5.38%)	0 / 38 (0.00%)
occurrences (all)	2	10	0
Oedema peripheral			
subjects affected / exposed	3 / 92 (3.26%)	5 / 93 (5.38%)	2 / 38 (5.26%)
occurrences (all)	3	8	2
Pyrexia			
subjects affected / exposed	14 / 92 (15.22%)	13 / 93 (13.98%)	3 / 38 (7.89%)
occurrences (all)	16	15	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 92 (6.52%)	10 / 93 (10.75%)	1 / 38 (2.63%)
occurrences (all)	6	11	1
Dysphonia			
subjects affected / exposed	11 / 92 (11.96%)	10 / 93 (10.75%)	4 / 38 (10.53%)
occurrences (all)	20	18	7
Dyspnoea			
subjects affected / exposed	2 / 92 (2.17%)	6 / 93 (6.45%)	1 / 38 (2.63%)
occurrences (all)	2	6	1
Hiccups			
subjects affected / exposed	3 / 92 (3.26%)	5 / 93 (5.38%)	0 / 38 (0.00%)
occurrences (all)	3	5	0
Pharyngolaryngeal pain			
subjects affected / exposed	5 / 92 (5.43%)	6 / 93 (6.45%)	2 / 38 (5.26%)
occurrences (all)	6	6	2
Psychiatric disorders			

Insomnia			
subjects affected / exposed	12 / 92 (13.04%)	5 / 93 (5.38%)	1 / 38 (2.63%)
occurrences (all)	13	5	1
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 92 (5.43%)	5 / 93 (5.38%)	1 / 38 (2.63%)
occurrences (all)	5	5	1
Weight decreased			
subjects affected / exposed	10 / 92 (10.87%)	14 / 93 (15.05%)	6 / 38 (15.79%)
occurrences (all)	16	19	7
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	17 / 92 (18.48%)	17 / 93 (18.28%)	5 / 38 (13.16%)
occurrences (all)	31	34	13
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 92 (6.52%)	5 / 93 (5.38%)	0 / 38 (0.00%)
occurrences (all)	6	9	0
Dysgeusia			
subjects affected / exposed	6 / 92 (6.52%)	6 / 93 (6.45%)	3 / 38 (7.89%)
occurrences (all)	6	8	5
Headache			
subjects affected / exposed	4 / 92 (4.35%)	9 / 93 (9.68%)	3 / 38 (7.89%)
occurrences (all)	8	9	3
Lethargy			
subjects affected / exposed	1 / 92 (1.09%)	3 / 93 (3.23%)	2 / 38 (5.26%)
occurrences (all)	1	3	2
Paraesthesia			
subjects affected / exposed	1 / 92 (1.09%)	1 / 93 (1.08%)	4 / 38 (10.53%)
occurrences (all)	1	3	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 92 (13.04%)	9 / 93 (9.68%)	2 / 38 (5.26%)
occurrences (all)	16	12	3
Leukopenia			

subjects affected / exposed	18 / 92 (19.57%)	11 / 93 (11.83%)	12 / 38 (31.58%)
occurrences (all)	25	15	16
Neutropenia			
subjects affected / exposed	12 / 92 (13.04%)	14 / 93 (15.05%)	5 / 38 (13.16%)
occurrences (all)	13	17	6
Thrombocytopenia			
subjects affected / exposed	2 / 92 (2.17%)	5 / 93 (5.38%)	1 / 38 (2.63%)
occurrences (all)	2	6	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	7 / 92 (7.61%)	7 / 93 (7.53%)	3 / 38 (7.89%)
occurrences (all)	7	8	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 92 (2.17%)	5 / 93 (5.38%)	1 / 38 (2.63%)
occurrences (all)	2	6	1
Constipation			
subjects affected / exposed	23 / 92 (25.00%)	21 / 93 (22.58%)	13 / 38 (34.21%)
occurrences (all)	27	25	14
Diarrhoea			
subjects affected / exposed	5 / 92 (5.43%)	10 / 93 (10.75%)	3 / 38 (7.89%)
occurrences (all)	5	10	3
Dry mouth			
subjects affected / exposed	2 / 92 (2.17%)	5 / 93 (5.38%)	1 / 38 (2.63%)
occurrences (all)	2	6	1
Dysphagia			
subjects affected / exposed	18 / 92 (19.57%)	32 / 93 (34.41%)	9 / 38 (23.68%)
occurrences (all)	30	54	22
Nausea			
subjects affected / exposed	44 / 92 (47.83%)	43 / 93 (46.24%)	16 / 38 (42.11%)
occurrences (all)	78	63	29
Odynophagia			
subjects affected / exposed	12 / 92 (13.04%)	8 / 93 (8.60%)	0 / 38 (0.00%)
occurrences (all)	13	8	0
Oedema mouth			

subjects affected / exposed	3 / 92 (3.26%)	5 / 93 (5.38%)	0 / 38 (0.00%)
occurrences (all)	3	6	0
Vomiting			
subjects affected / exposed	32 / 92 (34.78%)	32 / 93 (34.41%)	12 / 38 (31.58%)
occurrences (all)	51	47	17
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 92 (3.26%)	3 / 93 (3.23%)	3 / 38 (7.89%)
occurrences (all)	3	3	3
Dermatitis			
subjects affected / exposed	8 / 92 (8.70%)	7 / 93 (7.53%)	4 / 38 (10.53%)
occurrences (all)	13	8	6
Erythema			
subjects affected / exposed	8 / 92 (8.70%)	11 / 93 (11.83%)	2 / 38 (5.26%)
occurrences (all)	11	19	2
Periorbital oedema			
subjects affected / exposed	0 / 92 (0.00%)	1 / 93 (1.08%)	2 / 38 (5.26%)
occurrences (all)	0	1	2
Pruritus			
subjects affected / exposed	2 / 92 (2.17%)	4 / 93 (4.30%)	4 / 38 (10.53%)
occurrences (all)	2	6	4
Swelling face			
subjects affected / exposed	2 / 92 (2.17%)	5 / 93 (5.38%)	0 / 38 (0.00%)
occurrences (all)	2	5	0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 92 (1.09%)	1 / 93 (1.08%)	2 / 38 (5.26%)
occurrences (all)	1	1	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 92 (1.09%)	6 / 93 (6.45%)	0 / 38 (0.00%)
occurrences (all)	1	8	0
Infections and infestations			
Candidiasis			
subjects affected / exposed	7 / 92 (7.61%)	9 / 93 (9.68%)	3 / 38 (7.89%)
occurrences (all)	7	10	3

Fungal infection			
subjects affected / exposed	4 / 92 (4.35%)	1 / 93 (1.08%)	2 / 38 (5.26%)
occurrences (all)	4	1	2
Oral candidiasis			
subjects affected / exposed	23 / 92 (25.00%)	21 / 93 (22.58%)	7 / 38 (18.42%)
occurrences (all)	24	26	9
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	14 / 92 (15.22%)	14 / 93 (15.05%)	3 / 38 (7.89%)
occurrences (all)	15	14	4
Dehydration			
subjects affected / exposed	8 / 92 (8.70%)	2 / 93 (2.15%)	1 / 38 (2.63%)
occurrences (all)	10	3	2
Hyperuricaemia			
subjects affected / exposed	3 / 92 (3.26%)	5 / 93 (5.38%)	2 / 38 (5.26%)
occurrences (all)	5	8	4
Hypokalaemia			
subjects affected / exposed	7 / 92 (7.61%)	6 / 93 (6.45%)	4 / 38 (10.53%)
occurrences (all)	8	7	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2005	Changes included: • In the chemoradiotherapy treatment regimen used in this study, cisplatin is administered as a radiosensitizer before RT on days 1, 22, and 43. Study investigators agreed that in this setting cisplatin should only be administered in association with RT. Therefore, only subjects scheduled to receive the optional "boost radiation" during week 7 were to receive cisplatin on day 43. Study procedures were clarified to reflect this. • The Performance Status Scale for HNC patients, Attitudes questionnaire and Clinical Symptoms questionnaires were removed from the study because these instruments were not deemed to provide data that would further support the objective of the study. In addition, 2 questions originally left out from the FACT-HN in error have been added, because they are a fundamental component of this PRO tool. • The exclusion criteria were amended to allow for the inclusion of subjects with curatively treated in situ cervical cancer, or basal cell carcinoma of the skin without evidence of disease for > 3 years. • As an additional safety measure, vital sign measurements were added immediately before the first dose of investigational product and within 1 hour after the first dose. • Documentation of socioeconomic status was added to review the possible correlation between socioeconomic status and disease outcome. • Pharmacy instructions were amended to include language on protection of study drug from light.
16 May 2005	Originally the main objective of this study was to evaluate the efficacy and safety of multiple weekly administrations of palifermin at the dose of 180 µg/kg to patients with advanced HNC receiving adjuvant RT/CT. However, following an independent DMC review of available safety data from subjects who received the 180 µg/kg dose in the setting of adjuvant RT with concomitant CT (including the first 7 subjects enrolled in this study) the DMC recommended to reduce the dose to 120 µg/kg weekly for this study in patients with advanced HNC postsurgery.
14 February 2006	• The original design compared two active treatment groups ("palifermin once weekly x 7"; "palifermin once weekly x 4") to placebo. The preferred dosing regimen was "palifermin once weekly x 7" based on the assumption that dosing throughout the entire duration of RT offered the optimal benefit to this population. In order to obtain robust efficacy data in a timely manner, Amgen decided to focus on the evaluation of this treatment group compared to placebo (90 subjects per arm, 180 subjects in total). Therefore, the protocol was amended throughout to reflect removal of the 4-dose arm. • The number of patients required for the interim futility analysis for efficacy was amended to reflect the reduction in sample size. • Clarification was provided for study drug administered after week 7. • Clarification of secondary endpoints relating to incidence of delays in RT and CT was made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported