



Clinical trial results:

A multicenter, randomized, double-blind, parallel group study to evaluate the efficacy and safety of two different doses of palonosetron compared to ondansetron in the prevention of CINV in pediatric patients undergoing single and repeated cycles of MEC or HEC

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2010-022872-30 |
| Trial protocol | GB HU AT BG EE DE FR CZ |
| Global end of trial date | 26 October 2012 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 17 April 2016 |
| First version publication date | 17 April 2016 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | PALO-10-20 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01442376 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Helsinn Healthcare SA |
| Sponsor organisation address | Via Pian Scairolo 9 , Lugano/Pazzallo, Switzerland, 6912 |
| Public contact | Spinelli Tulla, Helsinn Healthcare SA, +41 91 985 21 21, tulla.spinelli@helsinn.com |
| Scientific contact | Spinelli Tulla, Helsinn Healthcare SA, +41 91 985 21 21, tulla.spinelli@helsinn.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 | 24 October 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 October 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Main objectives of the trial:

- The primary objective is to evaluate the efficacy of two different doses of IV palonosetron in the prevention of chemotherapy induced nausea and vomiting in moderately emetogenic (MEC) or highly emetogenic (HEC) patients through 120 hours after start of chemotherapy in single and repeated chemotherapy cycles.

Protection of trial subjects:

For all patients, written informed consent signed by the parent(s)/legal guardian(s) was obtained prior to enrollment. For patients of appropriate age and intellectual maturity, the signed assent form was obtained in compliance with local laws and regulations.

Background therapy:

NA

Evidence for comparator:

Ondansetron (Zofran®), another 5-HT₃ receptor antagonist, was chosen as the active comparator in this study because it is one of the most frequently prescribed antiemetic agents and is approved for intravenous (IV) and oral use in adults and children for CINV in many countries.

| | |
|---|-------------------|
| Actual start date of recruitment | 12 September 2011 |
| 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 | Chile: 29 |
| Country: Number of subjects enrolled | Peru: 19 |
| Country: Number of subjects enrolled | Romania: 58 |
| Country: Number of subjects enrolled | Argentina: 4 |
| Country: Number of subjects enrolled | Russian Federation: 50 |
| Country: Number of subjects enrolled | Serbia: 27 |
| Country: Number of subjects enrolled | Ukraine: 27 |
| Country: Number of subjects enrolled | United States: 27 |
| Country: Number of subjects enrolled | Poland: 65 |
| Country: Number of subjects enrolled | Austria: 20 |
| Country: Number of subjects enrolled | Bulgaria: 20 |
| Country: Number of subjects enrolled | Czech Republic: 63 |
| Country: Number of subjects enrolled | Estonia: 8 |
| Country: Number of subjects enrolled | France: 7 |

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Hungary: 65 |
| Worldwide total number of subjects | 493 |
| EEA total number of subjects | 310 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 45 |
| Children (2-11 years) | 298 |
| Adolescents (12-17 years) | 150 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The target population was pediatric patients aged from full-term neonates to <17 years scheduled to receive at least one moderately or highly emetogenic chemotherapeutic agent for histologically or cytologically confirmed malignant disease. For patients aged ≥ 10 years ECOG PS ≤ 2 was requested.

Pre-assignment

Screening details:

Out of total 502 randomized patients, 8 patients (2 palonosetron 10 mcg/kg, 4 palonosetron 20 mcg/kg and 2 ondansetron) did not receive the study drug and 1 patient (palonosetron 10 mcg/kg) received study drug but did not receive highly or moderate emetogenic chemotherapy (HEC or MEC), was excluded from the FAS, but included in Safety Population.

Period 1

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

Arms

| | |
|------------------------------|------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Palonosetron 10 mcg/kg |

Arm description:

Palonosetron and placebo to Ondansetron

Intervention:

Drug: Palonosetron

Palonosetron: Single dose Palonosetron IV 10 mcg/kg up to a maximum total dose of 0.75 mg

Placebo to Ondansetron

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Palonosetron |
| Investigational medicinal product code | NA |
| Other name | Aloxi |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single dose Palonosetron IV 10 mcg/kg up to a maximum total dose of 0.75 mg.

| | |
|--|------------------------|
| Investigational medicinal product name | Placebo to Ondansetron |
| Investigational medicinal product code | NA |
| Other name | NA |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single dose matching placebo IV.

| | |
|------------------|------------------------|
| Arm title | Palonosetron 20 mcg/kg |
|------------------|------------------------|

Arm description:

Palonosetron and Placebo to Ondansetron

Intervention:

Drug: Palonosetron

Palonosetron: Single dose Palonosetron IV 20 mcg/kg up to a maximum total dose of 1.5 mg

Placebo to Ondansetron

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|------------------------|
| Investigational medicinal product name | Palonosetron |
| Investigational medicinal product code | NA |
| Other name | Aloxi |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single dose Palonosetron IV 20 mcg/kg up to a maximum total dose of 1.5 mg.

| | |
|--|------------------------|
| Investigational medicinal product name | Placebo to Ondansetron |
| Investigational medicinal product code | NA |
| Other name | NA |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single dose matching placebo IV.

| | |
|------------------|-------------|
| Arm title | Ondansetron |
|------------------|-------------|

Arm description:

Ondansetron and placebo to Palonosetron

Drug:

Comparator: Ondansetron

Ondansetron: Single three (every 4 hours) Ondansetron IV doses 0.15 mg/kg up to a maximum total dose of 32 mg

Placebo to Palonosetron

| | |
|--|------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Ondansetron |
| Investigational medicinal product code | NA |
| Other name | Zofran |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single three (every 4 hours) Ondansetron IV doses 0.15 mg/kg up to a maximum total dose of 32 mg.

| | |
|--|-------------------------|
| Investigational medicinal product name | Placebo to Palonosetron |
| Investigational medicinal product code | NA |
| Other name | NA |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single dose matching placebo IV.

| Number of subjects in period 1 | Palonosetron 10 mcg/kg | Palonosetron 20 mcg/kg | Ondansetron |
|---------------------------------------|------------------------|------------------------|-------------|
| Started | 166 | 165 | 162 |
| Completed | 166 | 160 | 159 |
| Not completed | 0 | 5 | 3 |
| Consent withdrawn by subject | - | - | 1 |
| Adverse event, non-fatal | - | 2 | 1 |
| Not eligible for subsequent cycles | - | 2 | - |
| Death | - | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|---|------------------------|
| Reporting group title | Palonosetron 10 mcg/kg |
| Reporting group description: | |
| Palonosetron and placebo to Ondansetron | |
| Intervention: | |
| Drug: Palonosetron | |
| Palonosetron: Single dose Palonosetron IV 10 mcg/kg up to a maximum total dose of 0.75 mg | |
| Placebo to Ondansetron | |
| Reporting group title | Palonosetron 20 mcg/kg |
| Reporting group description: | |
| Palonosetron and Placebo to Ondansetron | |
| Intervention: | |
| Drug: Palonosetron | |
| Palonosetron: Single dose Palonosetron IV 20 mcg/kg up to a maximum total dose of 1.5 mg | |
| Placebo to Ondansetron | |
| Reporting group title | Ondansetron |
| Reporting group description: | |
| Ondansetron and placebo to Palonosetron | |
| Drug: | |
| Comparator: Ondansetron | |
| Ondansetron: Single three (every 4 hours) Ondansetron IV doses 0.15 mg/kg up to a maximum total dose of 32 mg | |
| Placebo to Palonosetron | |

| Reporting group values | Palonosetron 10 mcg/kg | Palonosetron 20 mcg/kg | Ondansetron |
|--|------------------------|------------------------|-------------|
| Number of subjects | 166 | 165 | 162 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 8.07 | 8.39 | 8.18 |
| standard deviation | ± 4.81 | ± 4.91 | ± 5.17 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 78 | 89 | 64 |
| Male | 88 | 76 | 98 |
| Age, customised | | | |
| Units: Subjects | | | |
| <2 years | 15 | 15 | 15 |
| 2 to <6 years | 54 | 54 | 54 |

| | | | |
|---|-----|-----|-----|
| 6 to <12 years | 46 | 46 | 44 |
| 12 to <17 years | 51 | 50 | 49 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 26 | 26 | 12 |
| Not Hispanic or Latino | 140 | 139 | 150 |
| Race Units: Subjects | | | |
| Asian | 2 | 0 | 0 |
| Black or African American | 2 | 0 | 0 |
| White | 156 | 154 | 159 |
| More than one race | 5 | 11 | 3 |
| Unknown or Not Reported | 1 | 0 | 0 |
| Emetogenicity of chemotherapy in Cycle 1 Units: Subjects | | | |
| MEC | 112 | 116 | 111 |
| HEC | 54 | 49 | 51 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 493 | | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 231 | | |
| Male | 262 | | |
| Age, customised Units: Subjects | | | |
| <2 years | 45 | | |
| 2 to <6 years | 162 | | |
| 6 to <12 years | 136 | | |
| 12 to <17 years | 150 | | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 64 | | |
| Not Hispanic or Latino | 429 | | |

| | | | |
|--|-----|--|--|
| Race | | | |
| Units: Subjects | | | |
| Asian | 2 | | |
| Black or African American | 2 | | |
| White | 469 | | |
| More than one race | 19 | | |
| Unknown or Not Reported | 1 | | |
| Emetogenicity of chemotherapy in Cycle 1 | | | |
| Units: Subjects | | | |
| MEC | 339 | | |
| HEC | 154 | | |

End points

End points reporting groups

| | |
|---|------------------------|
| Reporting group title | Palonosetron 10 mcg/kg |
| Reporting group description: Palonosetron and placebo to Ondansetron Intervention: Drug: Palonosetron Palonosetron: Single dose Palonosetron IV 10 mcg/kg up to a maximum total dose of 0.75 mg Placebo to Ondansetron | |
| Reporting group title | Palonosetron 20 mcg/kg |
| Reporting group description: Palonosetron and Placebo to Ondansetron Intervention: Drug: Palonosetron Palonosetron: Single dose Palonosetron IV 20 mcg/kg up to a maximum total dose of 1.5 mg Placebo to Ondansetron | |
| Reporting group title | Ondansetron |
| Reporting group description: Ondansetron and placebo to Palonosetron Drug: Comparator: Ondansetron Ondansetron: Single three (every 4 hours) Ondansetron IV doses 0.15 mg/kg up to a maximum total dose of 32 mg Placebo to Palonosetron | |

Primary: Proportion of Patients With Complete Response 0 to 24 Hours (Acute Phase) in Cycle 1

| | |
|--|--|
| End point title | Proportion of Patients With Complete Response 0 to 24 Hours (Acute Phase) in Cycle 1 |
| End point description: Complete Response (CR) was defined as no vomiting, no retching, and no use of antiemetic rescue medication from 0 to 24 hours (acute phase) after T0 (start of administration of the most emetogenic chemotherapy) during first cycle. Time 0 (T0) is defined as the time when the patient starts the first cycle of chemotherapy. Full Analysis Set (FAS) population which included all randomized patients receiving the active study drug and HEC or MEC. Following the intent-to-treat principle, patients were assigned to the study treatment group according to the randomized treatment. | |
| End point type | Primary |
| End point timeframe: 0 to 24 hours after T0 | |

| End point values | Palonosetron 10 mcg/kg | Palonosetron 20 mcg/kg | Ondansetron | |
|----------------------------------|------------------------|------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 166 | 165 | 162 | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 54.2 (46.3 to 61.9) | 59.4 (51.5 to 66.9) | 58.6 (50.6 to 66.2) | |

Statistical analyses

| Statistical analysis title | Palonosetron 20 mcg/kg vs. Ondansetron |
|---|--|
| Statistical analysis description: | |
| The stratum adjusted Mantel-Haenszel method was used to compute the confidence interval (CI) of the difference in proportion. If the lower bound of the 97.5% CI of either the difference (CR0-24h palonosetron 20 mcg/kg - CR0-24h ondansetron) or the difference (CR0-24h palonosetron 10 mcg/kg - CR0-24h ondansetron) was strictly superior to the non-inferiority margin ($\delta=-0.15$) then the null hypothesis (H0) was rejected. A power of 80% was used for sample size computation. | |
| Comparison groups | Palonosetron 20 mcg/kg v Ondansetron |
| Number of subjects included in analysis | 327 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.36 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -11.7 |
| upper limit | 12.4 |

Notes:

[1] - Non-inferiority margin of 15% at an alpha level of 2.5% in a 1-sided test (equivalent to 5.0% 2-sided test) to reject the null hypothesis that the study drug was inferior to the active control drug by more than the non-inferiority margin.

| Statistical analysis title | Palonosetron 10 mcg/kg vs. Ondansetron |
|---|--|
| Statistical analysis description: | |
| The stratum adjusted Mantel-Haenszel method was used to compute the confidence interval (CI) of the difference in proportion. If the lower bound of the 97.5% CI of either the difference (CR0-24h palonosetron 20 mcg/kg - CR0-24h ondansetron) or the difference (CR0-24h palonosetron 10 mcg/kg - CR0-24h ondansetron) was strictly superior to the non-inferiority margin ($\delta=-0.15$) then the null hypothesis (H0) was rejected. A power of 80% was used for sample size computation. | |
| Comparison groups | Ondansetron v Palonosetron 10 mcg/kg |
| Number of subjects included in analysis | 328 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -4.4 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -16.4 |
| upper limit | 7.6 |

Notes:

[2] - Non-inferiority margin of 15% at an alpha level of 2.5% in a 1-sided test (equivalent to 5.0% 2-sided test) to reject the null hypothesis that the study drug was inferior to the active control drug by more than the non-inferiority margin.

Secondary: Proportion of Patients With Complete Response >24 to 120 Hours (Delayed Phase) in Cycle 1

| | |
|---|---|
| End point title | Proportion of Patients With Complete Response >24 to 120 Hours (Delayed Phase) in Cycle 1 |
| End point description: | |
| Complete Response (CR) was defined as no vomiting, no retching, and no use of antiemetic rescue medication from >24 to 120 hours (delayed phase) after T0 (start of administration of the most emetogenic chemotherapy) during first cycle. Full Analysis Set (FAS) population. | |
| End point type | Secondary |

End point timeframe:

>24 to 120 hours (delayed phase) after T0

| End point values | Palonosetron 10 mcg/kg | Palonosetron 20 mcg/kg | Ondansetron | |
|----------------------------------|---------------------------|---------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 166 | 165 | 162 | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 28.9 (22.3 to 36.5) | 38.8 (31.4 to 46.7) | 28.4 (21.7 to 36.1) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days post treatment

Adverse event reporting additional description:

Safety population (SAF), which allocated patients to treatment groups based on the treatment actually received. Patients received study treatment on Study Day 1 of each cycle for up to 4 cycles. The number of patients included in the SAF at each cycle was the following: 494 (cycle 1), 260 (cycle 2), 146 (cycle 3) and 69 (cycle 4).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Palonosetron 10 mcg/kg |
|-----------------------|------------------------|

Reporting group description:

Palonosetron and placebo to Ondansetron

Intervention:

Drug: Palonosetron

Palonosetron: Single dose Palonosetron IV 10 mcg/kg up to a maximum total dose of 0.75 mg

Placebo to Ondansetron

| | |
|-----------------------|------------------------|
| Reporting group title | Palonosetron 20 mcg/kg |
|-----------------------|------------------------|

Reporting group description:

Palonosetron and placebo to Ondansetron

Intervention:

Drug: Palonosetron

Palonosetron: Single dose Palonosetron IV 20 mcg/kg up to a maximum total dose of 1.5 mg

Placebo to Ondansetron

| | |
|-----------------------|-------------|
| Reporting group title | Ondansetron |
|-----------------------|-------------|

Reporting group description:

Ondansetron and Placebo to Palonosetron

Drug:

Comparator: Ondansetron

Ondansetron: Single three (every 4 hours) Ondansetron IV doses 0.15 mg/kg up to a maximum total dose of 32 mg

Placebo to Palonosetron

| Serious adverse events | Palonosetron 10 mcg/kg | Palonosetron 20 mcg/kg | Ondansetron |
|---|------------------------|------------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 68 / 167 (40.72%) | 62 / 163 (38.04%) | 70 / 164 (42.68%) |
| number of deaths (all causes) | 0 | 3 | 3 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm progression | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 167 (3.59%) | 3 / 163 (1.84%) | 7 / 164 (4.27%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 1 / 163 (0.61%) | 2 / 164 (1.22%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 2 / 164 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Fatigue | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Medical device complication | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Tachypnoea | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Apathy | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 6 / 167 (3.59%) | 6 / 163 (3.68%) | 4 / 164 (2.44%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 8 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 3 / 163 (1.84%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Radiation skin injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 163 (0.61%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute disseminated encephalomyelitis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Grand mal convulsion | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neurotoxicity | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy | | | |

| | | | |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 27 / 167 (16.17%) | 30 / 163 (18.40%) | 23 / 164 (14.02%) |
| occurrences causally related to treatment / all | 0 / 31 | 0 / 38 | 0 / 35 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 17 / 167 (10.18%) | 14 / 163 (8.59%) | 15 / 164 (9.15%) |
| occurrences causally related to treatment / all | 0 / 21 | 0 / 17 | 0 / 17 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 12 / 167 (7.19%) | 10 / 163 (6.13%) | 11 / 164 (6.71%) |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 13 | 0 / 14 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 14 / 167 (8.38%) | 8 / 163 (4.91%) | 9 / 164 (5.49%) |
| occurrences causally related to treatment / all | 0 / 17 | 0 / 11 | 0 / 11 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 10 / 167 (5.99%) | 4 / 163 (2.45%) | 9 / 164 (5.49%) |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 7 | 0 / 16 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 6 / 167 (3.59%) | 2 / 163 (1.23%) | 6 / 164 (3.66%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 2 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile bone marrow aplasia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Agranulocytosis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemolysis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 167 (2.40%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 2 / 163 (1.23%) | 2 / 164 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 2 / 164 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Caecitis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal inflammation | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal mucosal disorder | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumatosis intestinalis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermatitis bullous | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin erosion | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal tubular disorder | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 4 / 167 (2.40%) | 1 / 163 (0.61%) | 3 / 164 (1.83%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 1 / 163 (0.61%) | 2 / 164 (1.22%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Candidiasis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Device related infection | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 2 / 163 (1.23%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 2 / 164 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 2 / 164 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrotising fasciitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic infection | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal skin infection | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection bacterial | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 3 / 163 (1.84%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 2 / 164 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cachexia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 163 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 163 (0.61%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemia | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 0 / 163 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Palonosetron 10 mcg/kg | Palonosetron 20 mcg/kg | Ondansetron |
|--|---------------------------|---------------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 126 / 167 (75.45%) | 112 / 163 (68.71%) | 125 / 164 (76.22%) |
| Investigations | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 10 / 167 (5.99%) | 9 / 163 (5.52%) | 10 / 164 (6.10%) |
| occurrences (all) | 13 | 12 | 19 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 12 / 167 (7.19%) | 15 / 163 (9.20%) | 15 / 164 (9.15%) |
| occurrences (all) | 14 | 18 | 24 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 17 / 167 (10.18%) | 9 / 163 (5.52%) | 16 / 164 (9.76%) |
| occurrences (all) | 24 | 10 | 28 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 65 / 167 (38.92%) | 60 / 163 (36.81%) | 61 / 164 (37.20%) |
| occurrences (all) | 107 | 89 | 105 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 11 / 167 (6.59%) | 4 / 163 (2.45%) | 4 / 164 (2.44%) |
| occurrences (all) | 13 | 4 | 7 |
| Leukopenia | | | |
| subjects affected / exposed | 37 / 167 (22.16%) | 27 / 163 (16.56%) | 43 / 164 (26.22%) |
| occurrences (all) | 74 | 59 | 104 |
| Neutropenia | | | |
| subjects affected / exposed | 35 / 167 (20.96%) | 31 / 163 (19.02%) | 22 / 164 (13.41%) |
| occurrences (all) | 60 | 51 | 40 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 35 / 167 (20.96%) | 33 / 163 (20.25%) | 37 / 164 (22.56%) |
| occurrences (all) | 69 | 61 | 90 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 32 / 167 (19.16%) | 19 / 163 (11.66%) | 21 / 164 (12.80%) |
| occurrences (all) | 40 | 35 | 38 |

| | | | |
|---|------------------|-------------------|-------------------|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 15 / 167 (8.98%) | 13 / 163 (7.98%) | 18 / 164 (10.98%) |
| occurrences (all) | 20 | 16 | 24 |
| Constipation | | | |
| subjects affected / exposed | 8 / 167 (4.79%) | 10 / 163 (6.13%) | 8 / 164 (4.88%) |
| occurrences (all) | 9 | 12 | 9 |
| Diarrhoea | | | |
| subjects affected / exposed | 13 / 167 (7.78%) | 6 / 163 (3.68%) | 14 / 164 (8.54%) |
| occurrences (all) | 14 | 7 | 15 |
| Nausea | | | |
| subjects affected / exposed | 8 / 167 (4.79%) | 6 / 163 (3.68%) | 13 / 164 (7.93%) |
| occurrences (all) | 10 | 8 | 19 |
| Stomatitis | | | |
| subjects affected / exposed | 11 / 167 (6.59%) | 12 / 163 (7.36%) | 12 / 164 (7.32%) |
| occurrences (all) | 15 | 14 | 16 |
| Vomiting | | | |
| subjects affected / exposed | 13 / 167 (7.78%) | 17 / 163 (10.43%) | 22 / 164 (13.41%) |
| occurrences (all) | 21 | 39 | 31 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 8 / 167 (4.79%) | 4 / 163 (2.45%) | 9 / 164 (5.49%) |
| occurrences (all) | 8 | 4 | 10 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 6 / 167 (3.59%) | 3 / 163 (1.84%) | 9 / 164 (5.49%) |
| occurrences (all) | 8 | 3 | 9 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

| |
|---------------|
| None reported |
|---------------|

Notes: