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 Receiving Radiotherapy With Concurrent Chemotherapy (RT/CT)

Summary

EudraCT number	2005-000213-35
Trial protocol	CZ HU AT DE IT
Global end of trial date	11 July 2016

Results information

Result version number	v1 (current)
This version publication date	30 June 2017
First version publication date	30 June 2017

Trial information

Trial identification

Sponsor protocol code	20020402

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00101582
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swedish Orphan Biovitrum AB
Sponsor organisation address	KISP, Stockholm, Sweden, 11276
Public contact	Medical Information, Swedish Orphan Biovitrum AB, 46 86972000, info@sobi.com
Scientific contact	Medical Information, Swedish Orphan Biovitrum AB, 46 86972000, info@sobi.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:

To evaluate the efficacy of palifermin administered at the dose of 180 µg/kg IV in 8 weekly doses relative to placebo in reducing the incidence of severe [World Health Organization Grade 3 or 4] oral mucositis (OM) in subjects with locally advanced HNC receiving RT/CT as definitive treatment for their disease.

Protection of trial subjects:

This study was conducted in accordance with US Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	United States: 56
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Czech Republic: 22
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	188
EEA total number of subjects	130

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	162
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 46 sites globally; 5 in Austria, 2 in Canada, 4 in the Czech Republic, 4 in Germany, 5 in Hungary, 4 in Italy, 4 in Poland and 18 in the United States.

Pre-assignment

Screening details:

Subjects were screened and received a unique number from IVRS. Randomization to one of the two treatment groups occured 24 hours before first dose of IMP. Subjects were also stratified before randomization based on disease stage (3 or 4) and primary anatomical location of the tumor (oral cavity oropharynx, nasopharynx, or hypopharynx / larynx)

Period 1

Period 1 title	Acute phase - Period A
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

A registration call was made into the IVRS within the 24 hours before the first dose of investigational product. At the completion of this call, a randomization number and drug box number(s) were assigned by the IVRS. From this point on, a subject was considered assigned to one of the two treatment groups.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received a single intravenous (IV) dose of placebo three days before the start of radiotherapy, and then 7 once weekly placebo doses during a 7-week radiotherapy/chemotherapy course. Chemotherapy consisted of 100 mg/m^2 cisplatin administered by IV infusion on Days 1, 22, and 43.

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

Dosage and administration details:

Placebo was given as intravenous bolus injections. Placebo was presented as lyophilized white powder in 6.25 mg single-dose vials to be reconstituted with 1.2 ml of sterile water for injection. The reconstituted solution contained 10 mM histidin (pH6.5), 4 % mannitol, 2 % sucrose, 0.010 % polysorbate 20 and no preservatives.

A single dose of placebo was administered 3 days before the start of RT, then once weekly throughout the RT/CT period for a total of 8 doses.

Arm title	Palifermin

Arm description:

Participants received a single intravenous dose of palifermin at 180 µg/kg three days before the start of radiotherapy, and then 7 once weekly palifermin doses at the same dose level during a 7-week radiotherapy/ chemotherapy course. Chemotherapy consisted of 100 mg/m^2 cisplatin administered by IV infusion on Days 1, 22, and 43.

Arm type	Experimental

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

Dosage and administration details:

Palifermin was given as intravenous bolus injections. Placebo was presented as lyophilized white powder in 6.25 mg single-dose vials to be reconstituted with 1.2 ml of sterile water for injection. The reconstituted solution contained 5 mg/mL (± 0.5 mg/mL) palifermin, 10 mM histidin (pH6.5), 4 % mannitol, 2 % sucrose, 0.010 % polysorbate 20 and no preservatives.

A single dose of palifermin was administered 3 days before the start of RT, then once weekly throughout the RT/CT period for a total of 8 doses.

Number of subjects in period 1	Placebo	Palifermin
Started	94	94
Completed	83	79
Not completed	11	15
Adverse event, serious fatal	-	3
Consent withdrawn by subject	1	-
Adverse event, non-fatal	4	5
Other	-	2
Subject request	-	2
Subjects who never received IMP	3	-
Protocol deviation	2	1
Noncompliance	1	2

Period 2

Period 2 title	Long-term follow up phase - Period B
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects who received placebo in Period A, acute phase.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Palifermin

Arm description:

Subjects who received palifermin in Period A, acute phase.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Placebo	Palifermin
Started	83	79
Completed	40	44
Not completed	51	50
Adverse event, serious fatal	51	50
Joined	8	15
Subjects not completed PeriodA counted in Period B	8	-
Subjects not completed PeriodA counted in PeriodB	-	15

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received a single intravenous (IV) dose of placebo three days before the start of radiotherapy, and then 7 once weekly placebo doses during a 7-week radiotherapy/chemotherapy course. Chemotherapy consisted of 100 mg/m^2 cisplatin administered by IV infusion on Days 1, 22, and 43.	
Reporting group title	Palifermin
Reporting group description:	
Participants received a single intravenous dose of palifermin at 180 µg/kg three days before the start of radiotherapy, and then 7 once weekly palifermin doses at the same dose level during a 7-week radiotherapy/ chemotherapy course. Chemotherapy consisted of 100 mg/m^2 cisplatin administered by IV infusion on Days 1, 22, and 43.	

Reporting group values	Placebo	Palifermin	Total
Number of subjects	94	94	188
Age categorical Units: Subjects			
Adults (18-64 years)	83	79	162
From 65-84 years	11	15	26
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	14	15	29
Male	80	79	159

Subject analysis sets	
Subject analysis set title	Placebo - safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects receiving at least one dose of IMP (placebo) in the in the acute phase	
Subject analysis set title	Palifermin - safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects receiving at least one dose of IMP (palifermin) in the in the acute phase	
Subject analysis set title	Placebo - full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects randomized to the placebo treatment group in the study	
Subject analysis set title	Palifermin - full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects randomized to the palifermin treatment group in the study	
Subject analysis set title	Placebo - LTFU analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received placebo in the acute phase of the study - Period A	

Subject analysis set title	Palifermin - LTFU analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who received palifermin during the acute phase of the study, period A.

Reporting group values	Placebo - safety analysis set	Palifermin - safety analysis set	Placebo - full analysis set
Number of subjects	91	94	94
Age categorical Units: Subjects			
Adults (18-64 years)	80	79	83
From 65-84 years	11	15	11
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	13	15	14
Male	78	79	80

Reporting group values	Palifermin - full analysis set	Placebo - LTFU analysis set	Palifermin - LTFU analysis set
Number of subjects	94	91	94
Age categorical Units: Subjects			
Adults (18-64 years)	79	80	79
From 65-84 years	15	11	15
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	15	13	15
Male	79	78	79

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received a single intravenous (IV) dose of placebo three days before the start of radiotherapy, and then 7 once weekly placebo doses during a 7-week radiotherapy/chemotherapy course. Chemotherapy consisted of 100 mg/m^2 cisplatin administered by IV infusion on Days 1, 22, and 43.	
Reporting group title	Palifermin
Reporting group description:	
Participants received a single intravenous dose of palifermin at 180 µg/kg three days before the start of radiotherapy, and then 7 once weekly palifermin doses at the same dose level during a 7-week radiotherapy/ chemotherapy course. Chemotherapy consisted of 100 mg/m^2 cisplatin administered by IV infusion on Days 1, 22, and 43.	
Reporting group title	Placebo
Reporting group description:	
Subjects who received placebo in Period A, acute phase.	
Reporting group title	Palifermin
Reporting group description:	
Subjects who received palifermin in Period A, acute phase.	
Subject analysis set title	Placebo - safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects receiving at least one dose of IMP (placebo) in the in the acute phase	
Subject analysis set title	Palifermin - safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects receiving at least one dose of IMP (palifermin) in the in the acute phase	
Subject analysis set title	Placebo - full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects randomized to the placebo treatment group in the study	
Subject analysis set title	Palifermin - full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects randomized to the palifermin treatment group in the study	
Subject analysis set title	Placebo - LTFU analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received placebo in the acute phase of the study - Period A	
Subject analysis set title	Palifermin - LTFU analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received palifermin during the acute phase of the study, period A.	

Primary: Incidence of Severe Oral Mucositis (WHO Grade 3 or 4)

End point title	Incidence of Severe Oral Mucositis (WHO Grade 3 or 4)
End point description:	
Participants underwent evaluations of oral mucosal (OM) surfaces (mucositis assessments) 2 times weekly throughout radio/chemotherapy, and 2 times weekly thereafter until severe OM returned to grade ≤ 2 or until Week 15. During each evaluation, the following anatomical areas were assessed: upper lip; lower lip; right cheek; left cheek; right ventral & lateral tongue; left ventral & lateral tongue;	

floor of the mouth; hard palate; soft palate. A trained evaluator documented the findings using the World Health Organization (WHO) oral toxicity scale according to the following: 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.

End point type	Primary

End point timeframe:

Up to week 15

End point values	Placebo - full analysis set	Palifermin - full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	94		
Units: subjects				
Yes	62	51		
No	29	43		
Unknown	3	0		

Statistical analyses

Statistical analysis title	Incidence of Severe Oral Mucositis (WHO Grade 3 or
Comparison groups	Placebo - full analysis set v Palifermin - full analysis set
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.1417
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2779
upper limit	-0.0056

Secondary: Duration of severe oral mucositis (WHO grade 3 or 4)

End point title	Duration of severe oral mucositis (WHO grade 3 or 4)

End point description:

The duration of severe oral mucositis (OM) was calculated as the number of days from the onset of severe OM (first time a WHO grade 3 or 4 was observed) to the day when severe OM was resolved (first time WHO grade 2 or less was observed after last WHO grade 3 or 4). Durations of 0 days were assigned to those participants who did not experience any WHO grade 3 or 4 during the study.

End point type	Secondary

End point timeframe:

Up to 15 weeks

End point values	Placebo - full analysis set	Palifermin - full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	94		
Units: Days				
median (inter-quartile range (Q1-Q3))	26 (0 to 50)	5 (0 to 40)		

Statistical analyses

Statistical analysis title	Duration of severe oral mucositis (grade 3 or 4)
Comparison groups	Placebo - full analysis set v Palifermin - full analysis set
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1122 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-8.865
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.6865
upper limit	-2.0435

Notes:

[1] - The reported p-value is an adjusted p-value based on Hochberg procedure for the Type 1 error. Original p-value was 0.0160.

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 (WHO Grade 3 or 4) oral mucositis (OM) was analyzed 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 severe OM.

End point type	Secondary

End point timeframe:

Up to 15 weeks

End point values	Placebo - full analysis set	Palifermin - full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	94		
Units: Number of subjects	62	51		

Statistical analyses

Statistical analysis title	Time to onset of severe oral mucositis
Comparison groups	Placebo - full analysis set v Palifermin - full analysis set
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1566 [2]
Method	Stratified Log-Rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6603
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4546
upper limit	0.9592

Notes:

[2] - Adjusted p-value was based on Hochberg procedure to control for the Type 1 error. Unadjustedl p-value was 0.0261.

Secondary: Incidence of Xerostomia (grade 2 or higher CTCAE v3.0 dry mouth/xerostomia scale) at month 4 visit

End point title	Incidence of Xerostomia (grade 2 or higher CTCAE v3.0 dry mouth/xerostomia scale) at month 4 visit

End point description:

The number of participants with grade 2 or higher xerostomia (dryness of the oral mucosa) at the Month 4 visit, graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 Dry Mouth/Xerostomia scale.

End point type	Secondary

End point timeframe:

Month 4

End point values	Placebo - full analysis set	Palifermin - full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	94		
Units: incidence				
Yes	57	37		
No	19	31		
Unknown	18	26		

Statistical analyses

Statistical analysis title	Incidence of Xerostomia at month 4
Comparison groups	Placebo - full analysis set v Palifermin - full analysis set
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2314 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.1291
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2542
upper limit	-0.0041

Notes:

[3] - Adjusted p-value was based on Hochberg procedure to control for the Type 1 error. Original p-value was 0.0463.

Secondary: Patient-reported mouth and soreness score

End point title	Patient-reported mouth and soreness score

End point description:

The average patient-reported mouth and throat soreness (MTS) score as reported on question 3 of the Oral Mucositis Weekly Questionnaire for Head and Neck Cancer [OMWQ-HN]): "How much mouth and throat soreness did you experience in the past 24 hours?" Participants 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.

End point type	Secondary

End point timeframe:

Assessed twice a week for up to 15 weeks.

End point values	Placebo - full analysis set	Palifermin - full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88	89		
Units: MTS score				
arithmetic mean (standard deviation)	1.86 (± 0.65)	1.66 (± 0.73)		

Statistical analyses

Statistical analysis title	Patient-reported MTS score
Comparison groups	Placebo - full analysis set v Palifermin - full analysis set
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2849 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	-0.2006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4033
upper limit	0.0022

Notes:

[4] - Adjusted p-value was based on Hochberg procedure to control for the Type 1 error. Original p-value was 0.0712.

Secondary: Total dose of opioid analgesic used (mg of IV morphine equivalents)

End point title	Total dose of opioid analgesic used (mg of IV morphine equivalents)

End point description:

The total dose of opioid analgesics (mg of intravenous [IV] morphine equivalents) used by all participants.
Participants with at least one reported administration of opioid analgesic (parenteral, peroral or transdermal) were considered to have received opioid analgesics. The total dose of opioid analgesics is the sum of all opioid analgesic administrations that have been converted to morphine equivalents.

End point type	Secondary

End point timeframe:

Up to 15 weeks

End point values	Placebo - full analysis set	Palifermin - full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	94		
Units: mg of IV morphine equivalents				
arithmetic mean (standard deviation)	1219.55 (± 1769.29)	1243.31 (± 2700.28)		

Statistical analyses

Statistical analysis title	Total dose of Opioid Analgesic used
Comparison groups	Placebo - full analysis set v Palifermin - full analysis set

Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6835 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	26.4885
Confidence interval	
level	95 %
sides	2-sided
lower limit	-639.9243
upper limit	692.9012

Notes:

[5] - Adjusted p-value was based on Hochberg procedure to control for the Type 1 error. Original p-value was 0.2384.

Secondary: Incidence of unplanned delay of 5 or more days and discontinuation of chemotherapy

End point title	Incidence of unplanned delay of 5 or more days and discontinuation of chemotherapy

End point description:

Cisplatin was administered on Days 1, 22, and 43. An unplanned break in cisplatin refers to a delay of ≥ 5 days from the scheduled Day 22 or Day 43 cisplatin administration or a discontinuation of cisplatin for any reason.

End point type	Secondary

End point timeframe:

During the 7 weeks of chemotherapy treatment

End point values	Placebo - full analysis set	Palifermin - full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	94		
Units: incidence				
Yes	42	49		
No	52	45		

Statistical analyses

Statistical analysis title	Unplanned delay of 5 or more days of CT
Comparison groups	Placebo - full analysis set v Palifermin - full analysis set
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6835 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0.0675

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0705
upper limit	0.2055

Notes:

[6] - Adjusted p-value was based on Hochberg procedure to control for the Type 1 error. Unadjusted p-value was 0.3417.

Secondary: Incidence of unplanned breaks in radiotherapy of >= 5 days Including discontinuation of radiotherapy

End point title	Incidence of unplanned breaks in radiotherapy of >= 5 days Including discontinuation of radiotherapy

End point description:

Participants with a duration of 5 days or more without an administration of radiotherapy or who discontinue radiotherapy prior to completion of planned radiotherapy were considered to have an unplanned break in radiotherapy.

End point type	Secondary

End point timeframe:

During the 7 weeks of radiotherapy

End point values	Placebo - full analysis set	Palifermin - full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	94		
Units: incidence				
Yes	11	13		
No	80	80		
Did not receive RT	3	1		

Statistical analyses

Statistical analysis title	Unplanned breaks or dicontinuation of RT
Comparison groups	Placebo - full analysis set v Palifermin - full analysis set
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9587 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.0027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1063
upper limit	0.1009

Notes:

[7] - Adjusted p-value was based on Hochberg procedure to control for the Type 1 error. Unadjusted p-value was also 0.9587.

Secondary: Overall tumor response at week 12 visit

End point title	Overall tumor response at week 12 visit

End point description:

End point type	Secondary

End point timeframe:

From start of treatment until Week 12

End point values	Placebo - safety analysis set	Palifermin - safety analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	94		
Units: subjects				
Complete response	39	37		
Partial response	40	33		
Stable disease	5	6		
Disease progression	0	2		
Unknown	7	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of serum anti-palifermin neutralizing antibodies

End point title	Incidence of serum anti-palifermin neutralizing antibodies

End point description:

End point type	Secondary

End point timeframe:

Up to week 12

End point values	Placebo - safety analysis set	Palifermin - safety analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91[8]	94[9]		
Units: incidence				
Baseline	0	0		
Week 4	0	0		
Week 8	0	0		

Week 12	0	0		
Overall	0	0		

Notes:

[8] - Number of subjects assessed at baseline was 88, and then 89, 84 and 82. Overall 90 subjects assessed

[9] - Number of subjects assessed at baseline was 88, and then 85, 81 and 79. Overall 89 subjects assessed

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of second primary tumors

End point title	Incidence of second primary tumors

End point description:

End point type	Other pre-specified

End point timeframe:

From first dose of investigational product until end of trial

End point values	Placebo - LTFU analysis set	Palifermin - LTFU analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	94		
Units: Number of subjects	11			

End point values	Placebo - LTFU analysis set	Palifermin - LTFU analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	94		
Units: Number of subjects	3	2		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

End point type	Other pre-specified

End point timeframe:

From first dose of investigational product until study end.

End point values	Placebo - LTFU analysis set	Palifermin - LTFU analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	94		
Units: Number of subjects	56	56		

Statistical analyses

Statistical analysis title	Progression free survival
Comparison groups	Placebo - LTFU analysis set v Palifermin - LTFU analysis set
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.726
upper limit	1.533

Other pre-specified: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

End point type	Other pre-specified

End point timeframe:

From first dose of investigational drug until study end.

End point values	Placebo - LTFU analysis set	Palifermin - LTFU analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	94		
Units: Number of subjects	51	50		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Palifermin - LTFU analysis set v Placebo - LTFU analysis set
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.935
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.984
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.663
upper limit	1.459

Other pre-specified: Incidence of leukoplakia

End point title	Incidence of leukoplakia

End point description:

End point type	Other pre-specified

End point timeframe:

From first dose of investigational product until study end.

End point values	Placebo - LTFU analysis set	Palifermin - LTFU analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	94		
Units: Number of subjects	3	3		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to local regional failure

End point title	Time to local regional failure

End point description:

End point type	Other pre-specified

End point timeframe:

From first dose of investigational product until end of trial.

End point values	Placebo - LTFU analysis set	Palifermin - LTFU analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	94		
Units: Number of subjects	26	18		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 12 weeks (up to 15 weeks, maximum)

Adverse event reporting additional description:

20020402 Primary Analysis

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	Eight-week palifermin

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Eight-week palifermin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 94 (37.23%)	26 / 91 (28.57%)	
number of deaths (all causes)	7	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal neoplasm			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal carcinoma			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 94 (2.13%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	4 / 94 (4.26%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cryptogenic organizing pneumonia			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	2 / 94 (2.13%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	1 / 94 (1.06%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pharyngeal inflammation			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal oedema			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngolaryngeal pain			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 94 (1.06%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression suicidal			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder due to a general medical condition			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin abnormal			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine abnormal			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood creatinine increased			
subjects affected / exposed	2 / 94 (2.13%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase abnormal			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood phosphorus decreased			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood sodium abnormal			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase abnormal			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	5 / 94 (5.32%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury asphyxiation			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy malfunction			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac disorders			

Cardiac failure			
subjects affected / exposed	2 / 94 (2.13%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 94 (2.13%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope vasovagal			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 94 (0.00%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Febrile neutropenia			
subjects affected / exposed	2 / 94 (2.13%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobinaemia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 94 (1.06%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 94 (1.06%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	5 / 94 (5.32%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	2 / 94 (2.13%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 94 (1.06%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 94 (3.19%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			

subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 94 (1.06%)	4 / 91 (4.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 94 (1.06%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (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			
Bronchitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis acute			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Catheter related infection			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	2 / 94 (2.13%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis pseudomembranous			
subjects affected / exposed	1 / 94 (1.06%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected epidermal cyst			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 94 (2.13%)	3 / 91 (3.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			

subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	2 / 94 (2.13%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 94 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 94 (4.26%)	9 / 91 (9.89%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food intolerance			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 94 (0.00%)	3 / 91 (3.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Eight-week palifermin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 94 (94.68%)	81 / 91 (89.01%)	
Vascular disorders			
Flushing			
subjects affected / exposed	6 / 94 (6.38%)	0 / 91 (0.00%)	
occurrences (all)	7	0	
Hypertension			
subjects affected / exposed	5 / 94 (5.32%)	4 / 91 (4.40%)	
occurrences (all)	8	5	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 94 (4.26%)	5 / 91 (5.49%)	
occurrences (all)	4	6	
Fatigue			
subjects affected / exposed	21 / 94 (22.34%)	20 / 91 (21.98%)	
occurrences (all)	29	30	
Malaise			
subjects affected / exposed	5 / 94 (5.32%)	1 / 91 (1.10%)	
occurrences (all)	6	2	
Oedema peripheral			

subjects affected / exposed	6 / 94 (6.38%)	4 / 91 (4.40%)	
occurrences (all)	9	5	
Pyrexia			
subjects affected / exposed	16 / 94 (17.02%)	19 / 91 (20.88%)	
occurrences (all)	20	24	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 94 (17.02%)	13 / 91 (14.29%)	
occurrences (all)	18	15	
Dysphonia			
subjects affected / exposed	11 / 94 (11.70%)	8 / 91 (8.79%)	
occurrences (all)	17	9	
Dyspnoea			
subjects affected / exposed	6 / 94 (6.38%)	5 / 91 (5.49%)	
occurrences (all)	9	5	
Pharyngolaryngeal pain			
subjects affected / exposed	20 / 94 (21.28%)	22 / 91 (24.18%)	
occurrences (all)	21	35	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 94 (9.57%)	8 / 91 (8.79%)	
occurrences (all)	9	8	
Depression			
subjects affected / exposed	5 / 94 (5.32%)	4 / 91 (4.40%)	
occurrences (all)	5	4	
Insomnia			
subjects affected / exposed	11 / 94 (11.70%)	10 / 91 (10.99%)	
occurrences (all)	11	10	
Investigations			
Blood creatinine increased			
subjects affected / exposed	7 / 94 (7.45%)	4 / 91 (4.40%)	
occurrences (all)	7	4	
Weight decreased			
subjects affected / exposed	25 / 94 (26.60%)	26 / 91 (28.57%)	
occurrences (all)	43	40	
Injury, poisoning and procedural complications			

Radiation skin injury			
subjects affected / exposed	25 / 94 (26.60%)	13 / 91 (14.29%)	
occurrences (all)	41	18	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 94 (3.19%)	5 / 91 (5.49%)	
occurrences (all)	5	6	
Dysgeusia			
subjects affected / exposed	18 / 94 (19.15%)	7 / 91 (7.69%)	
occurrences (all)	23	8	
Headache			
subjects affected / exposed	10 / 94 (10.64%)	5 / 91 (5.49%)	
occurrences (all)	10	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 94 (22.34%)	32 / 91 (35.16%)	
occurrences (all)	23	46	
Leukopenia			
subjects affected / exposed	21 / 94 (22.34%)	11 / 91 (12.09%)	
occurrences (all)	28	16	
Neutropenia			
subjects affected / exposed	10 / 94 (10.64%)	6 / 91 (6.59%)	
occurrences (all)	11	9	
Thrombocytopenia			
subjects affected / exposed	2 / 94 (2.13%)	6 / 91 (6.59%)	
occurrences (all)	4	8	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	11 / 94 (11.70%)	7 / 91 (7.69%)	
occurrences (all)	14	7	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	31 / 94 (32.98%)	24 / 91 (26.37%)	
occurrences (all)	39	29	
Diarrhoea			
subjects affected / exposed	7 / 94 (7.45%)	14 / 91 (15.38%)	
occurrences (all)	8	16	

Dry mouth			
subjects affected / exposed	9 / 94 (9.57%)	5 / 91 (5.49%)	
occurrences (all)	12	7	
Dyspepsia			
subjects affected / exposed	5 / 94 (5.32%)	4 / 91 (4.40%)	
occurrences (all)	7	7	
Dysphagia			
subjects affected / exposed	27 / 94 (28.72%)	19 / 91 (20.88%)	
occurrences (all)	37	35	
Nausea			
subjects affected / exposed	47 / 94 (50.00%)	42 / 91 (46.15%)	
occurrences (all)	76	65	
Odynophagia			
subjects affected / exposed	9 / 94 (9.57%)	5 / 91 (5.49%)	
occurrences (all)	14	6	
Oesophagitis			
subjects affected / exposed	5 / 94 (5.32%)	0 / 91 (0.00%)	
occurrences (all)	5	0	
Oral pain			
subjects affected / exposed	9 / 94 (9.57%)	3 / 91 (3.30%)	
occurrences (all)	9	3	
Vomiting			
subjects affected / exposed	24 / 94 (25.53%)	24 / 91 (26.37%)	
occurrences (all)	36	41	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 94 (6.38%)	1 / 91 (1.10%)	
occurrences (all)	6	1	
Dermatitis			
subjects affected / exposed	4 / 94 (4.26%)	10 / 91 (10.99%)	
occurrences (all)	4	11	
Rash			
subjects affected / exposed	9 / 94 (9.57%)	4 / 91 (4.40%)	
occurrences (all)	10	4	
Skin hyperpigmentation			

subjects affected / exposed	5 / 94 (5.32%)	1 / 91 (1.10%)	
occurrences (all)	6	1	
Infections and infestations			
Candidiasis			
subjects affected / exposed	11 / 94 (11.70%)	14 / 91 (15.38%)	
occurrences (all)	15	17	
Oral candidiasis			
subjects affected / exposed	17 / 94 (18.09%)	11 / 91 (12.09%)	
occurrences (all)	21	12	
Oral fungal infection			
subjects affected / exposed	5 / 94 (5.32%)	6 / 91 (6.59%)	
occurrences (all)	5	9	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	13 / 94 (13.83%)	10 / 91 (10.99%)	
occurrences (all)	14	13	
Dehydration			
subjects affected / exposed	10 / 94 (10.64%)	12 / 91 (13.19%)	
occurrences (all)	12	18	
Hypokalaemia			
subjects affected / exposed	19 / 94 (20.21%)	8 / 91 (8.79%)	
occurrences (all)	19	11	
Hypomagnesaemia			
subjects affected / exposed	5 / 94 (5.32%)	3 / 91 (3.30%)	
occurrences (all)	6	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2004	• The language regarding the administration of investigational product was changed to stress the need for not giving investigational product too close to CT administration. The rationale for giving the investigational product less than 24 hours before, during, or within 5 half-lives of the last chemotherapeutic agent, or 16 ours after completion of chemotherapy administration (whichever is longer), was that the impact of palifermin on the pharmacokinetics of 5-fluroruracil (5-FU) is unknown, nor is it known how 5-FU may impact the pharmacokinetics of palifermin. Thus, until any potential drug interactions are known, it was prudent to separate their administration from one another by an appropriate period of time based on the half-life of the drugs. • Opioid analgesic administration data were to be collected through the month 4 visit of phase B. The rationale for the collection of this data beyond week 12 was that some patients may still have been taking opioid analgesics for oral mouth pain, and the sponsor wanted to capture the end date of these medications. As the study was designed, the month 4 visit of phase B presented the next logical time to collect these data. • The rationale for the change in calculation of duration of OM (applied to all OM duration calculations, not just "severe") was to more appropriately capture data over the entire time frame from onset to resolution of an episode of OM.
29 March 2005	• The chemotherapy regimen has been changed from cisplatin and 5-fluorouracil (5-FU) administered during weeks 1 and 5 to cisplatin as a single agent administered during weeks 1, 4, and 7. Clinical sites expressed feasibility concerns about the cisplatin/5-FU combination regimen due to high toxicity and logistical requirements associated with the 5-FU continuous infusion; also, 5-FU was not considered standard of care in most clinical centers. This change was expected to make this study acceptable to more potential clinical study sites. No subjects had been enrolled at the time of this amendment. • The treatment arm of 4 weekly doses of palifermin was removed to make this a 2-arm study comparing 8 weekly doses of palifermin 180 µg/kg with 8 weekly doses of placebo; the number of subjects per treatment was to be 90, with same power as previously designed. The change in the study design from a 3-arm to a 2-arm study was based on the fact that clinical and preclinical data to date indicated that 8 weekly doses of palifermin was the schedule of primary interest. The efficacy of the 4 weekly doses palifermin treatment arm was to be evaluated in other studies of the palifermin clinical development program. • The PRO instrument was reduced from 8 to 5 questionnaires.

17 January 2006	The main reason for this amendment was guidance from the US FDA regarding one of the Early Stopping Guidelines for Safety (section 10.5.3 of the protocol). In amendment 2 dated 10 June 2005, language describing the first of 3 early stopping rules was changed and linked to the definition of PSLTs. Based on the FDA recommendations to include hematologic adverse events, the early stopping rule language was clarified accordingly. The following changes were also made: • A sentence was added to section 10.2.2.3 of the protocol (Patient-reported Outcome Evaluable Subset) addressing regulatory agency questions concerning analyses of PRO data of this study. • Language in section 10.5.2 of the protocol was removed to clarify and confirm that Amgen has no intention of performing an unplanned interim analysis.
15 December 2008	The sponsorship was transferred from Amgen Inc to Biovitrum AB.
27 July 2015	• For reducing the long-term safety follow-up (LTSF): At the time of the last analysis (10 April 2015), all subjects with locally advanced head and neck cancer in Study 20020402 who are still alive and stayed in the LTFU have had an opportunity to be followed for at least 9 years. Approximately 46% (86/185) of subjects who were treated with investigational product remain alive. The event rates in LTFU have been very low; therefore, relatively few events are expected to occur annually in future years. This rate of events is consistent with the type and stage of tumor treated in this study. Therefore, the endpoint for the duration of LTFU for the study was changed to limit LTFU to until death, loss to follow-up, or for up to 10 years from the last subject randomized. • Updates have been made to the sponsor contacts. • The informed consent form template has been removed from the appendices and references to that appendix in the body of the protocol have been removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported