



## 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 occurred 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     |
| <b>Arm title</b>             | 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<sup>2</sup> 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.

|                  |            |
|------------------|------------|
| <b>Arm title</b> | 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<sup>2</sup> 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 ( $\pm$  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.

| <b>Number of subjects in period 1</b> | 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             |
| <b>Arm title</b>                                                            | Placebo         |
| Arm description:<br>Subjects who received placebo in Period A, acute phase. |                 |
| Arm type                                                                    | No intervention |
| No investigational medicinal product assigned in this arm                   |                 |
| <b>Arm title</b>                                                            | Palifermin      |

Arm description:

Subjects who received palifermin in Period A, acute phase.

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

| <b>Number of subjects in period 2</b>                 | 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<br>counted in Period B | 8       | -          |
| Subjects not completed PeriodA<br>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<sup>2</sup> 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<sup>2</sup> 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<br>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<br>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<br>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<br>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<sup>2</sup> 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<sup>2</sup> 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                                                                                                                                                                                                                                                                                                                                                                                   |                                                      |

| <b>End point values</b>               | 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

|                                         |                                                              |
|-----------------------------------------|--------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[1]</sup>                                      |
| 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. Unadjusted 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

|                                         |                                                              |
|-----------------------------------------|--------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[3]</sup>                                      |
| 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.                                                                                                                                                                                                                                                                                                 |                                           |

|                                      |                             |                                |  |  |
|--------------------------------------|-----------------------------|--------------------------------|--|--|
| <b>End point values</b>              | 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

|                                         |                                                              |
|-----------------------------------------|--------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[4]</sup>                                      |
| 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

|                                   |                                                              |
|-----------------------------------|--------------------------------------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[5]</sup>        |
| 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

|                                         |                                                              |
|-----------------------------------------|--------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[6]</sup>                                      |
| 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 $\geq 5$ days Including discontinuation of radiotherapy

|                 |                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------|
| End point title | Incidence of unplanned breaks in radiotherapy of $\geq 5$ 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 discontinuation 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 <sup>[7]</sup>                                      |
| 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 <sup>[8]</sup>             | 94 <sup>[9]</sup>                |  |  |
| 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                          | 6                              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Incidence of other malignancies

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Incidence of other malignancies |
|-----------------|---------------------------------|

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                           | 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

|                                         |                                                              |
|-----------------------------------------|--------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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**

|                                         |                                                              |
|-----------------------------------------|--------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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          |  |
| Bronchopneumonia                                |                |                |  |
| 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          |  |
| Candidiasis                                     |                |                |  |
| 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          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| 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 %

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

|                                                                           |                        |                        |  |
|---------------------------------------------------------------------------|------------------------|------------------------|--|
| Radiation skin injury<br>subjects affected / exposed<br>occurrences (all) | 25 / 94 (26.60%)<br>41 | 13 / 91 (14.29%)<br>18 |  |
| Nervous system disorders                                                  |                        |                        |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)             | 3 / 94 (3.19%)<br>5    | 5 / 91 (5.49%)<br>6    |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)             | 18 / 94 (19.15%)<br>23 | 7 / 91 (7.69%)<br>8    |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)              | 10 / 94 (10.64%)<br>10 | 5 / 91 (5.49%)<br>6    |  |
| Blood and lymphatic system disorders                                      |                        |                        |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)               | 21 / 94 (22.34%)<br>23 | 32 / 91 (35.16%)<br>46 |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)            | 21 / 94 (22.34%)<br>28 | 11 / 91 (12.09%)<br>16 |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)           | 10 / 94 (10.64%)<br>11 | 6 / 91 (6.59%)<br>9    |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)      | 2 / 94 (2.13%)<br>4    | 6 / 91 (6.59%)<br>8    |  |
| Ear and labyrinth disorders                                               |                        |                        |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)              | 11 / 94 (11.70%)<br>14 | 7 / 91 (7.69%)<br>7    |  |
| Gastrointestinal disorders                                                |                        |                        |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)          | 31 / 94 (32.98%)<br>39 | 24 / 91 (26.37%)<br>29 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)             | 7 / 94 (7.45%)<br>8    | 14 / 91 (15.38%)<br>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<br>occurrences (all) | 5 / 94 (5.32%)<br>6 | 1 / 91 (1.10%)<br>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   | <ul style="list-style-type: none"><li>• 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-fluorouracil (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.</li><li>• 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.</li><li>• 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.</li></ul> |
| 29 March 2005 | <ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li><li>• The PRO instrument was reduced from 8 to 5 questionnaires.</li></ul>                                                                                                                                                |

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 January 2006  | <p>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.</p> <p>The following changes were also made:</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> </ul>                                                                                                                                                                     |
| 15 December 2008 | The sponsorship was transferred from Amgen Inc to Biovitrum AB.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 27 July 2015     | <ul style="list-style-type: none"> <li>• 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.</li> <li>• Updates have been made to the sponsor contacts.</li> <li>• 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.</li> </ul> |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported