Clinical trial results:
A Phase 1/2 Study to Evaluate Safety, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of Weekly Doses of Palifermin (Recombinant Human Keratinocyte Growth Factor, rHuKGF) for the Reduction of Oral Mucositis in Subjects with Locally Advanced Head and Neck Cancer (HNC) Receiving Postoperative Radiotherapy with Concurrent Chemotherapy

Summary

EudraCT number	2004-001716-31
Trial protocol	DE
Global end of trial date	28 July 2015

Results information

Result version number	v1 (current)
This version publication date	26 May 2017
First version publication date	26 May 2017
Summary attachment (see zip file)	20040124 CSR synopsis LTFU (20040124 CSR synopsis LTFU.pdf)

Trial information

Trial identification

Sponsor protocol code	20040124

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00626639
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	28 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2015
Global end of trial reached?	Yes
Global end of trial date	28 July 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetic profile and biological activity on buccal mucosae of palifermin administered at the dose of 120 µg/kg IV in a cohort of at least 16 (3 palifermin : 1 placebo) locally advanced HNC subjects receiving RT with concurrent CT as adjuvant treatment for their disease (post-operative setting).
To evaluate the safety and tolerability of palifermin when administered at the dose of 120 µg/kg weekly for up to 8 consecutive weeks to patients with locally advanced HNC receiving RT with concurrent CT as adjuvant treatment for their disease (post-operative setting).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 July 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	Germany: 5
Worldwide total number of subjects	5
EEA total number of subjects	5

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)	3
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at one site in Germany. 5 subjects were randomized to the acute phase of the study. The plan was to enroll 40 subjects but the study was closed due to administrative changes at the site and slow enrollment. After the acute phase of the study (Period 1) the study continued with a long term follow-up phase (Period 2).

Pre-assignment

Screening details:

Subjects ≥18 years of age with newly diagnosed histologically confirmed squamous cell carcinoma involving either the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx, post surgical resection (R0, R1) and who were candidates for adjuvant RT/CT were eligible for enrollment.

Period 1

Period 1 title	Acute phase
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:

Eligible subjects were randomized by calling an Interactive Voice Response System (IVRS) within 24 hours before the first dose of investigational product. They were randomized in a 3:1 ratio (palifermin:placebo) in PK/PD/BMD cohort and 1:1 ratio (palifermin:placebo) in the other cohort, and stratified by post surgical residual tumor stage to receive either one dose of placebo or palifermin on day –3 prior to start of CT/RT then once weekly prior to onset of grade ≥3 OM (maximum 8 doses).

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo was given as intravenous bolus injections.

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:

Three days before the start of radiotherapy (Day -3), participants received a single intravenous (IV) bolus injection of matching placebo. During radiotherapy (beginning on Day 1), participants received a weekly single IV bolus injection of matching placebo after the last radiation fraction of that week (usually on Fridays) until grade ≥3 oral mucositis occurred, or for a maximum 8 doses (completion of radiotherapy). Participants also received cisplatin 100 mg/m^2 on days 1, 22 and 43.

Arm title	Palifermin

Arm description:

Palifermin was given as intravenous bolus injections.

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

Dosage and administration details:

Three days before the start of radiotherapy (Day -3), participants received a single intravenous (IV) bolus injection of palifermin at 120 µg/kg. During radiotherapy (beginning on Day 1), participants received a weekly single IV bolus injection of palifermin at 120 µg/kg after the last radiation fraction of that week (usually on Fridays) until grade ≥3 oral mucositis occurred, or for a maximum 8 doses (completion of radiotherapy). Participants also received cisplatin 100 mg/m^2 on days 1, 22 and 43.

Number of subjects in period 1	Placebo	Palifermin
Started	2	3
Completed	2	2
Not completed	0	1
Adverse event, serious fatal	-	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Palifermin

Arm description:

Subjects who received palifermin during the active phase of the study.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo

Arm description:

Subjects who received placeboduring the active phase of the study.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Palifermin	Placebo
Started	2	2
Completed	1	0
Not completed	1	2
Adverse event, serious fatal	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo was given as intravenous bolus injections.	
Reporting group title	Palifermin
Reporting group description:	
Palifermin was given as intravenous bolus injections.	

Reporting group values	Placebo	Palifermin	Total
Number of subjects	2	3	5
Age categorical Units: Subjects			
Adults (18-64 years)	1	2	3
From 65-84 years	1	1	2
Gender categorical Units: Subjects			
Female	0	0	0
Male	2	3	5

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 active 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 active phase	
Subject analysis set title	Palifermin - per protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects who received all 8 investigational product doses (palifermin).	
Subject analysis set title	Palifermin - LTFU analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received palifermin during the active phase of the study and were followed in the long term follow up phase.	
Subject analysis set title	Placebo - LTFU analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received placebo during the active phase of the study and were followed in the long term follow-up phase.	

Reporting group values	Placebo - safety analysis set	Palifermin - safety analysis set	Palifermin - per protocol set
Number of subjects	2	3	1
Age categorical Units: Subjects			
Adults (18-64 years)	1	2	0
From 65-84 years	1	1	1
Gender categorical Units: Subjects			
Female	0	0	0
Male	2	3	1

Reporting group values	Palifermin - LTFU analysis set	Placebo - LTFU analysis set	
Number of subjects	2	2	
Age categorical Units: Subjects			
Adults (18-64 years)	1	1	
From 65-84 years	1	1	
Gender categorical Units: Subjects			
Female	0	0	
Male	2	2	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo was given as intravenous bolus injections.	
Reporting group title	Palifermin
Reporting group description:	
Palifermin was given as intravenous bolus injections.	
Reporting group title	Palifermin
Reporting group description:	
Subjects who received palifermin during the active phase of the study.	
Reporting group title	Placebo
Reporting group description:	
Subjects who received placeboduring the active phase of the study.	
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 active 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 active phase	
Subject analysis set title	Palifermin - per protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects who received all 8 investigational product doses (palifermin).	
Subject analysis set title	Palifermin - LTFU analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received palifermin during the active phase of the study and were followed in the long term follow up phase.	
Subject analysis set title	Placebo - LTFU analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received placebo during the active phase of the study and were followed in the long term follow-up phase.	

Primary: Buccal mucosal cell proliferation assayed by staining for cell cycle proliferation marker Ki67.

End point title	Buccal mucosal cell proliferation assayed by staining for cell cycle proliferation marker Ki67.[1]
End point description:	
The effect of palifermin on cell proliferation was to be assayed by staining for the cell cycle proliferation marker Ki67 in buccal mucosal biopsy samples taken prior to the first dose and either 24 or 48 hours after the first dose. Due to the small sample size, this analysis was not performed.	
End point type	Primary
End point timeframe:	
Day -3 predose and 24 or 48 hours post-dose	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the small sample size no analysis was performed on the primary endpoint.

End point values	Placebo	Palifermin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: number				

Notes:

[2] - Due to the small sample size these analyses were not performed.

[3] - Due to the small sample size these analyses were not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of Palifermin

End point title	Pharmacokinetics of Palifermin

End point description:

The following PK secondary endpoints were to be considered, but due to the small sample size the analyses were not performed: PK endpoints will include, but are not limited to: systemic clearance (CL), volume of distribution at steady state (Vss), estimated initial concentration (C0), area under the concentration-time curve from
time 0 to the time of the last quantifiable concentration (AUC(0-t)) and to infinity (AUC(0-∞)), terminal half-life (t1/2,z), mean residence time (MRT).

End point type	Secondary

End point timeframe:

Day -3, predose and at 2, 5, 15, 30, 60, and 90 minutes and 2, 4, 6, 8, 10, 12, 24 and 48 hours after the first dose

End point values	Placebo - safety analysis set	Palifermin - safety analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[4]	0[5]		
Units: number				

Notes:

[4] - Due to the small sample size these analyses were not performed.

[5] - Due to the small sample size these analyses were not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics of Palifermin

End point title	Pharmacodynamics of Palifermin

End point description:

The following PD secondary endpoints were to be considered, but due to the small sample size of only 5 subjects the analyses were not performed: Cell proliferation, Apoptosis, Cell differentiation, Expression of de-toxifying enzymes involved in oxidative stress, Expression of KGF receptor.

End point type	Secondary

End point timeframe:

Day -3 predose and 24 or 48 hours post-dose.

End point values	Placebo - safety analysis set	Palifermin - safety analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[6]	0[7]		
Units: number				

Notes:

[6] - Due to the small sample size these analyses were not performed

[7] - Due to the small sample size these analyses were not performed

Statistical analyses

No statistical analyses for this end point

Secondary: Acute phase Efficay and Safety endpoints

End point title	Acute phase Efficay and Safety endpoints

End point description:

Due to the small sample size these analyses ware not performed.

End point type	Secondary

End point timeframe:

From baseline 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	0[8]	0[9]		
Units: number				

Notes:

[8] - Due to the small sample size these analyses were not performed.

[9] - Due to the small sample size these analyses were not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression or Recurrence of Primary Disease During Long-Term Follow-up

End point title	Progression or Recurrence of Primary Disease During Long-Term Follow-up

End point description:

End point type	Secondary

End point timeframe:

From baseline until death, lost to follow up or study end

End point values	Palifermin - LTFU analysis set	Placebo - LTFU analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	2		
Units: Subjects	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Second Primary Tumor, Other Malignancy, Lost to Follow-up, or Leukoplakia During Long-Term Follow-up

End point title	Second Primary Tumor, Other Malignancy, Lost to Follow-up, or Leukoplakia During Long-Term Follow-up

End point description:

End point type	Secondary

End point timeframe:

From baseline until death, lost to follow up or study end.

End point values	Palifermin - LTFU analysis set	Placebo - LTFU analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	2		
Units: Subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Deaths During Long-Term Follow-up

End point title	Deaths During Long-Term Follow-up

End point description:

End point type	Secondary

End point timeframe:

From week 12 until death.

End point values	Palifermin - LTFU analysis set	Placebo - LTFU analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	2		
Units: Subjects	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 weeks from first dose of IP for subjects without severe oral mucositis (OM); Up to 15 weeks or resolution for those with severe OM, whichever occurs first

Adverse event reporting additional description:

20040124 Primary Analysis

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Palifermin

Reporting group description: -

Serious adverse events	Placebo	Palifermin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	2 / 3 (66.67%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Red blood cell count increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			

subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gum neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
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			
Leukopenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Peritonitis bacterial			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Palifermin	
Total subjects affected by non-serious adverse events subjects affected / exposed	2 / 2 (100.00%)	3 / 3 (100.00%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Body temperature increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Lymphadenitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Facial pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	3	
Gastrointestinal disorders			

Ascites			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Dysphagia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 2 (100.00%)	2 / 3 (66.67%)	
occurrences (all)	6	2	
Oral pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Salivary hypersecretion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Skin discolouration			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	2	2	
Infections and infestations			
Bacteriuria			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			

subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2005	The protocol was predominately amended to reflect a decrease in dose from from 180 µg/kg to 120 µg/kg.
15 December 2008	The protocol was updated to reflect the sponsor change from Amgen to Biovitrum.
15 June 2015	To reduce the long-term safety follow-up from "until death or lost to follow up" to "subjects will be followed for up to 10 years from last subject randomized".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 May 2007	The study was closed to further enrollment on 25 May 2007 due to administrative changes at the study center and slow enrollment.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Pharmacokinetic, pharmacodynamic, safety and efficacy endpoints were not evaluable due to the limited number of subjects enrolled.

Notes: